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Session TA1: Symposium: Hemorheology & more: in Memoriam Prof. Holger Schmid-Schönbein (1937–2017)

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O1(IL)

HEMODIALYSIS AND RHEOLOGICAL EFFECTS

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Improving the performance of dialyzers in extracorporeal blood circuits has become the number one target for the optimization of dialysis therapy. This also includes hemorheological parameters, such as blood flow through capillary membranes as well as the flow of dialysis fluids in the inter-capillary compartment of filters.

Blood flow through the lumen of capillary membranes considerably depends on the cylindrical geometry of hollow fibers. Stenosis or aneurisms, formed by inadequate production quality of hollow fibers, lead to the formation of erythrocyte clots and, thus, to the loss of filter performance. When erythrocytes move along the internal path of a capillary, their cytoplasmic membrane rotates around the cytoplasm. This rotation is considered to be the reason for an optimal oxygen transport across the membrane because "local mixer" are formed under flow conditions. This phenomenon has been elucidated several decades ago by Holger Schmid-Schönbein and been perfectly described in a scientific movie. A short excerpt of this movie will be shown for a better understanding.

Ultrafiltration of water from the blood to the dialysis fluid compartment primarily depends on transmembrane pressure and membrane permeability. Recent investigations, however, have shown that a geometric modification of the membrane surface has a large impact on ultrafiltration efficiency either.

Dialysis fluid flow between all capillaries in a dialyzer is of central importance for filter performance. Dialysis fluid must be able to enter the hollow fiber bundle up to its center in order to maintain the concentration gradient for diffusion across all capillary membranes. Specific modifications of capillary geometry in terms of micro-marcel allows for a constant distribution of dialysis fluid flow all across the fiber bundle.

Conclusion: Flow pattern of liquids and cells in dialyzers with capillary membranes determine their performance to a high extent and must always been kept in mind.

O2(IL)

HEMORHEOLOGY AND MORE

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Objectives: Computational analysis plays an increasingly important role in bioengineering, particularly in the design of implantable ventricular assist devices (VAD). Numerical simulation of blood flow and associated physiological phenomena has the potential to shorten the design cycle and give the designers important insights into causes of blood damage and suboptimal performance.

Methods: The staggering complexity of physiological phenomena leading to red blood cell damage, or hemolysis, made near-black-box experimental correlations the primary means of relating damage to detailed flow conditions as obtained from simulation. Going beyond that approach and identifying its applicability ranges requires a more detailed consideration of the behavior of individual red blood cells. Pioneering work of Schmid-Schönbein points out the main mechanisms of interaction between an erythrocyte and the surrounding flow, including dispersion, tumbling, stretching, and tank-treading. A family of so-called morphology tensor models uses that information to introduce a first-principles yet affordable description of the red blood cells and the associated hemolysis.

Results: During the course of development of the morphology tensor model, we have progressed from Lagrangian to Eulerian description, from primitive variable to log-conformation formulation, and have included the mechanism of pore formation in the erythrocyte membrane. Each of these steps improved the efficiency and robustness of the approach. Moreover, computational predictions can be now compared to a growing body of experimental data obtained for a simplified blood pump geometry in the recent Food and Drug Administration round-robin study.

Discussion: The introduction of the morphology tensor model was important for quantitative computational damage prediction in the highly unsteady and inhomogeneous flow environment of artificial heart pumps. The observation concerning the critical flow areas can be used to drive design decisions for the next generation of devices.

O3(IL)

SYNERGETIC PHYSIOLOGY - PHYSIOLOGICAL SYNERGETICS

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Prof. Dr. med. Holger Schmid-Schönbein led the Institute of Physiology at the Technical University of Aachen from 1974 to 2003, and had been the dean of the Medical Faculty from 1982 to 1984. In these three decades he created a sophisticated work place for trans-disciplinary research and education. The Institute of Physiology transformed to a melting point for young researchers coming from both medicine and engineering. This multi-disciplinary meeting first culminated in creative solutions for microcirculatory and rheological investigations. The development of video recording and rheological measurement systems of blood flow, non-invasive multi-sensor hardware for peripheral circulation, as well as the development of software packages for physiological system analysis characterized this progress. But Schmid-Schönbein was anxiously conscious to translate basic research in physiology to the clinical domain. His genuine interest in thrombosis research and blood flow disturbances in various disease states was completed by inter-disciplinary efforts in designing advanced artificial organs. For these achievements in the field of hemorheology, Schmid-Schönbein received the Fahraeus-Medal-Award in 1985.

In the eighties Schmid-Schönbein was confronted with the thought of Hermann Haken, who established the trans-disciplinary complex system theory termed Synergetics. Schmid-Schönbein realized that this paradigm not only conceptualized his prior work on blood rheology and microcirculatory flow, but had the potential to transcend the reductionist knowledge collected in physiology to the level of complex system interactions in the body: The double coined project Synergetic Physiology – Physiological Synergetics (SPPS) was born. From then on Holger Schmid-Schönbein devoted his scientific carrier to investigate complex physiological processes, first the rhythms in the circulatory system then the interactions during neuro-dynamic transitions. In his last years he made vast efforts to extend SPPS on the level of cell energy metabolism and dynamics.

O4(IL)

TEACHING AND MEASURING PAIN: A CHALLENGE TO A PHYSIOLOGIST?

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Introduction: Pain is a phenomenon concerning all faculties of the individual. Such ubiquitousness comes at the price of a dilemma: neither the patient can prove to be plagued by pain, nor the therapist can prove that the patient is not plagued by pain. That translates into a serious challenge to physiologists attempting to measure pain. Instead of using direct measures of pain, physiological research studies responses of physiological measures as indirect indicators to physical pain stimuli. However, pain perceived involves always psychological faculties. To tell physiology and psychology apart is at the core of the dilemma.

Method: H. Schmid-Schönbein, a "pontifex" in modern medicine, suggested triggering cold induced toothache and record high resolution time series of cardio-vascular-respiratory measures to establish objective means to at least bypass the dilemma. Born rather spontaneously, this approach bore a pragmatic solution since toothache is equally feared (= psychological response), as it is physiologically distinct.

To this end, a digital controlled cold-pain stimulator (CPS) was developed and tested in an in-vitro model and in an in-vivo self-test. Heart rate variability and respiratory activity were used to monitor physiological responses.

Results and Discussion: A horse tooth model demonstrated the CPS to decrease temperature within the dental cavity at rates of 6.9° C/s. This sufficed apparently to evoke cold pain. An in-vivo test in a human volunteer confirmed that this cold production was perceived subjectively as painful. Pain perception changed wavelet analyzed cardiac and respiration rhythms.

Precisely controlled ethically tolerable pain stimuli are useful in medical education and psychophysiology.

O5(IL)

SCHMID-SCHÖNBEIN

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Holger Schimid-Schoenbein and Roe Wells reported for the first time the key rheological behaviour of red blood cells (RBC) under flow conditions: "The fluid drop-like behaviour of erythrocytes in shear flow (Science 1969)". A droplet suspended, or more correctly emulsified in another immiscible fluid, is deformed under shear into ellipsoids. This provided evidence on the Non-Newtonian behaviour of whole blood. This new insight led to the initiation of manifold activities and scientific investigations in a new direction, generally called as rheology of blood or shorter haemorheology, with meticulous differentiation of blood plasma or whole blood viscosity. A vast number of experimental and clinical investigations deal with other related effects of erythrocyte membrane

alterations, their aggregation, the local distribution in vessels of different diameters and possible associated pathological disorders. Here, examples are introduced and reviewed, as well as more recent investigations related to artificial organs. Furthermore, results are presented, demonstrating the impact of erythrocytes distribution on "local" haemolysis generation in heart assisting devices, and the role of RBC deformation in gas exchange devices and blood gas analysers.

SESSION TA3: BLOOD TRAUMA

O6

EFFECT OF SUPRAPHYSIOLOGICAL SHEAR STRESS ON BLOOD: INSIGHTS FROM HAEMORHEOLOGY

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Background: Blood trauma is an unintended consequence of mechanical circulatory support. To date, much has been achieved in improving circuit design for the reduction of overt blood cell damage (e.g., haemolysis), although multiple clinical outcomes highlight that microcirculatory dysfunction is yet to be resolved. Accumulating evidence through haemorheological assessment indicates that shear exposure below levels that induce haemolysis (i.e., subhaemolytic shear stress) leads to sublethal changes to the erythrocyte that likely contribute to microcirculatory dysfunction. Whole blood viscosity has been shown to decrease during surgery that requires rotary blood pumps, potentially indicating excessive haemolysis. On the other hand, high shear blood viscosity has been shown to increase in the absence of haemolysis during 4 h of mechanical circulation. The micro-rheological processes that determine such changes in blood viscosity are becoming increasingly studied, and several groups have now demonstrated that cellular deformability and aggregability of erythrocytes appear altered following blood exposure to subhaemolytic shear stresses. Whether these changes in erythrocyte properties and function are transient, or permanent, is an important topic of current investigation. Moreover, how blood cells behave under physiological flow conditions (e.g., low-shear conditions) subsequent to sublethal trauma is of particular relevance to understanding potential clinically-related outcomes.

Aim: This presentation will provide an update on the current understanding of sublethal changes to erythrocytes induced by subhaemolytic shear stress. Discussion of the value of incorporating micro-rheological, subcellular, and biophysical assessments in blood trauma studies will be encouraged.

O7

DOES THE SUBHAEMOLYTIC THRESHOLD ACCURATELY PREDICT WHETHER ERYTHROCYTES ARE SUBLETHALLY DAMAGED FOLLOWING SHEAR EXPOSURE?

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Objectives: It is now understood shear stress exposure below the level required to induce haemolysis may induce sublethal damage to erythrocytes; however, accurate methods to determine the tolerance of these cells to shear has been elusive. A method of detecting the subhaemolytic threshold was recently proposed; thus we examined whether prolonged shear stress exposure: i. matched to, ii. 10 Pa above, and iii. 10 Pa below, this threshold predictably altered erythrocyte properties.

Methods: Individual subhaemolytic thresholds were calculated for 12 healthy male donors; given the dynamic relation between shear stress and exposure duration at the subhaemolytic threshold, for each individual, the shear stress equivalent to this threshold was calculated for exposure durations of 1, 4, and 16 s. Erythrocyte suspensions in a viscous suspending medium were then exposed to the three shear conditions (matched/10 Pa above/10 Pa below) for each of these durations, resulting in 9 experimental conditions for each donor. Immediately following each shear condition, erythrocyte deformability was measured via ektacytometry.

Results: The mechanical sensitivity of erythrocytes was not altered following exposure to the precise shear – duration combination that matched the subhaemolytic threshold. When erythrocytes were exposed to 10 Pa above the subhaemolytic threshold, however, impaired mechanical properties were detected, especially in the 4 and 16 s experiments. Intriguingly, mild improvements in cell mechanics could be detected when blood was exposed to 10 Pa below the subhaemolytic threshold.

Discussion: The salient finding of this study was the confirmation of the recently proposed subhaemolytic threshold model. Specifically, conditioning shears above this threshold consistently resulted in poor cell mechanics when compared with baseline.

O8

VISUALISATION OF THE ERYTHROCYTE DAMAGE PROCESS INDUCED BY SUBLETHAL SHEAR STRESS

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Objectives: Sublethal blood trauma is still reported in current generation artificial organs that were designed to minimize overt blood damage. At present, the process of mechanical stress inducing sublethal changes to erythrocytes and eventual overt damage remains poorly understood. The present study aimed to visually identify the stages of sublethal damage that precipiates hemolysis. **Methods:** Erythrocytes from healthy volunteers were suspended in polyvinylpyrrolidone solutions and inserted into a prototype shearing system. This prototype flow chamber utilizes a counter rotating mechanism of an acrylic cone and glass plate to generate a "quasi Couette flow", whereby erythrocytes in shear flow can be visualized with an inverted microscope. Erythrocyte suspensions were exposed to shear magnitudes of 10, 30, 40 and 60 Pa for 300 s, and erythrocyte behavior was recorded with an integrated CCD camera.

Results: With successful visualization of erythrocytes in shear flow, prolonged exposure to the 64 Pa condition resulted in abnormal rheological behavior. Initially, the cells deformed under high shear, after which atypical behavior was observed: cells undulated in flow, prior to fragmentation being observed in some cells. It was found that the level of shear stress and the exposure time, resulted in elevated blood damage. Novel image analysis provided evidence that subpopulations of cells lost their deformability at different rates, and that the variance within the population increased.

Conclusion: We successfully visually quantified the damage process of erythrocytes in sublethal shear flow.

O9

SPATIALLY-RESOLVED HEMOLYSIS EVALUATION WITH GHOST CELLS AS A NOVEL BLOOD SUBSTITUTE

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Objectives: Hemolysis evaluation of cardiovascular devices is currently based on *discontinuous* blood sample photometry lacking *spatial* resolution providing the overall hemolysis rate. The novel Fluorescent Hemolysis Detection Method (FHDM) allows continuous *and* spatial hemolysis detection by means of calcium-loaded ghost cells (GCs). The main restriction of FHDM is the small production scale of only 5mL per batch and day.

The aim of this study is to apply an economic method upscaling the production to an amount of GCs sufficient for cardio-vascular device testing, while maintaining the physiological rheology of blood.

Method: The previously presented GC production from porcine erythrocytes (RBCs) was improved by means of an automated process to increase the output of loaded GCs while maintaining the consistency of their properties. The cells were then suspended in a buffer solution, loaded with calcium-citrato complex and Polyvinylpyrrolidone (PVP) to achieve physiological viscosity. After restoration of membrane impermeability, GCs were suspended in artificial plasma including fluorescent calcium indicator. Once the membrane ruptures, the indicator and calcium interact, resulting in a detectable fluorescent signal.

Results: A standardized and reproducible batch production process for loaded GCs up to 502mL per day was established. There are no significant differences in the rheological behavior between RBCs and PVP-loaded GCs up to a shear rate of $1850s^{-1}$.

Discussion: The method to produce sufficient quantities of GCs allows spatially-resolved hemolysis testing of blood carrying devices particularly at hemolysis hotspots that cannot be assessed with currently existing methods. The hemolysis data provides valuable information for the development and optimization of medical devices and allows the validation of numerical hemolysis models. In order to imitate rheological characteristics of blood, it is necessary to increase intracellular viscosity during lysis with PVP. Further research will focus on hemolysis testing of commercial blood pumps.

O10

A MOCK CIRCULATION LOOP WITH A SMALL BLOOD VOLUME TO ASSESS CRITICAL REGIONS OF ROTARY BLOOD PUMPS

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Objectives: Continuous flow left ventricular assist devices (LVADs) have evolved from short time therapy into permanent or destination therapy. For long-term the high number of complications and adverse events limit the clinical use. A critical complication is the formation of thrombi inside the pump at bearings and areas with low shear rates, which lead to critical events like pump thrombosis and strokes. The objective is the development of a mock circulation loop which reduces the effort of thrombus formation experiments. By reducing the blood volume, human whole blood of a single donator can be used instead of 2-3 liters of animal blood.

Methods: A mock circulation loop was developed in which the flow in critical regions of blood pumps, such as bearings or flow straighteners, are simulated using a small

amount of fluid and only a partial flow. 10-15 mL of citrated human whole blood of a single donator with activated platelets is used, which is recalcified during the experiment to enable the thrombus growth. The flow is generated by a peristaltic pump.

Results: In the test cycle, the growth of both red and white thrombi can be investigated under controlled conditions at different flow geometries with the advantages of using human blood. Based on the results and with the help of flow simulations, geometry optimizations are carried out to prevent or reduce the risk of thrombus formation in these areas.

Conclusions: With this setup the investigation of thrombus formation in blood pumps can be investigated with less effort and can be integrated into the optimization cycle. It is possible to use human blood of a single donator for the experiments. This makes it easier to optimize the geometry concerning the risk of thrombosis.

O11

ARTIFICIAL THROMBUS: A MODEL FOR IN VITRO VAD EVALUATION

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Objectives: Continuous flow blood pumps as implantable ventricular assist devices (VAD) are meanwhile an established therapy for end stage heart failure. Complication rates reported decreased in the last era, although pump thrombosis is still a severe complication, not yet fully understood and late to diagnose. For standardized in vitro investigations of VAD behavior in case of thrombus and for qualified analysis of existent and new thrombus detection systems, we established an artificial thrombus model.

Methods: After requirement specification analysis, eight artificial thrombus materials were systematically investigated with regard to stability and durability for expected use, density, handling in dosage, drying, operation condition, and removal, as well as economic parameters. Different test methods were used including datasheet information, sheer peel test (tensile test), weighing, visual control methods as well as testing in a mock circulation loop under intended operation conditions. Experiments were repeated for statistical evaluation. An evaluation grid with scoring system was used for objective assessment of the verification values.

Results: Two out of eight potential materials (milk/chymosin, fibrin sealant) were excluded in early evaluation phase due to economic and handling reasons. All other six potential materials underwent extensive evaluation. Lacquer, acrylic compound, gelatin, and modeling clay showed insufficient performance in durability and in testing under intended operation conditions. Although cyanoacrylate showed very good performance in drying test, it underlay silicon in all other handling, operation, and economic specifications.

Conclusion: We were able to establish a silicon based artificial pump thrombus, which is easy, precise, and reliable to position on typical VAD areas. This enables researchers to systematically investigate VAD behavior (e.g. vibration and variation of pump parameters) in case of pump thrombus. Moreover, we could already use this artificial thrombus in our in vitro set up to evaluate an acoustic method for early pump thrombus detection.

SESSION TA4: NUMERICAL SIMULATIONS: VADS AND HEARTS

O12

LEFT VENTRICULAR UNLOADING DURING ECMO: ATRIAL SEPTAL DEFECT VS IMPELLA. A SIMULATION STUDY

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Objective: veno-arterial extracorporeal membrane oxygenation (VA ECMO) causes an increase of the left ventricle (LV) afterload. The realization of an Atrial Septal Defect (ASD) or the Implantation of Impella hav been proposed for LV unloading in combination with VA ECMO. The aim of this work is the haemodynamic changes in VA ECMO patients after Impella or ASD realization using a numerical model of the cardiovascular system.

Methods: A previously developed lumped parameter model of the human cardiovascular system was adopted to this specific study. Heart chambers are represented by variable elastance models, while pheripheral sections are represented by windkessel models. ASD was modelled as a resistance separating the two atrial. VA ECMO and Impella were modelled starting from their pressure-flow characteristics. The baseline condition of a patient undergoing VA ECMO implantation was reproduced starting form haemodynamic and echocardiographic data and then the effect of different size ASD or different Impella support were simulated.

Results: The Impella implantation in the VA ECMO patient caused an increment of the mean arterial pressure

(MAP) up to 67%, a decrement in mean pulmonary pressure (PAP) up to 8%, a decrement in LV end systolic volume (LVESV) up to 11% with a reduction up to 97% of the LV cardiac output (LVCO). The realization of a calibrated ASD reduces the left atrial pressure up to 19%, increases right atrial pressure up to 22%, increases the MAP up to 17%, decreases the LVESV up to 10%, increase the right ventricular volume up to 31% and decreases the LVCO up to 51%.

Conclusion: Simulations showed a higher capability of the Impella in LV unloading during VA ECMO in comparison to ASD with a concomitant lower right ventricular overload.

O13

ASSESSMENT OF VAD HYDRAULIC AND BLOOD DAMAGE PERFORMANCES BY MEANS OF DYNAMIC PRESSURE SIMULATIONS

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Objectives: The aim of this work is to investigate the hydraulic and blood damage performance of Ventricular Assist Devices (VAD) under pulsatile conditions using Computational Fluid Dynamics.

Methods: The fluid domains of CentriMag, HeartMate II (HM2) and HVAD were extracted from the CAD files, and numerical simulations were performed using ANSYS CFX. Grid independence was ensured, and the sampling frequency was chosen based on available computational resources. Dynamic pressure behaviour simulating heart failure conditions, at different pump speeds, was investigated. A total of five cardiac cycles were simulated and analysed for each condition. The calculated dynamic pressure-flow (HQ) loops were compared against static HQ conditions, and the regions of potential thrombus formation were assessed.

Results: The effect of the pulsatile condition was observed to operate around a certain range within the static HQ solution. Varying pump speed shifted the range and altered the size of the loop. Within each cycle, fluid efficiency, forces and shear stresses were calculated, and flow patterns analysed. Critical areas for thrombus formation in the HM2 were identified around the front bearing, in the blade channels and diffuser gap region; in the HVAD around the cutwater, top of blades and bottom channels. Ongoing work is focused on validating this pulsatile model and investigating HM3, HVAD, HM2 at different speeds and pulsatile conditions.

Discussion: This pulsatile model is a useful tool in predicting VAD performance, providing clinicians with a better understanding of flow rate estimation and the risk of thrombus formation, compared to the current constant pressure condition modelling. This novel approach potentially eliminates the need for mock circulatory pulsatile loops during VAD development, hence reducing costs. Furthermore, this pulsatile model could provide greater detail of blood flow behaviour, as well as quantifying accessible parameters, such as fluid efficiency, force and shear stress.

O14

GENERATING CFD BOUNDARY CONDITIONS FOR LVAD CALCULATIONS ON THE BASIS OF

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Objectives: The lack of precise and accepted boundary conditions represents one of the main reasons for the rarity of comparative and interdisciplinary studies by means of CFD and in-vitro approaches. Especially the dynamic behavior and the resulting mean values of the boundary pressure and flow in adult LVADs require a precise definition. INCOR as a CE approved device features precise measurement of flow parameters and provides unsteady and mean values of flow and pressure difference at constant rotational speed.

Methods: Time traces of the axial rotor force and the resulting flow and pressure difference of more than 600 INCOR patients were analyzed. More than 180 patients providing reasonable information were selected and investigated in more detail. Some patients had software features as PFC (Periodic Flow Change) enabled. Those data sets had to be cleaned in order to obtain comparable values. The modified patient database was eventually inspected with regards to both, the pulsatile and the mean values of pump flow, pressure difference and rotational speeds.

Results: As a result of the analysis, the mean pump flow supporting the adult LVAD patients is 4.3 l/min at a pressure difference of 61 mmHg. The dynamic change in flow due to the remaining heart contractility is 2.4 l/min corresponding to a change in pressure difference of 63 mmHg. To implement reasonable boundaries for dynamic CFD calculations representative flow and pressure curves for different patient groups were defined.

Discussion: In order to achieve comparable standards in CFD investigations of LVADs, well defined and accepted boundary conditions should be applied. In this study, the analysis of INCOR patient data led to a definition of clinically relevant boundary conditions for the numerical investigation. These data can be used to achieve a well-defined comparable standard in CFD investigation of LVADs

O15

CFD MODELING OF AORTA COARCTACTION FOR A SPECIFIC PATIENT: A PREOPERATIVE AND HEMODYNAMIC STUDY

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Objectives: Coarctation of the aorta (CoA) accounts for 6%–8% of congenital heart defects. This pathology increases afterload and reduces peripheral perfusion pressures. Particularly, pressure increases in upper extremities and head, aorta and aortic valve dilate. Otherwise, pressure decreases in lower extremities, so that perfusion to kidney decreases and it is possible to cause reversed flow in posterior intercostal arteries. The aim of this work is to develop a 3D model useful to improve the preoperative planning by means of a 3D-printed model and a Computer Fluid Dynamic (CFD) model to study the hemodynamic changes due to a surgical intervention.

Methods: A 3D patient-specific model of the aorta of a 10-year-old patient affected by CoA with three epiaortic vessels was obtained from *in vivo* CT-scan slices using a commercial software. The derived faced surface was simplified for the CFD analysis by using the reverse engineering process. A 3-D model was realized by means of a 3-D printer, and a multi-scale study, realized coupling a 3D CFD analysis and a lumped-parameters model (0D boundary conditions), was carried out by using COMSOL 5.3 (COMSOL Inc, Sweden). Ascending aorta flow waveforms were mapped to the inlet of CFD models.

Results: The printed model was used to simulate an endovascular access and a stent positioning procedure. The numerical results indicate that the flow after endovascular procedure can increase by 10% in the descending aorta, and the maximum pressure differences between inlet and outlets decrease by 9%. The results are validated by means of clinical data measured before and after the hemodynamic procedure.

Discussion: The obtained results are in agreement with literature and highlight that simulations based on CT anatomical data and adequate flow conditions can be used successfully to predict the hemodynamic changes in patients with CoA.

O16

THEORETICAL AND NUMERICAL MODEL EXPERIMENTALLY VALIDATED TO OPTIMIZE THE HYDRAULIC PERFORMANCES OF CORWAVE UNDULATING MEMBRANE BASED LVAD

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Objectives: Currently implanted Left Ventricular Assist Devices (LVAD) relay on a rotating impeller that often causes major adverse events. CorWave created the first LVAD based on oscillations of a flexible membrane. Hydraulic efficiency and hemocompatibility of this novel pump are linked to the interaction of the membrane with the motion actuator, the blood and with rest of the pump structure.

The aim of the study is to develop and validate a set of design and investigation tools and methods used to enhance the hydraulic and haemodynamic performances of CorWave LVAD.

Method: The authors used a combination of theoretical, numerical and experimental techniques to characterize the performances of the LVAD pump head. A mathematical model has been developed to predict the axis-symmetric and non-axis-symmetric 3D deformation modes of the flexible membrane in blood. Fluid structure interactions simulations using a custom defined contact model performed with COMSOL were validated with optical visualization techniques both for the flexible membrane and for the fluid motion.

Results: The membrane mathematical model guides the FSI simulations by providing modal frequencies and geometrical parameters. Visualization allows, through a fluid layer absorption method, to track the position of the membrane with a ±0.1 mm accuracy while particle flow visualization, as a Particle Imaging Velocimetry (PIV) technique, highlights areas of energy losses. These data are compared with theoretical and numerical results. With the use of this strategy we decreased by 29 % the actuation frequency to generate 5 lpm and 100 mmHg of average hydraulic output, resulting in better hemocompatibility.

Discussion: The mathematical model showed accuracy limitations in predicting the motion of the flexible membrane when compared with optical measurements. It provided though similar design guidelines at much less demanding computational power, which led to this significant improvement of hydraulic performances of the LVAD.

O17

HEARTMATE 3 HEMODYNAMICS UNDER DYNAMIC OPERATING CONDITIONS - EFFECT OF CARDIAC PULSATILITY AND ARTIFICIAL PULSE FEATURE

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Objectives: The objective of this study was to assess the consequences of dynamic changes in operating conditions, induced by the native cardiac activity or the implemented speed change sequence (artificial pulse), on the fluid dynamics of the Heartmate 3, focusing on Eulerian and Lagrangian flow features linked to hemocompatibility.

Methods: Using computational fluid dynamics (CFD), we compared the isolated effect of remaining cardiac activity and the artificial pulse sequence to a baseline case with constant speed and pressure head. CFD simulations employed high spatial (10mio elements) and temporal ($\Delta t=2°$) resolution and one-way coupling to a lumped parameter model of the cardiovascular system for physiologic pressure boundary conditions. Pump speed was adjusted to mean cardiac output of 5L/min in all investigated cases, resulting in 58 rotations per cardiac cycle and 59 for one artificial pulse. Lagrangian particle tracking and passive scalar advection were implemented to probe blood cell paths and overall pump washout. CFD results were validated against experimental measurements on a mock circulation.

Results: We observed good washout in all three investigated situations, although multiple areas of low velocities were identified. Viscous stresses were overall lower than in other clinical VADs (Heartmate 2 and HVAD). The artificial pulse severely destabilized flow, increasing turbulence and thus total stresses compared to the cardiac cycle or constant operation.

Discussion: The observed good washout appears to reflect a favorable design (e.g. large gap sizes) and fits clinical experience. Stresses were frequently higher than levels suspected to lead to von Willebrand factor damage and platelet activation. Additionally, destabilization of the flow in the artificial pulse increased stresses on blood components, which might contribute to hemocompatibility-related problems observed clinically. While the exact biological consequences of turbulence on cells are yet unclear, the increased turbulence content during dynamic operation might be of clinical relevance.

SESSION TB1: WORKING GROUP APHERESIS AND ADSORPTION: EMERGING APPLICATIONS IN APHERESIS AND EXTRACORPOREAL

O18(IL)

SELECTIVE CRP APHERESIS AS A NEW TREATMENT OPTION IN ACUTE MYOCARDIAL INFARCTION: FIRST RESULTS OF THE CAMI1 STUDY

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Background: Therapy of acute ST-Elevation Myocardial Infarction (STEMI) is based on early recanalization of the occluded coronary artery to limit myocardial damage. High serum levels of C-reactive protein (CRP), the protoype human acute phase protein, are associated with a poor prognosis in STEMI. CRP may contribute to myocardial damage in STEMI by activating the complement system. The CRP adsorber (PentraSorb®CRP) allows selective lowering of CRP serum levels in humans. We present preliminary data of the ongoing human multi-center-matched-control pilot study **C**RP-apheresis in **A**cute **M**yocardial **I**nfarction (CAMI1).

Methods: After complete coronary revascularization, 30 Patients with STEMI received CRP-apheresis, whereas 30 patients treated by standard protocols served as controls. CRP-apheresis was performed 24h and 48h after onset of symptoms. In case of a rapid increase in CRP serum levels following the second session, a third treatment was carried out 24h later. In each apheresis session, 6000 ml plasma were treated via peripheral venous access. Primary study endpoint was myocardial infarction size as determined by Cardiac Magnetic Resonance Imaging (MRI) 5±3 days and 12±2 weeks after STEMI.

Results: Apheresis sessions were well tolerated with no relevant side effects. CRP baseline levels were 25 mg/l (median) (range 12-279 mg/l). CRP apheresis resulted in an average 64% reduction in CRP plasma levels. Myocardial infarct size in the CRP apheresis-treated STEMI patients was 51% smaller ($p=0.0035$) compared to controls, and circumferential strain was 12% ($p=5x10^{-10}$) better while the longitudinal strain was 17% ($p=9x10^{-11}$) better already 5±3 days after STEMI. In the follow-up period (≤12 months), 3 major adverse cardiac events (MACE) occurred in the control group and none in the CRP-apheresis group.

Conclusion: CRP apheresis following STEMI seems feasible and safe. First results show a significant beneficial effect on myocardial infarction size and wall motion. Selective CRP-apheresis may emerge as a new therapeutic approach in the treatment of acute myocardial infarction.

O19

HLA DESENSITIZATION USING RITUXIMAB/ IMMUNOADSORPTION BEFORE KIDNEY TRANSPLANTATION

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Introduction: Many kidney-transplant (KT) candidates are sensitized against HLA-antigens, making it difficult to find a suitable HLA-compatible donor. Pretransplant HLA-desensitization strategies have shown improved patient survival after transplantation.

Purpose: This single-centre study included 14 KT candidates (of which seven had a potential living-donor) that underwent kidney transplantation after desensitization comprising two rituximab injections (375 mg/m²) with concomitant immunosuppression [tacrolimus + mycophenolic acid + steroids, and semi-specific immunoadsorption (IA) (GlobaffinÒ columns)]. IA sessions were performed until anti-HLA alloantibodies become ≤3,000 mean fluorescent intensity (MFI). At transplantation, all patients were induced with ATG. On average, recipients of a living-kidney had 12 (12-15) pretransplant IA sessions; at transplant their donor-specific alloantibodies (DSA) had MFI of ≤3,000 except for 2 with no rebound at posttransplant. Recipients of deceased donors had 15 (8-83) pretransplant IA sessions; all of them had a DSA at transplantation; however, MFI was ≤4,000 in all cases but one (anti-DPA1 at 7,000). After transplantation, there was no prophylactic IA therapy in both groups. No living-kidney recipients and one deceased-donor recipient had antibody-mediated rejections (ABMR), which was successfully treated with eculizumab. Follow-up kidney biopsies (at a median of 12 months posttransplantation) were normal except for two cases in which there were signs of subclinical ABMR. There was no significant infectious complications.

Conclusion: Semi-specific immunoadsorption was very effective at achieving HLA desensitization

O20(KL)

PAEDIATRIC DATA FROM THE WAA REGISTER - UP DATE

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Objective: The electronic registration through a web-page has been possible, at no cost, since 2002. So far 36 centres from 17 countries have entered data. An up date of results of pediatric patients including change over time will be reported.

Methods: Electronic registration of each apheresis procedure includes demographic data and treatment procedures as well as outcome data . Application and data catch is made at the www.waa-registry.org, supported by the World Apheresis Association (WAA).

Results: 36 centres from 17 countries have entered data. A total of 87147 procedures (12853 patients) have been reported up to 01/18, 2018. A total of 598 children (4.7%) represented the age 0 to 18 years and 162 with the age 19 or 20 years (1.3%) with 3519 (4.0% of all) and 1115 (1.3%) procedures, respectively. Most treatments were stem cell collection (51%), plasma exchange by centrifugation (31%) or filtration (3%), photopheresis (5%), lipid apheresis in 9 children.

The extent of work load in the units for these children was most pronounced for centrifugation (31%), photopheresis (25%), lipid apheresis (14%), and cell collection 12%). No documented child or young adult died due to apheresis. Side effects appeared during procedures in children, young adults versus adults either as mild (in 1.9, 2.3 versus 2.4%), moderate (2.3, 1.8, 3.3%) or severe (0.2, 0.2, 0.3%). The most common diagnoses treated were mainly oncological diseases (40%), haematological (24%), neurological (9%) and transplantation related reasons (8%). The distribution of the treatments over the years will be reported.

Discussion: Six percent of apheresis activities are performed on children and young adults. Although most children are treated for stem cell collection due to malignant diseases these are not the most frequent procedures.

O21(IL)

IMPACT OF C-REACTIVE PROTEIN ADSORPTION ON FREE CRP AND ON CRP-CARRYING EXTRACELLULAR VESICLES

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Background: An association of C-reactive protein (CRP) with extracellular vesicles (EVs) has been reported both *in vivo* and *in vitro*, and binding of CRP to EVs has been suggested to induce changes in the conformation of CRP and a shift towards pro-inflammatory characteristics.

Objectives: We characterized the association of CRP with EVs in plasma from sepsis patients and tested the effect of a commercial CRP adsorbent (PentraSorb) on both, free CRP and CRP associated with EVs.

Methods: Total EV counts and counts of CRP+ EVs were determined in plasma samples from 30 sepsis patients using flow cytometry. Plasma levels of free CRP were quantified by ELISA. Plasma samples were incubated with the CRP adsorbent (10 vol%) or 30 and 60 min, and CRP+ EVs as well as free CRP were quantified before and after incubation.

Results: Septic plasma samples contained 227.0±88.6 mg/L CRP *vs.* 0.7±0.4 mg/L for healthy controls. Both, total EV counts and levels of CRP+ EVs were significantly elevated in septic plasma as compared to healthy controls

(14732±14657 EVs/μL with 45.9±17.2% CRP+ EVs *vs.* 3741±2328 EVs/μL with 0.2±0.2% CRP+ EVs). Incubation of plasma with the CRP adsorbent resulted in almost complete depletion of free CRP (258.1±93.9 mg/L before *vs.* 4.4±1.7 mg/L after adsorbent treatment for 60 min) as well as in a significant reduction in CRP+ EVs (14412±4400 EVs/μL with 57.7±6.3% CRP+ EVs before *vs.* 9470±2457 EVs/μL with 5.9±7.8% CRP+ EVs after adsorbent treatment for 60 min), while free CRP and CRP+ EVs remained unaffected in the control without adsorbent.

Conclusion: Septic plasma contains significantly elevated levels of both total EVs and CRP+ EVs. As the total EV concentration remains stable, while the percentage of CRP+ EVs decreases upon incubation with the CRP adsorbent, CRP seems to be detached from the surface of EVs by adsorbent treatment.

O197(IL)

PERLIFE: PURIFICATION STRATEGIES IN ORGAN RECONDITIONING FOR TRANSPLANTATION

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Objectives: Organ ex vivo reconditioning (EVR) is a technique which is gradually being adopted in clinical transplantation to perfuse solid organs in an ex vivo circuit providing the opportunity to assess and to improve their suitability, in order to beat organ shortage and increase the number of successfully performed transplants. Specific therapies need to be applied to improve machine perfusion (MP), transforming it in organ reconditioning and regeneration to contribute reducing the impact of ischemia reperfusion injury (IRI) or the immune response on organ suitability. We tried to evaluate which molecules are responsible for IRI whether their removal by aphaeresis systems could contribute increasing organ, also the marginal ones, recover for transplantation with the main aim to develop EVR systems with dedicated aphaeresis devices applied as an immunomodulatory therapy to improve EVR results.

Methods: As lungs have the highest discard rates, we evaluated IL6, IL10, GCSF, MCP1 levels in perfusion fluid at the beginning and at the end of 18 ex vivo lung perfusions (EVLP). Increased and higher levels of cytokines levels during EVLP were correlated with negative EVLP. Those results did confirm some literature evidences, also present for other solid organs, and allowed us to identify the adsorption as the most appropriate aphaeretic approach to combine with MP in order to have an immunomodulatory effect during MP. We studied the technical features needed for the integration between absorption and MP.

Results: Starting from the analysis of the currently available MP methods and considering organs' different anatomical and functional characteristics, we developed the PerLife system for kidney or liver EVR, allowing to perform organ-tailored perfusion in different temperature modes (hypothermic, sub-normothermic, normothermic) combined with automatically managed absorption.

Discussion: MP with aphaeresis therapies could boost EVR treatments, leading to the increase of suitable organs for transplantation.

SESSION TB2: KIDNEY FAILURE: BEYOND THE CLASSICAL TREATMENT OPTIONS

O22

ADSORPTION OF HYDROPHOBIC UREMIC TOXINS BY EXTRACORPOREAL ADSORBER PARTICLES

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Objectives: Hydrophobic uremic toxins are accumulating in the blood of patients with chronic kidney disease (CKD) and contribute to the high risk of cardiovascular disease (CVD) in these patients. The removal of hydrophobic uremic toxins by current dialysis techniques is difficult due to their high binding affinity to plasma proteins. This greatly increases their molecular weight and prevents their removal through the pores of the dialysis membrane. Adsorber techniques be an appropriate alternative and may offer increased uremic toxin removal rates. We developed and investigated an extracorporeal adsorber particle with a modified surface for the adsorption of hydrophobic uremic toxins to improve the existing high-flux hemodialysis techniques.

Methods: The "Netphob" particle consists of a porous, activated charcoal core with a hydrophobic surface coating of cross-linked polyvinylpyrrolidone. The adsorption capacity of the particles was tested by incubation or perfusion with blood, serum albumin or a buffer solution containing mixtures of hydrophobic uremic toxins as found in the blood of CKD patients. Bound toxins were quantified by analytical chromatography. The hemocompatibility of the particles was assessed by quantifying the production of the thrombin-antithrombin III complex (TAT) and complement component 5a (C5a) as well as the leukocyte and thrombocyte counts.

Results: A time-dependent increase in uremic toxin adsorption was depicted and all tested toxins showed a

high binding affinity to the "Netphob" particles. The investigation of the hemocompatibility showed no significant increase either in C5a or TAT, or in thrombocyte concentration after incubating blood with the "Netphob" particles, although leucocyte counts were reduced.

Discussion: In conclusion, the "Netphob" particle shows a high adsorption capacity to all tested uremic toxins and a good hemocompatibility. Thus, the newly synthesized "Netphob" particle is an interesting candidate for further in vivo studies with the aim to improve the treatment of CKD patients.

O23

LOCAL VASCULAR REMODELING AND HEMODYNAMIC CHANGES IN PATIENT-SPECIFIC ARTERIOVENOUS FISTULAE FOR HEMODIALYSIS

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Objectives: Autogenous arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis, but it has high rate of non-maturation and early failure due to vascular stenosis. Convincing evidence supports a key role of local hemodynamics in vascular remodeling, suggesting that unsteady and disturbed flow conditions may be related with stenosis formation. The purpose of our study was to explore the feasibility of coupling contrast-free magnetic resonance imaging (MRI) and computational fluid dynamics (CFD) to relate AVF structural changes to local hemodynamic changes over time.

Methods: We acquired contrast-free fast spin echo MRI (CUBE T1) of the arm vasculature at 1 and 6 weeks after AVF creation in 2 patients. We generated 3D models using Vascular Modelling Toolkit and evaluated lumen cross-sectional area of AVF limbs. We solved transient Navier-Stokes equations using OpenFoam, with flow waveforms from Ultrasound examinations as boundary conditions at the proximal and distal artery. We then characterized the AVF blood flow phenotype using velocity streamlines and localized normalized helicity (LNH).

Results: CUBE T1 yielded high-resolution images, suitable for reliable segmentation of vessel lumen and AVF model generation. Both patients showed homogeneous dilatation in the proximal artery, while we observed a more pronounced increase in the venous outflow segment as compared to the juxta-anastomotic vein (JAV). Velocity streamlines and LNH isosurfaces suggest that flow is highly disturbed in the JAV at 1 week and evolves to an helical pattern over time, as result of vascular remodeling.

Discussion: Coupling contrast-free MRI and high-resolution CFD represents a promising approach to shed more light in mechanisms of vascular remodeling and can be used for prospective clinical investigations aimed at identifying critical hemodynamic factors that contribute to AVF failure, with the final goal of improving AVF clinical outcome and patients' life quality.

O24

TOWARDS OPTIMISED DIALYSIS REMOVAL OF PROTEIN-BOUND URAEMIC TOXINS

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Patients with renal failure retain a large variety of solutes, of which protein-bound uraemic toxins (PBUTs) are known to exert damage to the (cardio)vascular system. Their removal during haemodialysis (HD) is strongly hampered due to their binding to proteins, such that different studies already focused on interfering with this binding to improve dialyser clearances. Kinetics of PBUTs are known to be even more complex than can be explained based on their protein binding. We therefore studied potential PBUT distribution in erythrocytes and transport through the erythrocyte cell membrane.

Blood samples of 6 HD patients were analysed to check erythrocyte concentrations of four anionic PBUTs: hippuric acid (HA), indole-3-acetic acid (IAA), indoxyl sulfate (IS), and *p*-cresyl sulfate (PCS). To quantify transmembrane transport, loading and unloading tests were performed *in vitro* with blood from 8 healthy subjects and 8 HD patients, respectively. Experimental data were further used in a kinetic model to derive transport characteristics of the studied PBUTs. Erythrocyte transmembrane transport was also explored by checking the impact of an inhibitor of anion exchange by Band 3 protein.

All four studied PBUTs were detected in erythrocytes from HD patients. Erythrocyte transmembrane transport was more enhanced for HA<IS<PCS<IAA, independent of their percentage protein binding. Remarkably, an uneven partition of intra- and extracellular concentrations was found at equilibrium, with relatively higher intracellular concentrations for HA and PCS, and even more increased for IAA and IS, suggesting that these solutes might bind to intracellular and/or membrane structures. Finally, inhibiting Band 3 protein affected erythrocyte transmembrane transport of IS and PCS and, to a lesser extent, of IAA,

while no impact was found for HA, all underlining their different kinetics.

By further exploring erythrocyte transmembrane transport of PBUTs, their kinetics can be better understood, and new strategies to increase their dialysis removal can be developed.

O25

HAEMODYNAMIC IMPACT OF THE CONNECTION TO CONTINUOUS RENAL REPLACEMENT THERAPY IN CRITICALLY ILL CHILDREN

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Objectives: Continuous Renal Replacement Therapies (CRRT) are the treatment of choice for critically ill children with acute kidney injury. Hypotension after starting CRRT is frequent but very few studies have analysed its incidence and clinical impact.

Methods: A prospective, observational study was performed including critically ill children treated with CRRT between 2010 and 2014. Hemodynamic data and connection characteristics were collected before, during and 60 minutes after CRRT circuit connection. Hypotension with the connection was defined as a decrease in >20% of mean arterial pressure from baseline or when intravenous fluid resuscitation or an increase in vasopressors was required.

Results: 161 connections in 36 children (median age 18.8 months) were analyzed. 28 patients (77.8%) were in the postoperative period of cardiac surgery, 94% had mechanical ventilation and 86.1% had vasopressors. The circuit priming solution was discarded in 8.7 % of the connections, the heparinised priming solution was infused in 18 % and the circuit was re-primed in the remaining 73,3% (with albumin (79.3%), red blood cells (4,5%) or another crystalloid solution without heparin (16,2%)). Hypotension occurred in 49.7% of the connections a median of 5 minutes after the beginning of the therapy. Fluid resuscitation was required in 38.5% and the dose of vasopressors was increased in 12.4% of the connections. There was no relationship between hypotension and age or weight. Repriming the circuit with albumin reduced the incidence of hypotension from 71.4% to 44.6% (p=0.004).

Discussion: Hypotension during the connection to CRRT is common in critically ill children. Re-priming the circuit with albumin improves hemodynamics and reduces the incidence of hypotension.

O26

EFFECTS ON MESOTHELIAL CELLS FROM A DIRECT OXIDATION OF PERITONEAL DIALYSATE: DIALYSATE: ARE GDPS THE REAL CULPRITS ?

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Objectives: Glucose in peritoneal dialysis (PD) assures ultrafiltration. We treated a 1.5%-glucose spent dialysate with electro-oxidation (EO) to lower urea and improve exchange efficacy, evaluating system biocompatibility on human mesothelial cells (Met-5A) and peripheral blood mononuclear cells (PBMCs).

Methods: Biocompatibility tests were performed, according to ISO-10993, to evaluate genotoxicity, cytotoxicity and immunotoxicity. Spent dialysate was treated by a continuous flow (8hrs) through an EO device and freezed after endotoxins exclusion (< 0.015 EU/ml). Genotoxicity was assessed by a bacterial reverse mutation test (Ames MPF PENTA I). Cytotoxicity was evaluated on PBMCs and Met-5A cells, treated with 50% PD dialysate, by flow cytometric assessment of cell viability-death (Annexin V and TO-PRO-3 Iodide), oxidative stress (CellROX™), mitochondrial (MT) mass and MT membrane potential (MMP) (TMRM and MTG™-FM). Moreover, we evaluated inflammatory response (TNF-α High Sensitivity,ELISA-kit) and cell migration (Scratch wound healing assay).

Results: EO removed 145.2mmol of urea from dialysate. Ames test showed no genotoxicity. Some cytotoxicity was present on both cellular types (Met-5A and PBMCs). Compared to initial values EO dialysate resulted in only a 4% PBMCs and 1% Met-5A cell viability at 48hrs colture while intracellular oxidative stress index doubled. A depolarization of MMP and a MT mass increase demonstrated mitochondrial damage. Scratch wound healing assay showed inhibition of cell migration (-10% wound closure). EO dialysate did not induce production of TNF-α.

Discussion: EO induced efficient urea removal, but biocompatibility on PBMCs and Met-5A is questionable. Data show a cell metabolic impairment linked to EO with mitochondrial dysfunction. Previous studies on plasma did not show these results and a possible culprit of damage could be related to EO induced degradation products (GDPs) from glucose, a specific element of peritoneal dialysate. GDPs include a wide range of toxic metabolites depending on dialysate pH, temperature and composition. Future studies are needed to validate hypothesis of a direct effect of EO on GDPs production.

O27

EVALUATION OF DIFFERENT HAEMODIALYSIS STRATEGIES IN PATIENTS WITH BLEEDING DISORDERS

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In patients with known bleeding disorder, heparin-free haemodialysis (HD) with conventional dialysers is routinely used. To explore the potential benefit of using heparin-coated dialysers we used a gold standard CT-scanning technique and registered different clotting parameters to quantify coagulation in heparin coated *versus* non-coated dialysers.

Six HD patients (4 male) with thrombocytopenia were dialysed 240min in a randomised cross-over study at midweek with EVODIAL 1.3 (Baxter, USA) or FX600 Cordiax® (Fresenius MC, Germany), each without extra anticoagulation. Median blood flow was 300mL/min, and ultrafiltration according to the patient's need (325±271mL/h). Blood samples were taken from the vascular access predialysis, and from arterial and venous bloodline at 5 and 240min after dialysis start. Predialysis blood samples were analysed for haemoglobin, haematocrit, thrombocytes, fibrinogen, and activated partial thromboplastin time. On venous and arterial samples, a viscoelastic measurement of blood coagulation was performed using a Sonoclot analyser (Sienco Inc, USA) measuring e.g. activated clotting time (ACT). After dialysis, dialysers were visually scored, subsequently dried for 24h, and scanned (resolution 25µm) at the Ghent University Centre for X-ray Tomography (UGCT). After image reconstruction, the open, non-coagulated fibers were counted in a representative cross-section at the dialyser outlet (ImageJ, Fiji).

No differences were observed between predialysis laboratory values using EVODIAL *versus* FX600. Post dialysis, EVODIAL had a better visual dialyser score *versus* FX600 (2.2±1.0 *versus* 3.5±0.8;P=0.04) and had more patent fibers (96.1±3.5 *versus* 54.8±36.6%;P=0.03). From 5 to 240min, ACT values remained in the normal range but decreased more in EVODIAL (arterial 173±44 to 135±26s and venous 160±41 to 107±30s) than in FX600 (arterial 176±39 to 150±34s and venous 107±30 to 122±31s).

In conclusion, dialysis with heparin-coated EVODIAL results in far less coagulated fibers. The differences in ACT between the EVODIAL with heparin layer and the FX600 are not yet well understood.

SESSION TB3:WORKING GROUP IN TISSUE ENGINEERING

O28

VASCULAR INTERVENTIONS INDUCE ISOLATION OF ENDOTHELIAL COLONY-FORMING CELLS IN PATIENTS WITH CORONARY ARTERY DISEASE

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Objectives: Endothelial colony-forming cells (ECFCs) are promising candidates for using in regenerative medicine. Peripheral blood has a low number of ECFCs precursors, so it's difficult them isolation in culture. The authentic source of CFECs is unknown, according to theory the vascular wall source of CFECs, its mechanical damage should lead to an increase number of precursors in the blood and abilily of CFECs isolation. Vascular interventions are associated with mechanical trauma of intima.

Therefore, the aim of this study was impact of mechanical damage during surgical revascularization on the ability of CFECs isolation.

Methods: Peripheral blood was collected from six patients at three time points: before the surgery (coronary artery bypass graft surgery or coronary artery angioplasty with stenting), immediately and 24 h after surgery. Mononuclear cells (MNCs) were isolated and cultured in EGM-2MV on collagen I- or fibronectin-coated dishes. ECFCs were defined as cells having "cobblestone" morphology, CD146+CD31+ CD309+CD144+vWF+ phenotype, internalizing acetylated low-density lipoprotein (AcLDL), binding *Ulex europaeus* agglutinin1 (UEA1), forming capillary-like tubes in Matrigel. We used phase contrast, fluorescence and confocal microscopy and flow cytometry methods.

Results: Isolation of ECFCs immediately after the surgery resulted in high cell yield in three out of six patients. In contrast, only one patient out of six has shown successful isolation at other time points. At all passages, ECFCs were characterized by a "cobblestone" shape and phenotype mature endothelial cells, an ability to uptake AcLDL and to bind UEA1, and assembled into tube-like structures in Matrigel.

Discussion: Immediately after vascular interventions increased ability ECFCs isolation from patients' blood was detected. Isolated ECFCs expressed phenotype of mature endothelial cells, in keeping with the hypothesis of their perhaps origin from injured arterial segments. Further studies are needed to clarify their (re)endothelialization and neovascularization capacity

O30(KL)

EVALUATION OF A FIBRIN-AGAROSE HUMAN ARTIFICIAL SKIN MODEL GENERATED AS A MEDICINAL PRODUCT

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Objectives: In the present work, we analyzed a new fibrin-agarose bioengineered skin model in preclinical studies and as a medicinal product in patients. Evaluation is carried out not only to fulfil all regulatory requirements for manufacturing according to GMP standards but also to assess the clinical results after implantation.

Methods: A bioengineered substitute of the human skin was initially generated by using fibrin-agarose nanostructured biomaterials. Briefly, small biopsies of the human skin were obtained and epithelial and stromal cells were isolated and maintained in specific culture media. Then, fibroblasts were immersed within a hydrogel consisting of human plasma obtained from blood donors and 0.1% agarose and keratinocytes were subcultured on top. This protocol was then adapted to fulfil all regulatory requirements for ATMP manufacturing according to GMP standards (GMP-grade products). Ex vivo and in vivo preclinical evaluation were previously carried out. With the authorization of the Spanish National Regulatory Agency for Medicines and Medical Devices, the medicinal product was applied and the results evaluated.

Results: The bioengineered skin model consisted of a stratified epithelial layer and a subjacent artificial stroma with fibroblasts immersed within the fibrin-agarose biomaterial. Postimplantation studies reveal the replacement of the artificial stroma by a structured connective tissue and a keratinized epidermis.

Discussion: Clinical-grade artificial skin were structurally similar to the human native skin and showed positive expression of relevant markers when analyzed after clinical implantation. These results suggest that this skin organ model generated as a medical product is biomimetic and therefore, suitable for clinical use.

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O31(KL)

BIODEGRADABLE SCAFFOLDS FOR BONE AND CARTILAGE TISSUE ENGINEERING

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(Invited talk at the Symposium of the WG "bioartificial" organs)

Many biomaterials have been proposed to produce scaffolds aiming the regeneration of many tissues. We have a particular interest in developing systems combining natural polymers and synthetic biodegradable polymers. By proposing those systems for those demanding applications, we aim at obtaining biomaterial systems with enhanced properties namely mechanical properties, processability, cell-friendly surfaces and tunable biodegradability. Our biomaterials may be processed by melting routes (solvent-free) into devices with wide applications such as biodegradable scaffolds, films or particles and adaptable to many biomedical applications.

Electrospinning has recently gained popularity as a simple and versatile technique to produce synthetic polymeric ultrafine fibers. The fiber diameters in the nanometer range have high surface area-to-volume ratio and high porosity. These nanofiber meshes can mimic the extracellular matrix of human tissues and can be used as scaffolds for Tissue Engineering. We have been developing functionalization strategies for those meshes, enhancing their performance for a range of TERM-related applications. The properties of those meshes may also be optimized by various functional modifications further improving the biological performance of the nanofibre meshes.

Many sources of cells were considered for tissue engineering. Embryonic, iPS and adult stem cells are among the most promising to achieve the cell numbers required to have therapeutic relevance. The ethical and political constraints surrounding embryonic stem cell line derivation led most research efforts to concentrate both in iPS and in adult stem cells. We have been proposing adult stem cells from different sources for bone and cartilage tissue engineering applications.

This talk will review our latest developments using biomaterials and nanofibre meshes in the context of bone and cartilage tissue engineering applications.

SESSION TB4:SCAFFOLDS & BIOMATERIALS

O32

INFLUENCE OF FIBER COMPOSITION AND FIBER DIAMETER ON DEGRADATION KINETICS OF ELECTROSPUN VASCULAR SCAFFOLDS

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Objectives: This study aims to establish a fabrication process for resorable electrospun scaffolds with tailor-made degradation kinetics as well as a standardized concept to assess degradation kinetics.

Methods: Electrospun scaffolds were fabricated from polycaprolactone (PCL) or blends of PCL/polylactide acid (PLA; w/w 2:1) with different concentrations (100, 150, 200mg/ml). Fiber diameter was analyzed via scanning

electron microscopy (SEM). Scaffolds were immersed in bi-distilled water, modified simulated body fluid (mSBF) and 0.1M NaOH solution (pH 14) for 7 and 14 days. Degradation process was analyzed by SEM, mass los, change in pH, Raman and Fourier-transform infrared (FTIR) spectroscopy.

Results: Fiber diameters ranged from 0.9μm (PCL 100mg/ml) to 1.1μm (PCL/PLA 150mg/ml) and 2.5μm (PCL 200mg/ml). Immersion in bi-distilled water or mSBF led to no degradation after 14d. Experiments with 0.1M NaOH resulted in a mass loss of 7% (PCL200), 12% (PCL100) and 20% (PCL/PLA) after 14d. While pH values were constant for PCL, a decrease to pH 9 was measured for PCL/PLA. SEM images showed massive damages in fiber structure. Raman and FTIR spectra remained unchanged for PCL, while changes in ester bondings were detected for PCL/PLA.

Discussion: This study demonstrates the influence of fiber size on degradation of PCL, which is known to be prone to surface degradation. This was confirmed by the increase in mass loss with decreasing fiber size (increasing specific surface). Blending of PCL/PLA typically results in larger amorphous areas in the polymer structure. This, combined with the higher degradation rate of PLA, leads to an increase in mass loss and a change in molecular structure.

Ongoing experiments aim to investigate the influence of flow conditions, increase in testing period and additional fiber sizes and compositions.

O33

DEVELOPMENT OF A NON-FOULING AND BIOCOMPATIBLE SURFACE INCORPORATING ALGINATE AND RGD IN HEMA-BASED MACROPOROUS CRYOGELS FOR BIOARTIFICIAL LIVER APPLICATION

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Objectives: Non-fouling properties and high cell loading capacity are necessary requirements in designing a cell scaffold suitable to develop an extracorporeal BAL device to support patients with liver failure. Acrylate-based cryogels were previously used by our group for blood detoxification purpose. The aim of this work is to investigate whether alginate combined with RGD functionalization could enhance the non-fouling and biological properties of 2-hydroxyethyl methacrylate (HEMA)-based cryogels in terms of reduction of a-specific protein absorption, targeted liver cell adhesion and enhanced cell biocompatibility.

Methods: Alginate was incorporated in HEMA-based cryogels both by copolymerization and by post-synthesis surface modification. The incorporation was confirmed by FTIR and Z-potential analysis. RGD peptide was synthesized by solid-phase method and coupled with the hydroxyl groups of the cryogels. The synthesis of peptide and the binding to the matrix were confirmed by mass spectroscopy analysis and spectrophotometric measurements respectively. The pore size and interconnectivity of pores were analysed by SEM and confocal imaging. Texture analysis was performed to evaluate the mechanical properties and BSA adsorption studies were conducted to test the surface non-fouling properties of the cryogels. MTT assay and live-dead imaging were carried out to assess the cryogel biocompatibility and cell-loading capacity.

Results: SEM and confocal images showed an open porosity with pore size up to 150μm for all the cryogel compositions. BSA adsorption studies revealed a reduction in protein adsorption onto alginate modified cryogels comparing with the plain versions. MTT assay and live-dead imaging indicated significantly increased cell adhesion and growth for the RGD-alginate modified cryogels after 1 week.

Discussion: All the cryogel compositions investigated possess an open macroporosity and an interconnected network of pores. Alginate incorporation improved the non-fouling properties and RGD functionalization enhanced the cell-loading capacity of the cryogels, indicating suitability as cell scaffold for BAL application.

O34

HISTOLOGICAL PROCESSING OF UN-/CELLULARIZED THERMO-SENSITIVE ELECTROSPUN SCAFFOLDS

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Objectives: In this study, we present an optimized low-temperature preparation method for the histological processing of thermo-sensitive PCL/PLA scaffolds (un-/cellularized; PCL: Tg=60°C, Tm=60°C; PLA: Tg=60°C, Tm=180°C). Furthermore, we tested enzymatic antigen retrieval methods for epitope demasking, immunohistological and immunofluorescence staining, and in situ padlock probe application.

Methods: We compared optimized dehydration and low-melting paraffin embedding of electrospun PCL/PLA scaffolds (un-/cellularized) to (a) automatized dehydration and standard paraffin embedding, (b) gelatin embedding followed by automatized dehydration and standard paraffin

embedding, (c) cryofixation, and (d) LR white resin embedding method. Additionally, we investigated pepsin and proteinase K antigen retrieval for its efficiency in epitope demasking at low temperatures. Further, we evaluated protocols for immunohistochemistry and immunofluorescence for Cytokeratin 7, and *in situ* padlock probe technology for Actin Beta (ACTB).

Results: Automatized dehydration and standard paraffin embedding of un-/cellularized PCL/PLA scaffolds resulted in the dissolution of the thermo-sensitive material. Gelatin stabilization followed by standard paraffin embedding, cryofixation, as well as LR white resin embedding led to an overall shrinkage and melting of fibers of un-/cellularized PCL/PLA scaffolds. In contrast, optimized dehydration and low-melting paraffin embedding preserved the un-/cellularized PCL/PLA scaffold with fibers unchanged in diameter and structure. In addition, cells attached to the PCL/PLA scaffolds showed no alterations in size or morphology compared to the unprocessed control. Epitope demasking by enzymatical pepsin digestion and immunostaining with anti-Cytokeratin 7 revealed that attached cells migrate into the membrane and invade 50% of the PCL/PLA scaffold. Expression of ACTB and Cytokeratin 7 was shown by the combination of mRNA based in situ padlock probe technology and immunofluorescence.

Discussion: The combination of low melting paraffin embedding and pepsin digestion as an antigen retrieval method offers a successful opportunity for histological investigations of temperature sensitive specimens.

O35

IMPACT OF HETEROGENOUS MICROSTRUCTURE OF PCL/GELATIN ELECTROSPUN SCAFFOLDS ON THE INFILTRATION OF FIBROBLASTS

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Objectives: While electrospinning is a remarkably protean method to create nanofibers, it poses cell infiltration challenges in scaffolds because the pore sizes are also correspondingly small. However, it is known that cells show better 3D attachment and proliferation in a nanofiber environment. The presented work combines these paradoxical requirements into a hybrid (both in terms of microstructure and composition) poly(ε-caprolactone) (PCL)/gelatin scaffold. The aim is to assess viability, infiltration depth and metabolic activity of cells seeded on these scaffolds.

Methods: Unblended electrospun PCL and horizontally (H) electrospun PCL/gelatin blend produced homogeneous microstructures while vertically (V) electrospun spun blends produced largely heterogenous microstructures (pore sizes ~26μm vs ~114μm respectively) beyond a critical concentration of gelatin. Following this, a 7 day live/dead assay and a 15 day infiltration study with 3T3 fibroblast cells were performed on these electrospun fiber mats (150μm thick and having same overall concentration of constituent polymers of 175mg/ml). Depths were calculated using confocal LSM. MTT assay (7 days) was performed to measure metabolic activity.

Results: A statistically significantly higher viability was observed in the vertically spun blends by day 7. As expected, PCL175 and PCL125g50H showed the lowest infiltration depths of 22±7μm and 22±3μm respectively after 15 days. Vertically spun blends on the other hand showed a much higher and faster infiltration of 37±13μm in PCL100g75V after 15 days and a substantial 67±17μm in PCL125g50V. Preliminary MTT assay results show an increasing metabolic activity in the following order till day 7 - PCL175, PCL125g50H, PCL100g75V, PCL125g50V.

Discussion: It can be clearly seen that a hybrid fiber morphology has a positive effect on seeded cell growth and infiltration. Therefore, the use of such electrospun scaffolds can be advantageous when fabricating thick structures like vascular grafts.

O36

MICROFLUIDICS

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Objectives: During recent years, microgels have emerged as an effective type of drug delivery system (DDS), due to their tuneable size, increased surface area and injectability. The current study focuses on the use of microfluidic techniques for the generation of monodisperse type-I collagen (col-I) microgels crosslinked with PEG-4S, encapsulating hollow collagen spheres with glial-derived neurotrophic factor (GDNF) and bone morphogenetic protein 2 (BMP-2) for regenerative therapies in Parkinson's Disease and bone repair, respectively.

Methods: Col-I (Collagen Solutions, UK) was crosslinked with 4S-Star-PEG succinimide glutarate (Jenkem, USA). Crosslinking occurred after merging col-I with PEG-4S crosslinker in the nozzle of a double-chamber capillary within an oil flow, gelification being completed in a coiled tube. Microgel size and mechanical properties were controlled with e.g. nozzle size and pH. Microgels were characterized with TNBS assay and their cytotoxicity with LIVE-DEAD® assay. Hollow spheres were prepared by covalently attaching collagen to silica templates which are

later dissolved with hydrofluoric acid. Morphochemical characterization included: scanning electron microscopy, and Fourier-Transform Infrared. Hollow spheres were loaded with GDNF and BMP-2, seeded with different cell-types and encapsulated in the microgels within the microfluidic device.

Results: Microgels with different size and stiffness were successfully synthetized in a glass microfluidic device. The microgels are non-cytotoxic to cells and foster cell growth at different crosslinker concentrations. In the synthesis of hollow spheres, no harmful by-products appeared, and their size ranged around 200 nm.

Discussion: We demonstrate that microfluidics is an adequate technique for automatically generating monodisperse collagen microgels, and provides a simple tool for the posterior encapsulation of nanospheres and cells. The combination of microgels encapsulating hollow spheres is expected to provide a controlled and sustained delivery system of different therapeutic molecules.

O37

STRUCTURAL AND MECHANICAL PROPERTIES OF CROSSLINKED AND STERILIZED NANOCELLULOSE-BASED HYDROGELS: AN "UNCONVENTIONAL" SCAFFOLD FOR CARTILAGE TISSUE ENGINEERING

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Objectives: The "conventional" ideal environment for cartilage engineering contains pores of 75-400 μm and a porosity of 75-97%. Previous studies show that nanocellulose (NC) hydrogels – biocompatible, non-cytotoxic, abundant and sustainable biopolymer – are an excellent candidate for 3D bioprinting of cartilage, yet their structural and mechanical understanding is missing. Here, we assess the impact of crosslinker concentrations and sterilization methods on the structure and mechanics of NC hydrogels.

Methods: NC hydrogels were crosslinked using 0.1M, 0.5M or 1.0M $CaCl_2$ and sterilized by UV (UV-C, 254nm, 1h), autoclave (121°C, 20min) or ethanol (70% EtOH). Pore size was determined based on scanning electron microscopy (SEM) images. Swelling and porosity were determined as percentages, based on dry and wet weight. Mechanical properties (*i.e.* Young's modulus) were measured using Bose Electroforce® 3200. Bacterial persistence was determined based on optical density and cell viability assessed via live/dead stain.

Results: Higher $CaCl_2$ concentrations yield stiffer and significantly less porous hydrogels (~36%, 1.0M and ~46%, 0.1M). Pore size and swelling negatively correlate with $CaCl_2$ concentrations (0.23μm *vs* 0.16μm and ~1200% *vs* ~1000% for 0.1M and 1.0M, respectively). All sterilization methods decreased bacterial content ($p \leq 0.0001$) showing no significant impact on porosity (~40-50%) or cell viability. Sterilization led to higher swelling percentages, with UV-treatment showing the highest impact (~1000% increase after sterilization, $p \leq 0.001$). Ethanol significantly altered the mechanical properties, increasing the Young's modulus in about 100%.

Discussion: NC hydrogels do not fall under the "conventional" chondrogenic environment described in the literature. The findings highlight the importance of fully characterizing biomaterials as the definition of "best chondrogenic environment" might be broader than anticipated.

SESSION TC1:BIOMATERIALS AND TISSUE INTERACTION

O38

PLATELET DEPOSITION ON COLLAGEN AND OTHER SURFACE COATINGS AT SHEAR RATES OVER 5000 1/S

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Objective: Objective of this study is the deposition of platelets and growth of thrombi at high shear rates on collagen and different surface coatings. In modern ventricular assist devices (VAD) the formation of thrombi and the resulting thrombo-embolic adverse events are still a major problem. In these continuous flow blood pumps high shear rates – over 5000 1/s – cannot be avoided. The high shear rates acts on the von Willebrand factor molecule. It is stretched and connects with platelets to form a clot. This clot can block the rotor of the blood pump. Can clots be avoided with better surface coatings?

Methods: A flow chamber was designed and fabricated to generate a blood flow with high shear rates. The flow channel is a rectangular channel with a contraction – an artificial stenosis. It is made of a Titanium laser cut plate. Its shape is designed after flow simulations to create the high shear rates. One side of the flow channel is a microscope cover glass. It is either covered with collagen as reference or with the test material. The deposition of platelets is observed with a microscope. The deposited platelets were recorded and analyzed. Fresh human blood from healthy donors was used.

Results: It could be observed that platelet deposition under high shear rates varies greatly with different surface coatings. Specific deposits form for different surfaces.

Especially some novel surface coatings based on polyglycerin show significantly lower deposition rates.

Discussion: The question is how novel surface coatings affect the initial deposition of platelets on the surface and thus the formation of platelet clots. Possibly thromboembolic adverse events could be reduced by the use of such surfaces coatings in future VADs.

O39

GRAPHENE OXIDE MEDIATES BIOCOMPATIBLE AND PRO-REGENERATIVE RESPONSES IN NEURAL CELLS AND TISSUES

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Objectives: Encouraged by the extraordinary physicochemical properties that graphene-derived materials present, along with the interest that their use is gaining in biomedicine, we investigate the biological responses that neural cells and tissues show to the exposure to 2D and 3D materials composed of reduced graphene oxide (RGO) through *in vitro* and *in vivo* tests.

Methods: *In vitro* studies were carried out with embryonic neural progenitor cells (ENPCs) isolated from cerebral cortices of rat embryos at E18. Cell viability, morphology and neural differentiation were explored on 2D thin RGO films, RGO microfibers and 3D porous RGO scaffolds by scanning electron microscopy and confocal laser scanning microscopy. *In vivo* studies were performed on a rat experimental model of spinal cord injury (complete right hemisection at C6 level). Immunofluorescence, histology and transmission electron microscopy techniques were used to characterize neural tissue responses including inflammation, glial scar formation, angiogenesis, and neural regeneration.

Results: Highly viable and interconnected neural cultures are formed on all the RGO substrates investigated. Specifically, ENPC cultures contain both neurons and glial cells, and are rich in dendrites, axons and synaptic connections. When implanted in the injured spinal cord, RGO scaffolds are rapidly colonized by cells mainly positive for vimentin and PDGFRβ. Interestingly, angiogenesis, axon growth and immunomodulatory phenomena are associated with the RGO implant from early chronic stages. Finally, some insights into the biological degradation of RGO by macrophages are observed.

Discussion: Both *in vitro* and *in vivo* results indicate the capacity of RGO substrates to adequately interact with neural cells and tissues. When compared with control groups (glass coverslips for *in vitro* studies, intact and hemisected rats without RGO implant for *in vivo* ones), biocompatible responses are identified. These findings underline graphene oxide-derived materials as attractive biomaterials for applications in neural tissue engineering and regenerative medicine.

O40

THE STUDY OF NANOSCALE INTERACTIONS BETWEEN CARDIAC CELLS AND NANOFIBROUS SCAFFOLDS

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Objectives: Fibrous scaffolds are often used in regenerative medicine to create the implants designed to replace damaged soft tissue, e.g. heart or skin tissue. The main purpose of such scaffolds is to replace native extracellular matrix that plays a crucial role in the development of any tissue as it determines cells proliferation, differentiation, phenotype. One of the important characteristics of the scaffold is its topography, which guides cell growth and contributes in the nutrition of the tissue. Electrospinning technique enables to create different configurations of a fibrous scaffold and to vary some of the parameters in a wide range. The interaction between cells, e.g. cardiomyocytes, and nanofibrous polymer scaffolds may vary in different configurations. This mechanism understanding can be useful to improve growth and viability of the tissue, enhancing its functional characteristics, loading artificial ECM with other sophisticated features like controllable drug release and electrical conductance or selection of the appropriate substrate topography and configuration in general.

Methods: To study the interaction of cardiac cells with single electrospun nanofibers, we used methods of confocal microscopy, scanning probe nanotomography (SPNT) and transmission electron microscopy (TEM).

Results: We found that cardiac cells actively interact with substrate nanofibers but in different ways. While cardiomyocytes often create a remarkable "sheath" structure, enveloping fiber and, thus, substantially increasing contact zone, fibroblasts interact with nanofibers in the locations of focal adhesion clusters without wrapping the fiber.

Discussion: This finding, if replicated, has interesting implications for the design of scaffold for tissue engineering, as well as controlled release of drugs.

O41

GLUCOSE MODIFIED GOLD NANORODS INTERACTION WITH HUMAN DERMAL FIBROBLASTS

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Objectives: The aim of the study was to investigate the influence of gold nanorods on function of eukaryotic cells. The viability and proliferation of human dermal fibroblasts (HDF) cultured in the presence of gold nanorods (GNR) modified with glucose was assessed. Understanding the interaction between glucose and gold nanorods is crucial because of existence of sugar in blood plasma. It can be expected that glucose in the blood serum affects the optical properties of GNR while they undergo *in vivo* experiments.

Methods: The *gold nanorods were* synthesized and characterized by transmission electron microscopy. Modified with glucose gold nanorods or unmodified gold nanorods were maintained with HDF cells (37°C, 5% CO2) in culture medium for 7 days. Cells cultured without any additives or with the addition of glucose served as a control. During the experiment after 24, 48, 72 hours and 7 days, the cellular mitochondrial activity was assessed in MTT test. Also, cell viability was examined by flow cytometry using propidium iodide. The aggregates creation was assessed by examination of the absorbance spectrum of gold nanoparticles.

Results: MTT tests showed that the cells cultured in the presence of nanorods in a concentration of 10^{-10} mol/L have higher mitochondrial activity comparing with cells cultured with nanorods in a concentration of $0.5x10^{-10}$ mol/L. The same trend was observed for culture with presence of modified and unmodified nanorods.

Discussion: The direct relation between the concentration of nanoparticles and mitochondrial activity of the cells is not obvious, because there is not linear correlation between GNR concentration and MTT absorbance. The aggregates creation effect can not be excluded. The further evaluations are needed

O42

SURFACE CHARACTERIZATION AND CELL ADHESION BEHAVIOR ON OLIGO-PROLINE IMMOBILIZED SUBSTRATE

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Objective: A large part of the extracellular matrix (ECM) proteins is a backbone forming helical secondary structures, except for the bioactive sequences which can specifically interact with cell surface receptors. The high content of imino acids, proline and hydroxyproline, requires to form stable helical structures like collagen triple helix and elastin beta-turn. Hence, we built a hypothesis that oligo-proline might not possess any biological function. In this study, we prepared oligo-proline immobilized surface, and analyzed their surface properties and fibroblast adhesion behavior.

Method: Oligo-prolines with a Cys residue at the N-terminal (Ac-Cys-$(Pro)_n$-$CONH_2$; n=6 (P6) and 9 (P9)) were synthesized by Fmoc solid phase procedure. Secondary structure of P6 and P9 were analyzed by Circular dichroism (CD) spectroscopy. P6 and P9 were immobilized on the gold vapor-deposited cover slip through Au-SH interaction. P6- and P9-immobilized surfaces were characterized by the water contact angle measurement and X-ray photoelectron spectroscopy. Fibroblasts (NIH/3T3 cells) were seeded and cultured for 3 hours on P6- and P9-immobilized surfaces in a serum containing medium, and the adhesion behavior of fibroblasts was observed.

Results: The CD spectra of P6 and P9 indicate a typical pattern of the polyproline-II structure, a strong negative band at 206 nm and a weak positive band at 226 nm. The P6- and P9-immobilized surfaces were hydrophilic, water contact angles of P6- and P9-immobilized surfaces were 26.7º and 24.0º, respectively. In the XPS analysis, the nitrogen (N1s) derived from oligo-proline was detected on the P6- and P9-immobilized surfaces. Adhesion of fibroblasts was suppressed on the oligo proline-immobilized surfaces, especially, P9-immobilized surface.

Conclusion: We have successfully prepared oligo proline (P6 and P9) immobilized surfaces. Interestingly, the adhesion of fibroblasts was suppressed by P9 much stronger than P6 immobilization, suggesting that the stability of poly proline-II structure affect to the suppression of cell adhesion. Our finding firstly showed the possibility of the oligo proline as a bio-inert oligo peptide.

O43

FABRICATION OF HYDROGELS WITH STIFFNESS GRADIENTS FOR STUDYING CELL RESPONSE TO MECHANICAL STIMULATION

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Background: Studies have shown that anchorage dependent cells are influenced by the substrate stiffness on which they rest. Substrate thickness can be used as a technique of

varying effective stiffness. Most studies in these areas have concentrated on how cells respond to a substrate of uniform stiffness. However, the stiffness of cell microenvironment displays high variations within the body and must be also considered.

Aim: This project investigates the cell response to biocompatible hydrogels with varying local stiffness, which has been altered due to variations in thicknesses and thicknesses gradients.

Methods: Flat and wedge-shaped chitosan- gelatin hydrogels were prepared. Briefly gels were prepared by solution in acetic acid. The mixture was then crosslinked by gradual addition of PA. Flat samples were cast in petri dishes at different volumes. For gradient samples a tiled stand with gradual inclination was used. Prepared gels were sterilised by UV radiation. 24hrs prior to use gels were protein conditioned in fresh media. 3T3 fibroblasts and MG63 Osteoblast like cells were seeded onto the hydrogels. Media was changed every 48h.

Result: Cells seeded on hydrogel gradients were seen to migrate until a site suitable for proliferation was encountered after which cells entered a proliferative state and divided. Very thick zones where the stiffness is low were observed to support a low number of cells. Morphology changes as function of gel thickness were also observed. Thinner zones where the stiffness is higher showed spreader shapes which diminished as sample thickness increased.

Conclusion: The results of this study showed that substrate thickness plays an important part in mechanosensing of MG63 and 3T3 cell lines. Thin zones supported actin cytoskeleton formation and proliferation, while, thick zones induced non-developed cytoskeleton structures, suppressed proliferation and maintained a rounded morphology. The results suggest that gel thickness affects the effective modulus as sensed by the studied cell linages.

SESSION TC2:LIVER SESSION

O44

COMPUTATIONAL MODEL OF THE DRUG PARTICLE TRANSPORT DURING TRANSARTERIAL THERAPY FOR TARGETED DRUG DELIVERY TO LIVER TUMORS

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. Unresectable HCC is currently being treated with local injections of chemotherapeutics or radioactive particles during transarterial liver catheterization. The latter aims to increase local drug concentrations in the region of tumor(s), while limiting systemic toxicity. Although this technique is promising, the optimal treatment conditions (such as the injection location and dose) are still unknown. Given that the hepatic vasculature feeding the tumor plays a key role in the drug transport, this study explored the added value of computational models to optimize targeted drug delivery for HCC.

A 3D hepatic arterial geometry was obtained based on micro-CT data of a human liver, and meshed resulting in 8.9 million volume elements. Computational fluid dynamics calculations simulated the blood flow (continuous shear-thinning fluid phase) as well as the drug transport (discrete phase) in the liver. Boundary conditions included a velocity inlet of 0.155 m/s at the hepatic artery, an outlet flow distribution (Murray's law) and a uniform surface injection of 10^4 particles. The impact of relevant parameters on the particle distribution was analyzed using a sensitivity study.

Results showed that the particle distribution depends largely on the cross-sectional injection location: a good choice of this parameter may allow targeting specific outlets or tumors. Other parameters with a significant impact on the particle distribution are the injection plane (proximal/distal catheter position), the particle density (1600-3600 kg/m^3), and the particle diameter (40-100 μm), leading to changes in the outlet-specific number of exiting particles up to ± 64%, 61%, and 79%, respectively.This feasibility study indicates the potential of patient-specific computational models to optimize targeted drug delivery for liver cancer. Future work will focus on validating and testing the model retrospectively in a patient cohort that underwent transarterial therapy.

O45

ALBUMIN DIALYSIS IN THE MANAGEMENT OF ACUTE ON CHRONIC LIVER FAILURE: A META-ANALYSIS OF POOLED INDIVIDUAL-PATIENT DATA

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Acute-on-chronic liver failure (ACLF) is a common complication of cirrhosis characterized by single or multiple organ failures and high short-term mortality. Treatment of ACLF consists in standard medical care (SMC), and

organ(s) support. Whether the efficacy of artificial liver support depends on the severity of ACLF and the intensity of this treatment is unclear. The study aimed to further assess these issues.

Methods: We performed an individual-patient-data meta-analysis (MA) assessing the efficacy of Molecular Adsorbent Recirculating System (MARS) in ACLF-patients enrolled in prior RCTs. The MA was designed to assess the effect of patient severity (ACLF-grade) and treatment intensity [low-intensity therapy (LIT): SMC alone or SMC plus ≤4 MARS sessions; high intensity therapy (HIT): SMC plus >4 MARS sessions] on mortality. Severity of ACLF-patients was assessed by an external validation of 303 ACLF patients enrolled in the CANONIC study.

Results: Through systematic literature review we identified three RCTs suitable for the MA (overall patients:285, ACLF-patients:165). ACLF-patients in the MA were significantly more severe than in the CANONIC study. As compared with SMC, SMC plus MARS (irrespective of number of sessions) did not improve survival, neither in the overall patients nor in ACLF-patients. However, when patients were analyzed according to treatment intensity, survival was significantly higher among patients receiving HIT, in the entire cohort (10-day survival: 98.6% vs. 82.8%, p=0.001; 30-day survival: 73.9% vs. 64.3%, p=0.032); and the ACLF-patients (10-day survival: 97.8% vs. 78.6%, p=0.001; 30-day survival: 73.3% vs. 58.5%, p=0.041). HIT appeared to increase survival independently of ACLF-grade. Independent predictors of survival were age, MELD, ACLF-grade, number of MARS sessions delivered and intensity of MARS therapy.

Conclusion: Adequately delivered albumin dialysis may have a potential beneficial effect in patients with ACLF. The appropriate dosage should be evaluated in future clinical trials.

O46

EFFECTIVENESS OF NEW CELL SOURCES FOR THE TREATMENT OF ACUTE LIVER FAILURE

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Background and aims: Acute liver failure is a rare but life-threatening disease that is mainly cause by viral infection and drug-induced liver injury. Although liver transplantation is the preferred treatment for these patients, it is limited by organ shortage. Cell-based therapy is envisaged as a useful therapeutic option to recover and stabilize the lost metabolic function despite the fact that clinical demand for hepatocytes cannot be met given the scarcity of current sources of liver tissue for cell isolation. This shortage of hepatocytes might be resolved with the use of neonatal livers to isolate hepatocytes and with the emergence of pluripotent stem cells which could provide an unlimited source of hepatocyte-like cells. The objective was to evaluate the effect of both cell types on the treatment acute liver injury.

Methods: We studied the efficacy of cells isolated from newborn organs and hepatocyte-like cells derived from embryonic stem cells in mice with acetaminophen-induced acute liver failure and evaluated the ability of these cells to engraft and proliferate.

Results: When transplanted into mice with acetaminophen-induced liver failure both cells types efficiently engrafted and proliferated and produced a reduction of transaminases levels, rescuing hepatic function.

Discussion: These results provide a proof of concept that replacement therapies using newborn cells or hepatocyte-like cells are effective for treating acute liver failure. Moreover, the improvement of the engraftment processes will be of clinical significance, i.e., for repeated cell transplants or for liver repopulation.

O47

ROLE OF HEMOFILTRATION TECHNIQUE IN THE PERFUSION OF EX VIVO ISOLATED LIVER

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Objectives: Hemofiltration techniques have been widely used in clinical practice for decades. With the development of extracorporeal circulation and ex vivo organ perfusion techniques, hemofiltration seems to be a promising tool in order to reduce toxic substances, thus influencing the preservation of organs and cell homeostasis.

The aim of the present study is to assess the role of hemofiltration in isolated pig liver perfusion.

Methods: Porcine livers (n = 8) were perfused during 18 hours with a perfusion machine developed in our laboratory, including hemoconcentrator BC 20 plus. An informatic program allowed a continuous register of hemodynamical parameters (pressures and flows) while biochemical parameters, related to perfusate quality, were obtained from perfusate and ultrafiltration samples at hours 0, 1, 3, 6, 12 and 18.

To evaluate the influence of hemofiltration on hepatic preservation, we studied the correlation between molecules known to be involved in cell homeostasis, and the hemofiltration rate. For statistical analysis, Spearman correlation was performed, considering $P<0.05$ as significant.

Results: Analysis results showed a statistical and positive correlation between extracted volume and potassium levels in perfusate, whereas a negative correlation was found with perfusate levels of sodium, calcium and glucose. On the other hand, no significant correlation was found between hemofiltration rate and lactate, urea, free hemoglobin and perfusate osmolality.

Discussion: Hemofiltration applied on ex vivo liver perfusion allows to control ion levels without any effect on larger molecules. In addition, its implementation does not increase hemolisis nor alter osmolality parameters. Further experimental studies should be made to clarify the influence of the studied parameters on organ preservation.

O48

HEPATIC CELL MICROENCAPSULATION FOR BIOARTIFICIAL LIVER: METABOLIC ACTIVITY IN STATIC CULTURE VERSUS PERFUSED CULTURE IN FLUIDIZED BED BIOREACTOR

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Objectives: Bioartificial livers are still one of the most promising approaches to assist patients with severe liver failure on waiting lists. Cell microencapsulation is an interesting alternative to standard cell immobilization. Furthermore, the perfusion of cells in a fluidized-bed bioreactor seems to boost the cell activity. However, to date, the biomass has been a major pitfall, since primary cells are not easily available, and cell lines such as C3A are limited in their functions. Therefore, we propose to assess the potential of HepaRG cells as biological compound in the alginate microbeads.

Methods: HepaRG cells (BioPredic International) were encapsulated in alginate microbeads at different densities. Both static culture (continuous orbital shaking) and dynamic culture (perfusion in fluidized bed bioreactor) were performed. Viability was assessed by fluorescent staining. Immunofluorescent staining was performed to assess cell differentiation over 14 days. Different cell activities (albumin, urea synthesis, ammonia detoxification, glucose release) were assessed by classical analytical means.

Results: The production of cell-containing alginate microbeads of diameter 800-1000 μm was successfully achieved, and high cell viability was observed. HepaRG continued to proliferate, differentiate and rearrange within the microbeads, forming spheroid-like structures of diameter 30-70 μm. Immunofluorescent staining (albumin, HNF4α, CYP3A4) and metabolic activity (e.g. albumin secretion around $0.7\mu g/h/10^6$, ammonia detoxification activity around $0.9\mu mol/h/10^6$) demonstrated that cells are differentiated at day 14 and suitable for bioartificial liver applications.

Conclusion: Here, we demonstrated the ability of HepaRG cells to display substantial liver functions. Cell encapsulation provides cells with a 3D microenvironment allowing the formation of spheroids, and protects them from the shear stress and the patient's immune system. The new active biomass could be thus implemented in the human size system previously developed in our laboratory.This work was funded by PIA RHU ILite (ANR-16-RHUS-0005).

O49

CRITICAL EVALUATION OF FACTORS AFFECTING MARS (MOLECULAR ADSORBENT RECIRCULATING SYSTEM) EFFICIENCY IN THE TREATMENT OF ACUTE-ON-CHRONIC LIVER FAILURE

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Objectives: The employment of liver supports in liver failure often gives conflicting results, mainly due to the lack of uniformity of patient populations (degree of liver failure, primary liver diseases) and treatment modalities. However, little attention is often paid to other factors affecting treatment efficacy. Aim of our work has been to review published data on the most employed method, i.e. MARS (Molecular Adsorbent Recurculating System) and to compare them with results obtained in our patients.

Methods: We treated with MARS 119 patients affected by acute on chronic liver failure (ACLF) secondary to different primary liver diseases. We revised the literature focusing on factors potentially affecting MARS efficacy in the removal of liver catabolites and restoring of acid-base balance: session duration and frequency, blood and albumin flows, pressure in both blood and albumin compartment, anticoagulant treatments, tolerability, treatment end points.

Results: MARS is well tolerated and improves blood pressure during treatment. Session duration and frequency are variable: high flows in daily treatments and low ones in continuous treatment like renal replacement therapy, for the acid-base balance and eventual body weight loss. Albumin flow is set similar to the blood one. Few careful data was found, about the different pressure between blood and albumin compartment. Anticoagulation is similar to hemodialysis. In our patients, the adoption of a protocol defining exact treatment

details allowed to obtain consistently positive results. The efficiency in the removal of hepatic catabolites has been increased by modifying the extracorporeal circuit by introducing two adsorption unit in parallel.

Discussion: according to our observations, MARS is usually employed without considering technical details (e.g. albumin and blood pressure difference) which are crucial for the treatment efficacy. Their revision can allow a better knowledge of liver support and the achievement of more efficient methods.

SESSION TC4:SYMPOSIUM: WHOLE-ORGAN BIOENGINEERING: FROM THE DRAWING BOARD TO PATIENTS

O50(IL)

KIDNEY BIOENGINEERING: CAN WE SUFFICIENTLY REPLACE ITS FUNCTION?

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In patients with chronic kidney disease (CKD) adequate renal clearance is compromised, resulting in the accumulation of a plethora of uremic solutes. These uremic retention solutes, also named uremic toxins, are a heterogeneous group of organic compounds with intrinsic biological activities, of which many are too large to be filtered and/or are protein-bound. Their renal secretion depends largely on active tubular secretion, which shifts the binding and allows for active secretion of the free fraction. To facilitate this process, renal proximal tubule cells are equipped with a range of transporters that cooperate in basolateral uptake and luminal excretion. In recent years, we and others have invested in the development of bioengineered kidneys that could potentially restore this essential function. For this, well characterized renal cells were combined with functionalized membranes.

This presentation addresses these developments in the context of renal tubular clearance mechanisms for uremic toxins. Furthermore, hurdles to take before a safe implementation of bioengineered kidneys in clinics becomes a realistic option will be discussed.

O51(IL)

BIOENGINEERING HUMAN LIVERS FOR TRANSPLANTATION: WHERE ARE WE NOW?

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Objective: Liver disease affects more than 650 million people worldwide and accounts for 4% of all deaths. It is particularly costly in terms of human suffering, healthcare resources and premature loss of productivity. To date, the only definitive treatment available is liver transplantation, which substantially improves survival and the quality of life of these patients. However, a lack of donor livers subsists, mainly due to expanding indications and the increase of patients on waiting lists. Current bioartificial organs still present significant limitations and are not a definitive alternative to transplantation yet. Furthermore, whole liver bioengineering is still years away of presenting itself as a tangible alternative to organ donation. It is then necessary to transversally develop novel methods and technologies that will further accelerate the development and translation into clinical application of bioengineered whole-livers.

Methods: Therefore, vital enabling technologies that are not always necessarily present in the whole-organ bioengineering field (advanced perfusion bioreactors, large-scale cell expansion, blood surrogate development, organ maintenance ex-vivo, etc), but are already quite advanced in other fields, need to be quickly integrated and adapted to this goal to further advance our progress towards bioengineered organs.

Results: This integration, associated with promising preliminary results of bioengineered human liver constructs with typical hepatic phenotypic markers and bile ducts, and vital liver functions (such as drug metabolism, protein synthesis/secretion and catabolism), demonstrate the feasibility of generating bioengineered human liver organoids using acellular organ scaffolds and primary human cells. Furthermore, the bioengineered liver tissue is now being useful in several different applications like cord blood derived hematopoietic stem cell expansion and differentiation, drug metabolism, stem cell biology and mechanobiology studies.

Discussion: Hence, this technology has the potential to shape novel developments in other scientific fields and ultimately, change transplantation medicine and the treatment of end-stage organ diseases.

O194(KL)

REGENERATION AND REPAIR: MOVING TOWARDS PATIENTS

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Congenital or acquired surgical conditions are associated to high morbidity and mortality and most of the time functional replacement of the missing or damaged organ remains an unmet clinical need. Tissue engineering led by advances in two specific fields, cell biology and material science, have combined to create the perfect biological substitution.

Our team has focused on deriving matrices from organs and tissues through decellularization. Using detergents and enzymatic solutions it is possible to derive natural scaffolds, which are not immunogenic but still maintain many of the characteristic of the tissue of origin. In 2010, using this process we were able to engineer a trachea, which was successful transplanted in a child. Following the clinical success we have focused on various other organs and preliminary data on bladder, kidney, oesophagus, intestine, lung, liver, pancreas and skeletal tissues have been obtained using similar methodologies. Decellularised matrices and cellular product could be combined in vitro and bioreactors could be used to plan in vivo translation.

Moreover, there is the opportunity to treat congenital malformation during the gestation or in the neonatal period. In particular, it has become evident that is possible to collect the stem cells at diagnosis, even before birth. Human amniotic fluid stem cells (AFSC) can be isolated during fetal development, and have have shown to be effective in various animal models of disease, and could represent an innovative tool for therapeutic application in the future of congenital malformation.

SESSION TD1:SOLID ORGAN ENGINEERING

O52

BIOENGINEERED HUMAN FETAL LIVERS: A NEW TOOL FOR THE PRODUCTION OF HEMATOPOIETIC PROGENITOR CELLS

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Background: Despite the progresses made in the *ex-vivo* expansion of cord blood-derived hematopoietic stem/progenitor cells (CB-HSPC), challenges remain regarding our capacity and ability to generate an appropriate number of cells capable of treating an adolescent or adult patient from a single unit of CB. During embryonic development, the liver is the principal organ of HSPC expansion and erythropoiesis.

Objective: We analyzed and studied whether suitable expansion of HSPC could be achieved *in vitro* under physiologic conditions provided by surrogate fetal liver microenvironments.

Methods: We generated three-dimensional (3D) bioengineered liver constructs made of matrigel where human hepatoblasts, hepatic stroma cells, and endothelial cells were seeded together. Once the organoid was formed, we added CB-HSCP with different media formulations for 7 days. Next, to characterize these organoids, we produced human embryonic stem cell-derived hepatoblasts (hES-HB) and co-cultured them for 7 days with CB-HSPC in static and dynamic environments.

Results: The largest expansion of HSPC in the 3D bioengineered liver constructs formed by human hepatoblasts, hepatic stroma cells, and endothelial cells was observed with a mixture of hematopoietic stem cell and endothelial media. On the other hand, the co-culture of hES-HB and CB-HSPC showed, in static conditions, a maintenance of the number of burst-forming unit-erythroid (BFU-E). However, in dynamic conditions with continuous flow of culture medium, a significant large expansion of BFU-E was detected, indicating a recreation of the hepatic microenvironment and its role in erythropoiesis during fetal development.

Discussion: Hence, bioengineered human fetal livers represent an innovate tool for the production of hematopoietic progenitor cells *in vitro*, which could have a great impact in the treatment of hematological diseases and in the study of their intrinsic biology.

O53

REVASCULARIZATION OF LIVER SCAFFOLDS USING VASCULAR INDUCTION AND MATURATION CYCLES

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Liver transplantation is the only effective treatment to extend the life of patients with terminal hepatic diseases. Organ bioengineering and regenerative medicine are promising new technologies that can help increase the number of available organs for transplantation. However, up to date, all the bioengineered livers lack a functional and patent vascular network which could enable their long-term transplantation into a living animal. Hence, in this study, we sought to recreate a functional re-endothelialized vascular tree *in vitro* in a decellularized liver scaffold.

To achieve this, we recellularized an acellular rat liver scaffold with human umbilical vein endothelial cells (hUVECS) and human mesenchymal stem cells (hMSCs) in a bioreactor perfusion system. Cells were perfused at several discrete pressure conditions, showing excellent scaffold distribution. Furthermore, we applied two sequential experimental conditions that enabled the induction of cell growth and vascular maturation.

Two weeks after seeding, we were able to observe a branched and large vascular network with the presence of vascular structures with different diameters, showing the formation of large, intermediate and small vessels. These structures were completely lined by endothelial cells, which were surrounded by hMSCs, as observable in native vessels. This reconstituted vascular tree was able to secrete prostacyclin, and capture Dil-Ac-LDL and FITC-conjugated Ulex europaeus lectin. It was also able to sustain heparinized blood flow for 30 minutes with minimal platelet adhesion and aggregation.

These results unveil a novel strategy to target organ scaffold revascularization yielding the generation of functional vessels with the potential to withstand blood perfusion *in vivo*.

O54

INVESTIGATION OF DECELLULARIZED LIVER TISSUE STRUCTURE BY NOVEL METHOD SCANNING PROBE NANOTOMOGRAPHY

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Objectives: Decellularization of organs and tissues is one of the perspective technique in tissue engineering and regenerative medicine. One of the main challenge in this field is evaluation of decellularization protocol success and quality of obtained extracellular matrix. The aim of work is to confirm success of decellularization protocol and to investigate three-dimensional structure of decellularized rat liver tissue by scanning probe nanotomography

Methods: Wistar rats were used as donor liver. Decellularization of liver tissue was performed by sequential incubation with three solutions of 0,1% SDS containing Triton X-100 in the following concentrations: 1%, 2% и 3%. The vascular network was visualized by perfusion of 0.5% dextran blue. H&E staining and optical microscopy were used. Extracellular matrix's and native tissue's DNA were extract by ethanol precipitation and DNA content was estimated by measuring the absorbance at 260 nm. Nanostructure of extracellular matrix was investigated by scanning probe nanotomography (SPM). 3Dreconstruction and visualization of the sample structure was carried out by integration of series of layer-by-layer SPM images with Image Pro AMS 6.0 software package

Results: The decellularized liver tissue was obtained, the vascular network was preserved. H&E staining of histological sections and SPM analysis confirmed the removal of cells. DNA content of extracellular matrix was equal to 0.7% of native tissue DNA content. Sinuous and rough topography of obtained matrix was shown. Highly nanoporous structure was revealed by 3Dreconstruction, with volume porosity value of 78.4% and surface-area to-volume ratio of 5.81 μm^{-1}. We detect micropores with dimensions ranging from 2.5 to 20 μm, and interconnected nanopores in decellularized matrix with dimensions ranging from 50 to 400 nm

Discussion: Offering method SPM is promising technique for research of matrix micro- and nanostructure, which is indispensable for modern development of tissue engineering

O55

TOWARDS A BIOHYBRID LUNG – LONG-TERM DYNAMIC CULTIVATION OF ENDOTHELIAL CELLS ON RGD-COATED PDMS MEMBRANES AND ITS GAS EXCHANGE PERFORMANCE IN BLOOD

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Objectives: Extracorporeal membrane oxygenation can ensure adequate gas exchange in patients with pulmonary dysfunction but its application is limited by poor hemocompatibility. Thus, we pursue a biohybrid approach with endothelial cells (ECs) seeded on gas permeable membranes to form a nonthrombogenic and antiinflammatory surface. To optimize gas exchange performance while maintaining an integral cell layer, we evaluated the long-term stability of cell-seeded gas permeable membranes as well as the impact of extended cultivation periods on gas exchange performance in blood.

Methods: Human umbilical vein endothelial cells were cultivated on RGD-coated Polydimethylsiloxane (PDMS+RGD) membranes. Dynamic cultivation was performed in a biohybrid lung model system under physiological wall shear stresses for up to 33 days. Subsequent to cultivation periods of three, 19, and 33 days, gas exchange performance of the membranes was tested. For this, pig blood was adjusted to venous values in accordance with ISO 7199. During testing, the system was flushed with oxygen on counter flow principle. Gas transfer rates were determined by blood gas analysis. EC morphology was accessed by immunocytochemistry.

Results: PDMS+RGD proved suitable for long-term dynamic cultivation of ECs for up to four weeks. The gas transfer tests

proved oxygenation of the blood via bare and cell-seeded membranes, with the performance of the bare membrane exceeding that of the latter membranes at all times because of the additional diffusion barrier. Furthermore, a performance decrease with increasing cultivation period for cell-seeded membranes was observable.

Discussion: This study has shown the long-term stability of an EC layer on PDMS membranes and its gas exchange performance in blood. Although the performance decrease with time needs to be further examined, the results demonstrate the feasibility of a biohybrid lung. Prospectively, limitations of in vitro trials will necessitate validation in an animal model.

O56

PORTAL-CAVA- JUGULAR VENOVENOUS BYPASS: EXTRACORPOREAL CIRCULATION MODEL DURING ORTHOTOPIC LIVER PIG TRANSPLANTATION

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Objetives: The unique characteristics of experimental liver pig transplantation model force to clamp Portal and Cava veins. This has deleterious consequences on hemodynamic parameters, such as splanchnic venous congestion and a decrease up to 50% of cardiac output, reducing the anhepatic phase to 25 minutes, with a significant increase in mortality. In order to increase operative time and achieve the hemodynamic stability during this phase, an extracorporeal portal-cava-jugular venovenous bypass, has been optimized.

Methods: Three orthotopic liver transplants were performed in anesthetized minipigs using this circuit. Continuous perioperative hemodynamic parameters were recorded through an invasive transpulmonary thermodilution monitoring system (PICCO2), which allows the continuous monitoring of CI, HR, MAP, DAP, SAP, ISVR and temperature. The circuit, developed in our laboratory, is composed of two afferent pathways (portal vein and cava vein) that converge in a centrifugal pump. From here, an efferent pathway leads the blood to a thermostatic circuit where it is re-warmed, returning to the jugular vein through a venous cannula. Hemodynamic data of the circuit was collected through a flow transducer, positioned on the efferent pathway, and pressure transducers, on the entry and exit line of the pump, with a sampling rate of 40 Hz. In addition, arterial blood gases were measured before implanting the bypass and hourly to control indicators of tissular hypoperfusion such as lactate and pH.

Results: Flows during the first minutes of entry to the bypass fluctuate around 0.5 L/min; while, once the full bypass is installed, the flow rate reaches up to 1 L/min. Cardiac index and MAP remained stable during the next two hours of bypass and markers of tissue hypoperfusion persisted in range.

Discussion: Venovenous bypass extends hemodynamic stability time at least 2 hours, in anhepatic phase during orthotopic hepatic transplant in pig model.

O57

RECENT PROGRESS IN STEM CELL-BASED METHODOLOGIES AND TISSUE ENGINEERING APPROACHES HAVE LED TO THE DEFINITION OF NOVEL REGENERATIVE MEDICINE STRATEGIES FOR THE TREATMENT OF KIDNEY DISEASE

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Objectives: to facilitate basic knowledge on kidney engineering providing novel approaches facilitating renal maturation and function

Methods: i) by mimicking embryonic steps sustaining renal development and differentiation we have generated kidney organoids from human pluripotent stem cells (hPSCs); ii) by decellularization/recellularization we have developed biomimetic inks for bioprinting 3D kidney structures; iii) by using a novel transplantation method we have further maturated and vascularized kidney organoids

Results/Discussion: we have generated novel methods for hPSCs differentiation into different renal cell types through organoid technology combined with the approaches described above. Our results provide innovative solutions when translating these technologies into the clinical setting.

SESSION TD2: SOFT TISSUE AND SENSORY ORGANS ENGINEERING

O58

A HISTOLOGICAL QUALITY CONTROL OF HUMAN ARTIFICIAL CORNEAS GENERATED AS A MEDICINAL PRODUCT

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Objectives: A bioengineered substitute of the human cornea was previously developed by the research group, and a clinical trial to determine biosafety and efficacy of this artificial cornea model is currently ongoing. Validation of this artificial organ should be carried out at the histological level to determine if artificial corneas are biomimetic of the native cornea. In the present work, we analyzed clinical-grade artificial corneas and compared them with the human control cornea.

Methods: Human corneas were generated for clinical use in a GMP facility using human cornea keratocytes and epithelial cell cultures obtained from donor sclero-corneal limbi and nanostructured fibrin-agarose biomaterials. Bioartificial corneas were fixed in formalin and analyzed histologically by using hematoxylin-eosin staining and immunohistochemically using anti-human pancytokeratin antibodies.

Results: The artificial cornea consisted of a stratified epithelial layer and a subjacent bioengineered stroma with keratocytes immersed within the fibrin-agarose biomaterial. Pancytokeratin expression was similar in native and artificial cornea epithelium.

Discussion: Clinical-grade artificial corneas were structurally similar to the human native cornea and showed positive expression of relevant proteins. These results suggest that these organs generated as a medical product are biomimetic and therefore, suitable for clinical use.

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O59

FIBRIN AGAROSE HYDROGEL: A VERSATIL NATURAL BIOMATERIAL IN PERIPHERAL NERVE REPAIR

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Objectives: Critical peripheral nerves defects are frequent with direct consequences on the quality of life of thousands of patients worldwide. The current best treatment alternatives of these injuries are nerve autograft and allografts, but they have several well-known disadvantages and are only efficient in the 50% of the cases. Thus, alternative treatments are still needed. The aim of this study was to design fibrin-agarose (FA) and nanostructured FA (NFA) bio-artificial substitutes containing adipose-derived mesenchymal stem cells (ADMSC) for peripheral nerve repair.

Methods: For this study 20 adult male Wistar rats were used and under general anesthesia 10-mm of the sciatic nerve was removed and bridged by using collagen conduits (CC), CC filled with FA containing ADMSC (FA-MSC), NFA containing ADMSC (NFA-MSC) and autograft (A-CTR). Animals were kept in the experimental unit until 12 weeks. Regeneration profile was determined by clinical, functional, electromyography (EMG) and histological analyses.

Results: Clinically, animals from all experimental groups showed different % of neurotrophic ulcers, but values were higher in CC followed by NFA-MSC, A-CTR and finally FA-MSC. Toe spread motor function test showed better recovery in FA-MSC (score 2) followed by NFA-MSC, A-CTR and CC (score 0). EMG revealed better muscle reinnervation in A-CTR followed by NFA-MSC, FA-MSC and CC groups. Histology confirmed peripheral nerve regeneration in all groups, especially A-CTR and FA-MSC groups.

Discussion: This study demonstrated that FA-based strategies were nearly comparable to the autograft technique. However, it is still necessary to improve these strategies in order to be a potential alternative to the nerve autograft technique.

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O60

HISTOLOGICAL ANALYSIS OF SCLERAL REPAIR AND REGENERATION BY USING

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Objectives: Scleral defects can result as consequence of traumatic injuries, infectious diseases and cancer removal. These structural defects are often repaired by using allogenic cadaveric scleral grafts. However, this method has a high risk of rejection, transmission of infectious agents and it is not always available. In this sense, the aim of this study was to evaluate the usefulness of nanostructured fibrin-agarose hydrogels (NFAH) and decellularized collagen membranes (DCM) as alternatives to repair scleral

defects in rabbits. Furthermore, the regeneration process was evaluated by using histological and histochemical techniques.

Methods: In this study, scleral defects of 5-mm diameter were made on 9 adult male New Zealand rabbits. Defects were repaired by using acellular NFAH, DCM (Zimmer Biomet Dental) and allogenic cadaveric scleral grafts (SC-CTR) as control. Animals were kept under controlled environment during 40 days until histology. For histological studies, eyes were fixed and embedded in paraffin. Sections were stained with hematoxylin-eosin, Alcian blue, Masson staining and picrosirius.

Results: Macroscopic and histology revealed that NFAH and DCM were comparable to SC-CTR repairing the scleral defects. NFAH were degraded by macrophages and replaced by a loose connective tissue composed by collagen fibers and proteoglycans. DCM histology confirmed the presence of the membrane which was disorganized and infiltrated by mononuclear cells. SC-CTR showed no degradation of the allograft which appeared edematized and disorganized increasing the thickness of the eye wall.

Discussion: This in vivo study demonstrated engineered NFAH tissue-like membranes are biocompatible, non-permanent, pro-regenerative and structurally efficient alternative to the use of allogenic cadaveric grafts and DCM to repair scleral defects in rabbits. However, large defects and long term studies are needed to demonstrate the potential clinical usefulness of these substitutes.

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O61

CHEMICALLY DECELLULARIZED PERIPHERAL NERVE ALLOGRAFTS SUPPORT PERIPHERAL NERVE REGENERATION AND FUNCTIONAL RECOVERY IN RATS

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Objetives: Peripheral nerve gaps are clinically repaired by microsurgery of an autologous graft, known as gold-standard method. Nevertheless, there are several drawbacks associated to this technique and novel therapeutic alternatives are in need. In this regard, the aim of this study was to compare the regeneration profile of three different chemically decellularized peripheral nerve allografts in a 10-mm nerve gap in rats. Nerve regeneration profile was determined clinically, functionally and histologically.

Methods: In this study 24 Wistar rats were anaesthetized and 10-mm sciatic nerve defect was created and repaired by using three different decellularized nerve allografts (Sondell, Hudson and Roosens methods) and autograft as positive control (n=6 each). After 12 weeks rats were subjected to Pinch test, Vonfrey, Hargreveas, muscle morphometry and histology.

Results: Clinical analysis of sensory and motor functions showed little differences between the three groups and between the gold standard method autograft showing no significant differences. However, both Vonfrey and Hargreveas test results showed a better recovery in Roosens group. Muscle atrophy was detected in all groups however, autograft group showed the lowest loss muscle percentage. Histology confirmed axonal regeneration in all experimental conditions and control.

Discussion: This study demonstrates the regenerative potential of these three decellularized nerve allografts in rats. These engineered strategies were almost comparable than to the current gold standard technique, the nerve autograft. However, further studies are needed to improve the regenerative potential of these substitutes as well as their potential clinical translation.

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O63

EXTRACELLULAR MATRIX CHARACTERIZATION AND OPTIMIZATION IN ORGANOTYPIC SKIN

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Keywords: extracellular matrix, elastin, collagen, hyaluronic acid, 3D skin culture.

Objectives: There is little and contradictory information about the synthesis and distribution of the main molecular components of the dermal extracellular matrix (ECM) (Collagen I and III, Hyaluronic Acid (HA) and Elastin). The aim of this study was to analyze the distribution of these molecules in normal human skin and in 3D bioengineered skin used to treat extensive burns and large wounds of different etiology.

Methods: To determine the amount and distribution of the ECM components, both organotypic skin cultures and skin biopsies were formalin fixed and paraffin embedded.

Elastin and HA were analyzed by immunohistochemistry using fluorescent specific antibodies. To visualized collagen I and III, Sirius Red staining and polarized light microscopy were used. Fluorescence intensity and distribution was measured by image segmentation.

Results: In skin biopsies we found HA and elastin forming gradients and different concentrations of collagen III and I. Contrarily, neither the amount nor the distribution of these molecules could be reproduced in the in vitro culture.

Discussion: These differences could be due to the relatively short time of maturation (17 days) of the in vitro cultures as compared to normal skin. Alternatively, the ECM synthetized in the in vitro cultures cannot reproduce that found in normal skin. This result is relevant for the design bioengineering.

SESSION TD3: EXPERIMENTAL MODELLING HEMODYNAMICS

O64

PREDICTION OF POST-STORAGE CARDIAC FUNCTION

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Introduction: Hypothermic cardiac preservation is a fundamental principle in heart transplantation and known to have restricted protection and cause reperfusion injury. Postoperative cardiac dysfunctions and graft failures cannot be entirely prevented since function assessment during hypothermic transportation is lacking.

This preclinical study aims to predict post-storage heart function by means of cardiac biomarker concentrations assessment within cardioplegic solution during hypothermic storage. Heart function is determined by cardiac output of hearts in the PhysioHeart platform. This work may improve cardiac function of the platform and outcomes of cardiac transplantations in clinics by providing information for instant and corrective treatments.

Methods: Hearts (n=8;450±30g) harvested from slaughterhouse pigs were arrested with St.Thomas cardioplegia (4ºC). After one hour, hearts were flushed with an additional litre from which samples were stored. After two hours, hearts were reperfused with blood in the ex vivo heart platform "PhysioHeart" to restore physiological cardiac performance in working mode. Stored samples were examined for troponin, lactate, phosphate, and ammonia. Pearson product moment was used to estimate correlations between biomarker concentrations and cardiac output.

Results: Significant correlations were determined between lactate (r=-0.857;p=0.01) and ammonia (r=-0.81;p=0.02) and cardiac output of revived hearts, while phosphate (r=-0.66;p=0.107) and troponin (r=-0.611;p=0.145) were not correlating. In contrast, troponin (r=0.786;p=0.02) was significantly correlating with warm ischemia times.

Discussion: This study can predict post-storage ex vivo cardiac function. The use of a different cardioplegic solution might be of favour for the anaerobic metabolism implied by lactate and ammonia. This technique could be applied to other cardiac arrest strategies like blood cardioplegia which would result in different marker concentrations. Lastly, the method is directly applicable in hospitals as implemented clinical assays were used.

O65

PASSIVE BEATING RIGHT HEART PLATFORM FOR TRAINING, TEACHING AND TESTING OF CATHETERBASED THERAPIES

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Objectives: In-vitro setups are standard during device development and regulatory approval of transcatheter therapies nowadays. These bench-tests, however, lack the anatomical similarity required for several of the newly developed devices aimed towards repair and replacement of the heart valves. The proposed ex-vivo simulator aims to bridge a gap between in-vitro and in-vivo setups, combining anatomical similarity with physiological flow and pressure properties.

Methods: The apex of the right side of a porcine heart is connected to a linear drive, tubing and a reservoir to form a circulatory loop. Compliances and resistances are added to allow for more physiological flow and pressure signatures. Pressure transducers monitor the pressure at the right ventricle, the right atrium and the pulmonary artery. The cardiac output is measured at the pulmonary position.

Results: Pressure and flow curves of the simulator are comparable to physiological values. Access ports at the ventricle, the atrium and the pulmonary artery allow for insertion of catheterbased devices to practice, teach and test their application through different access routes. An endoscopic camera can additionally be introduced to visualize the procedure or the deployed device in-situ. Echocardiographic assessment can be used for further investigation of the inside of the porcine heart.

Discussion: The passive beating heart platform is a cost-effective and user-centric in-vitro bench test, suitable for the application of catheterbased therapies in an almost

physiological environment. It aims to fill a gap between in-vitro laboratory and in-vivo animal studies at a reasonable time and cost efficiency.

O66

DEVELOPMENT OF A NONINVASIVE METHOD FOR BLOOD PRESSURE MEASUREMENTS USING THE FACIAL ARTERY

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Objectives: The drug Contergan was prescribed in West-Germany from 1957 to 1961. Taken during pregnancy, it led to severe deformities, e.g. the babies were born without arms or legs. It is impossible for these people (also for amputees and people suffering from obesity) to have their blood pressure taken using the upper arm cuff measurement method. An alternative, non-invasive method was developed using the facial artery.

Methods: The blood pressure is measured using a mouthpiece, which consists of a light diode, a photo detector and a pressure pad. The intensity of the light signal depends on the amount of blood inside the facial artery. 112 measurements were performed on five healthy subjects (4 male, 1 female, average age: years). Using the upper arm cuff method on both arms, two reference values for the blood pressure were recorded during each check-measurement. The first five reference values for each subject were used to determine an individual *calibration-equation.*

Results: The results show that once the *calibration-equation* for a subject is determined, the results given by the cheek-measurement and the classical upper arm cuff are in good agreement. The average absolute error for systolic values is 5.98 mmHg, with a standard deviation of 4.50 mmHg. The diastolic values have an absolute error of 5.15 mmHg and a standard deviation of 3.46 mmHg.

Discussions: Currently, two approaches are being researched/pursued to find the correlation between different subjects and the *calibration-equation*. One by conducting further measurements to determine an empiric equation that suits all subjects, the other to tailor the equation to each subject, given the physical characteristics of the subject.

OH67

EVALUATION OF ATRIAL INFLOW CONDITIONS ON THE INTRAVENTRICULAR FLOW PATTERN

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Objectives: Investigation of the intraventricular flow patterns during Left Ventricular Assist Device (LVAD) support is commonly performed via Computational Fluid Dynamics (CFD). However this approach requires the definition of boundary conditions that are usually too simplistic to describe the real nature of the flow. Complex inflow conditions from the left atrium constitute an often overlooked parameter that might affect the whole ventricular flow patterns. In this study a ventricular flow model was developed and validated by Particle Image Velocimetry (PIV). Additionally the influences of atrial inflow condition on the ventricular flow patterns were investigated.

Methods: A PIV setup with a defined inflow section and flow straighteners was used for validation purposes. A 3D CFD model of a LVAD-supported ventricular discretized by five million tetrahedral cells was employed for CFD simulation. Two different transient simulations with k-ω shear stress transport (SST) model were performed (pump speed: 2800 rpm, flow rate: 3.5 L/min); A base simulation with no additional effect at the inflow and a second simulation adding a rotational speed at the inlet (35 rpm) due to the rotational nature of atrial flow. The relative error (E) as well as the Q-Value were calculated as quantitative analysis.

Results: The validation PIV experiment with well-defined inflow conditions showed good agreement with the CFD simulation in terms of mean velocity at different planes (Coronal plane: E=0.17 and sagittal plane: E=0.33). Interestingly, using rotational inflow conditions caused relevant changes and even dissolved some recirculation regions, reported by Q-Value: (PIV: 0.45, CFD: 0.46, rotational CFD: 0.38).

Discussion: Flow patterns inside a ventricle are complex and influenced by many factors. Even small perturbations of the atrial inflow conditions can induce large modifications of the ventricular flow patterns. The formation of recirculation regions, which is usually linked to thrombus formation, is therefore influenced by atrial conditions.

O68

VISUALIZATION OF THE VENTRICULAR FLOW FIELD IN THE ASSISTED ISOLATED BEATING HEART USING ULTRASOUND PARTICLE IMAGE VELOCIMETRY

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Introduction: Alterations in the ventricular flow field during cardiac support with continuous left ventricular assist devices (LVAD) are suspected to promote thromboembolic events. Current in-vitro models of the ventricular flow fields are limited by their geometric and functional simplifications (e.g. heart valves, trabecular structures, contraction patterns). Aim of this study was to evaluate the feasibility of Echo-Particle Imaging Velocimetry (Echo-PIV) to visualize the ventricular flow fields during LVAD support in the isolated large animal heart.

Methods: Hearts from pigs (n=2) were explanted and connected to an isolated heart apparatus. The hearts were resuscitated using warm, oxygenated blood and a Medtronic HVAD was implanted via the apex. Once hemodynamics stabilized, the setup was switched to the working mode, in which the left ventricle pumps blood from the atrium to the aorta as in reality. Micro-air-bubbles were injected via the left atrium and visualized within the left ventricle using B-mode in long axis view (Philipps iE33, X5-1 xMatrix probe) with a frame rate of up to 100Hz. An iterative PIV algorithm, using correlation domain averaging and beam sweep correction, was applied to determine the flow fields in partial and full support.

Results: Full (aortic valve closed) and partial support (aortic valve open) conditions were achieved in the isolated heart setup. The main blood flow travels along the left ventricle and exits the heart via the LVAD. Further, large rotational patterns are induced during diastole. Additionally flow patterns in the left ventricular outflow tract can be observed with this model, which cannot be modeled in vitro.

Conclusion: These preliminary results indicate the feasibility of Echo-PIV to quantify left ventricular flow patterns in the real heart. The superior accessibility of the isolated heart allowed the influence of different support regimes to be identified. On-going experiments will refine the methods and investigate further operating conditions.

O69

CAN WE IMPROVE THE FLOW OF ORGANS DURING THE INSERTION OF VENTRICULAR ASSISTANCE DEVICES? AN EXPERIMENTAL STUDY IN A PORCINE MODEL

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Objetives: Studies have reported organ blood flow responses to the administration of different anesthetics, but this effect during left ventricular assist device (LVAD) support remains unclear. The aim of the study is to compare the end-organ blood flow responses to the administration of two anaesthetics (sevoflurane and propofol) after partial cross-clamping of thoracic aorta and during LVAD.

Methods: Ten healthy minipigs were divided into 2 groups (5 per group) according to the anesthetic drug received (sevoflurane or propofol). After a medial sternotomy was performed, we proceeded to the partial lateral clamping of the ascending Aorta during twenty minutes for implanted a Biomedicus centrifugal pump. Organ blood flow (brain, heart, lung, liver, kidney and ileum) (measured by colored microspheres), markers of inflammation and tissue injury, and measure of nitric oxide (NO) were assessed at baseline (before partial aortic cross-clamping), 30 min after removal of partial aortic cross-clamping and after 30 minutes of partial support. For statistical analysis, T-Student was performed, considering $P<0.05$ as significant

Results: There were no significant differences in age and weight between both. After partial clamping, no statistically significant differences were found in organic blood flow, inflammatory response or NO bioavailability between the two groups of study. Sevoflurane increased blood flow in the brain, liver, and heart tissue after implantation of an LVAD under conditions of partial support. No statistically significant differences were found in inflammatory response, tissue injury or NO Bioavailability.

Discussion: Sevoflurane and propofol, as anesthetic agents, have the same influence on the organic blood flow and inflammatory response after partial lateral clamping of the thoracic ascending aorta. However, sevoflurane could be superior to propofol with respect to organic blood flow in a porcine model with LVAD. Further clinical trials should be made to clarify the influence of this finding on partial campling of Thoracic Aorta.

SESSION TD4:EXPERIMENTAL MODELLING VADS

O70

THE EFFECT OF LVAD PRESSURE SENSITIVITY ON LEFT VENTRICULAR UNLOADING

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Objectives: Pressure-sensitivity (PS) is the capability of LVADs to change flow based on pressure changes in the left ventricle (LV) or aorta at constant speed. High PS has

known advantages such as transmission of the residual pulse reducing the need for speed changes. However, the effects of different levels of PS on ventricular unloading are not completely understood.

Methods: Two laboratory-pumps are constructed with mean PS of 0.06 and 0.35l/min/mmHg up to 10l/min including cannulae. The two pumps are tested on an established mock circulation loop (MCL) comprising active chambers and systemic and pulmonary circulations. The MCL is set to reproduce left heart failure (LHF) and mitral insufficiency (MI, modeled by a controllable bypass) and the two pumps are run in full support mode. The LV in the MCL exhibits a linear filling characteristic with a gradient of 0.058mmHg/ml. The experimental results are correlated with numerical results obtained with a validated cardiorespiratory simulator reproducing exercise hemodynamics in LHF condition.

Results: The experiments show that the LV PV-loop is shifted leftwards on the filling characteristic for high PS compared to low PS at comparable arterial blood pressure and identical cardiac output, pulmonary and systemic vascular resistance and ventricular contractility. This effect is due to the increased unloading during systole based on the LVAD flow waveforms. Results evidenced also a decrease in left atrial pressure of 10-19%, depending on the grade of MI. Similarly, the numerical results show that the VAD with high PS can assure a better left ventricular unloading during exercise.

Discussion: In addition to the known benefit of pulse transmission, LVADs with higher PS unload the LV to a higher degree compared to LVADs with limited PS causing a concurrent decrease of pulmonary wedge pressure. For high PS, the unit LV+LVAD exhibits a behavior similar to an increased inotropy.

O71

INDEPENDENT CONTROL OF LEFT AND RIGHT SIDE OF TAH FOR SIMPLE ADJUSTMENT OF FLOW RATES FROM EACH SIDE TO ALLOW FOR BRONCHIAL CIRCULATION

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Objectives: It is a well-known fact that due to the bronchial circulation, the left side of the heart pumps approximately 4-10% more blood than the right side, depending on the species. This is something that manufacturers of total artificial hearts (TAH) need to handle in their design to succeed in the pre-clinical and clinical development stage.

RealHeart is a positive displacement TAH designed to mimic the anatomy of the natural heart. The TAH consists of two independently operated pumps, each with its own atrium and ventricle, and delivers pulsatile flow by atrioventricular plane movement.

The objective of this study was to confirm that RealHeart's left pump can consistently deliver 4-10% greater volume of blood than the right pump through stroke length adjustments.

Methods: RealHeart was connected to a system test rig that mimics the resistance of the human body. The system was programmed to deliver 4.5 liters of fluid from the right side of the TAH and 4-10 % more on the left side. Both sides of the TAH pumped synchronously, just like the natural heart. The test was performed using an automated test software, that lets the user define a test matrix. The flow rate was recorded via a clamp-on flow transducer (em-tec, Germany) connected to the PC running the test software.

Results: The results from the automated lab tests showed that it is possible and simple to pump more blood from the left side of RealHeart, by changing the stroke length.

Discussion: These successful tests show that the challenge of delivering different flow rates for the left and right side of a TAH can be solved by controlling the two sides independently, whilst synchronizing them electronically to maintain a common pulse.

O72

HEMODYNAMIC PERFORMANCE OF A PEDIATRIC PULSATILE VAD

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Objectives: To assess hemodynamic performance of a 15 ml stroke volume VAD designed to provide cardiac assistance as a bridge to transplantation in children.

Methods: Acute tests were performed in white large piglets under biventricular cardiac assistance (n = 6, 10 ±1 Kg body weight). ECG, aortic flow, arterial and left atrial pressures were recorded and stored for off line analysis. Cardiac output (Swan Ganz catheter) and body surface area were measured to determine cardiac index. Physiological parameters were measured at basal (control), post-thoracotomy, post cannulation and every 20 min after assistance started. Chronic left ventricle assistance was evaluated in juvenile sheep with an actively contracting ventricle (n=8, 20-30 Kg body weight) undergoing LV assistance with a target implant time of 30 days. VADs were implanted in fully anesthetized animals in the apical to aortic cannulation after left thoracotomy. Post-surgery anticoagulation was maintained with LMW heparin. Animal experiments were made in compliance with the Institutional Animal Care and Use Committee guidelines.

Results: Acute biventricular assistance resulted in stable cardiac index >3 L/min/m^2 in all animals. Five animals met the target period of left ventricular assistance of 30 days in good conditions. Causes of death in animals that did not survive up to the end point were systemic infection (n=2) and bleeding in the immediate post-operative period (n=1). No clinical indicators of embolization or relevant pathology findings were observed. Plasma free hemoglobin remained within acceptable levels

O73

WIRELESS POWERING OF VAD: HISTORY, CURRENT STATUS AND FUTURE PROSPECTS

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Objectives: The aim of this work is to provide a general overview of the evolution of the VAD inductive powering technique and to define key directions for further studies. Also, we propose a design strategy for inductive powering unit with high-stable output characteristics.

Methods: The development of the inductive energy transfer (IET) unit for VAD has started as early as in the 60s, but up to the 90s, there was no room for full utilization of the IET advantages, since pulsatile devices with additional pneumatic percutaneous driveline was in use. Nevertheless, several key solutions have been found and they can be summarized as follows:

- flat pancake coils with external diameter of about 5..10 cm;
- operating frequency in the range of 0.1...1 MHz;
- implantable rechargeable back-up batteries.

As rotary blood pumps have become widely used, interest for IET has grown up. Nevertheless, up to now IET has not become a common technique of the VAD powering. Coils displacement represents a major challenge. To overcome this problem, we propose design strategy for IET unit which includes next major features:

- algorithm for coil geometry optimization which ensures strong coupling between coils;
- method for a person-specific external coil design;
- frequency-tracking technique which provide stable output of the IET unit.

Results: Prototype IET unit was designed and testing. The output power of about 5±0.5 W was ensures in the range of axial distance of about 10..20 mm and lateral distance of about 0..20 mm.

Discussion: The design of the reliable IET unit should be a big step towards further improvement of the VAD design in general. Coils displacement represents a major challenge. We have proposed design strategy to overcome this problem. Experimental studies verify our approach. Our future work is to perform initial animal study.

O74

EXPERIMENTAL INVESTIGATION OF THREE-DIMENSIONAL FLOW VELOCITY AND TURBULENCE IN THE HEARTMATE 3 ROTARY BLOOD PUMP

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Objectives: Flow fields inside rotary blood pumps (RBPs) are of profound interest being closely associated to blood trauma and consequent adverse events. The HeartMate 3 (HM3) is among the newest clinical RBPs, featuring an active magnetic levitation system. The aim was to experimentally investigate both the averaged and fluctuating (i.e. turbulent) velocities in the HM3 employing three-dimensional particle tracking velocimetry (3D-PTV).

Methods: 3D-PTV is a non-invasive measurement technique for capturing the three-dimensional flow velocity field by tracking the motion of tracer particles seeded into the fluid. For optical accessibility, the titanium volute casing of an explanted HM3 pump was replaced by an acrylic model. A refractive index matched fluid and fluorescent rhodamine particles (d=200μm) were used. The optical setup included a high-speed camera, a diode-pumped Nd-YLF laser, and an image splitter mimicking a stereoscopic four-camera setup. Images were recorded at 5,000fps with a pump speed of 5,000rpm under two flow rates: 2.7L/min and 5.7L/min.

Results: The velocity field and turbulent kinetic energies (TKE) in the volute casing and underneath the rotor were derived from the images and averaged over several rotations. Mean kinetic energies (MKE) for the 5.7L/min case are more uniformly distributed than for the lower flow. At 2.7L/min, the flow in the gap between the rotor and housing circulates at higher velocities. TKE is also higher (2-3 times) in this region and in the narrower part of the volute casing.

Conclusion: 3D-PTV was used to experimentally identify the flow field in an original HM3 pump with a transparent lower housing, a clinically relevant rotational speed, and under two flow conditions. For the first time, we measured turbulence in a clinical RBP and found significant levels at both flow conditions. At a lower flow rate, higher MKEs and TKEs inside the pump indicate increased blood trauma potential.

O75

IDENTIFICATION OF HYDRAULIC CHARACTERISTICS OF ROTARY BLOOD PUMPS AND THE INFLUENCE OF THE EXPERIMENTAL SETUP

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Objective: To derive a hydraulic pump model of a rotary blood pump (RBP), it is usually characterized in vitro under static and dynamic operating conditions. The experimental setup has an influence on the measurement results which may be the reason for the discrepancies of different reported hydraulic characteristics for the same RBP. In this study, we aimed to investigate the variation of common settings and their influence on the measured hydraulic characteristics of RBPs.

Methods: For identifying the static and dynamic hydraulic model, two axial (Abbott HeartMate II, Berlin Heart Incor) and two radial RBPs (Abbott HeartMate 3, Medtronic HVAD) were examined over the entire range of operating conditions in an in-vitro setup. We investigated the effects of in- and outflow cannulas, tubing, the location of pressure measurement, the behavior in the second quadrant of the HQ curve (negative flow) and the influence of varying viscosities for different hematocrits.

Results: The pressure drop of tubing mimicking the outflow graft of radial pumps was low compared to rigid bended inflow and outflow cannulas of axial pumps (HeartMate II: 20 mmHg pressure drop at 7 L/min). Pressure measurements at different positions along the circumference of a cannula directly downstream of the elbow can lead to variations of up to 4.5 mmHg. The fluid inertia in the hydraulic pump model increased by 50% to 90% when taking the periphery (cannula/tubing) into account.

Discussion: Most of the deviations of the hydraulic characteristics are dependent on the flow rate and therefore more prominent at a high flow rate and low head pressure. The detected steepness of the HQ curve is dependent on pump speed, range of flow rate investigated and whether periphery is taken into account or not.

SESSION FA1:NUMERICAL SIMULATIONS: VADS AND HEARTSII

O76

THE INFLUENCE OF LVAD CANNULATION ANGLES ON THE RISK OF INTRAVENTRICULAR THROMBOSIS IN A MULTISCALE NUMERICAL MODEL

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Objectives: Left ventricular assist devices (LVADs) can affect intraventricular flow dynamics and cause intraventricular thrombosis. With apically implanted LVADs, the inflow cannula is generally pointed towards the mitral valve (MV); however, the effect of inflow cannula alignments is not well understood from the perspective of intraventricular flow. This study aimed to numerically investigate the risk of LV thrombosis with varying inflow cannulation angles.

Methods: A dilated patient-specific LV was apically cannulated based on a HeartWare HVAD inflow cannula. A reference cannulation angle (0°) was aligned with the mitral valve (MV) and two further cannulation angles towards the septum (25°, 20°) and free wall (20°, 30°), restricted by endocardial contact, was evaluated. A validated one-way coupled lumped parameter network and fluid-structure interaction model, simulating a heart failure condition, was implemented to evaluate the risk of thrombosis based on LV blood residence time, LV washout (the rate of clearance of pre-existing blood), localised energy densities, apical blood stagnation and a pulsatility index map.

Results: Compared to the reference angle, LV blood residence times were similar (< 1% difference) for septal-oriented cannula angles, but >5% longer when aligned towards the free wall. Angulation towards the septal wall increased LV washout. The maximum apical energy density reduced as the cannula rotated from the septum towards the free wall (1856 vs. 1674 J/m^3 – reference = 1779 J/m^3). After the E-wave, no apical blood stagnation was found for all cases. Severe angulation towards the septal or free wall reduced pulsatility indices around the left ventricular outflow tract.

Discussion: The ideal inflow cannulation angle was achieved when orientated towards the MV or at 20° towards the septum. Angulation towards the free wall, which aligned with the mitral jet, was foreseen to be unfavourable due to early clearance of incoming blood.

O77

VISUALIZATION OF BLOOD FLOW THROUGH THE FUSIFORM ANEURYSM EQUIPPED WITH THE FLOW DIVERTER STENT– COMPUTATIONAL FLUID DYNAMICS (CFD) INVESTIGATIONS

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Objectives: The primary objective of this research was to analyze the impact of a flow diverter stent, located in the fusiform aneurysm of the aorta, on the blood flow determined by means of the numerical analysis (CFD). It is claimed that the flow diverter stents are better than the others since they do not block the flow through perforators. Due to this it was decided to verify such an assumption by analyzing their impact on the flow velocity, vorticity, washout study and wall shear stress distribution.

Methods: The patient-specific arterial model was reconstructed basing on the DICOM image sets deriving from the angiographic Computed Tomography examination. The reconstruction process was performed in the own software (MeMoS) followed by the model face smoothing in SolidWorks software. Ansys Mesher was used to generate the volumetric meshes with prism elements near the artery wall. The transient numerical analyses (Ansys CFX) enabled simulation of 4 full cardiac cycles, where the time-variant boundary conditions were taken from the literature.

Results: It was proven that the flow diverter impacts the blood flow. The creation of a vessel results in a new lumen observed. A low value of the blood velocity was observed in the aneurysm sac.

Discussion: The flow diverter stent inserted into the descending aorta aneurysm leads to the decrease of the blood velocity which initiates the blood clotting process in the low-velocity zones. However, it does not block the flow through the perforators branching from the aneurysm sac wall. The clotting process has not been entirely explained and CFD can be a useful tool to provide additional information to understand this phenomenon.

O78

BUILDING NON-HOMOGENEOUS HAEMATOCRIT DISTRIBUTION INTO VAD MODELLING

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Objectives: Ventricular assist devices (VADs) improve patients' survival rates and quality of life however complications exist such as haemolysis. Improvement have been achieved since early designs. In design process, computational fluid dynamics (CFD) has been employed to help safeguard these achievements while engineers and clinicians address further challenges (e.g. thrombosis, bleeding). Aim of this research is to utilise CFD for better predictions of blood damage in VADs by introducing red blood cells (RBC) transport model.

Methods: Blood in current blood damage models for VADs is treated as homogenous fluid despite the dense multi-phase suspension nature of it. For more accurate location of RBC concentration in flows, particle transport and scalar transport model for RBCs are introduced. Particle transport allowsZRBCs to be expressed as particles that exchange momentum with blood fluid hence influencing RBCs concentration in flows. The scalar transport model consist of diffusion coefficient computing the haematocrit distribution in domain. Comparison of both models are done to evaluate accuracy of RBC flow in pipe. Haemolysis calculation by power law function of shear stress and exposure time is then implemented to the more suitable model for VAD analysis thus locating more accurate RBC damage sites.

Results: Initial results show successful implementation of the model for pipe flow against published data. Haematocrit distribution was modelled in a VAD and the differences in sites of haemolysis within the VAD can be highlighted depending on whether a homogenous or non-homogeneous haematocrit is used. This study is still ongoing, more simulations are required to compare models and their resulting effect on blood damage predictions.

Discussion: Current research promises more accurate RBC concentration on flow. Further work will investigate differences in blood haemolysis prediction in axial and centrifugal VADs due to the addition of transport model, which will be presented as well.

O79

LES IN A ROTARY BLOOD PUMP: VISCOUS SHEAR STRESS COMPUTATION AND COMPARISON WITH URANS

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Purpose: Numerical flow analysis (CFD) in combination with the prediction of blood damage is an important procedure to investigate the hemocompatibility of a blood pump, since blood trauma due to shear stresses remains a problem in these devices. Today, the numerical damage prediction is conducted using Unsteady Reynolds-Averaged NavierStokes simulations (URANS). Investigations with Large-eddy simulations (LES) are rarely being performed for blood pumps. Hence, aim of the study is to examine the viscous shear stresses of an LES in a blood pump and compare the results with URANS.

Methods: The simulations were carried out at two operation points in a blood pump. The flow was simulated on a 100M element LES mesh and a 20M element URANS mesh. As a first step, the LES was verified by analyzing internal dissipative losses within the pump. Afterwards,

the pump characteristics and mean and turbulent viscous shear stresses (TVSS) were compared between LES and URANS.

Results: The verification showed that the LES is able to reproduce the significant portion of dissipative losses, which is a global indication that the equivalent viscous shear stresses are adequately resolved. The comparison with URANS revealed that the hydraulic parameters were in agreement, but differences for the shear stresses were found.

Conclusion: The results show the potential of LES as a high-quality comparative case to check the suitability of a chosen RANS setup and turbulence model. Furthermore, the results lead to suggest that LES is superior to URANS when instantaneous stresses are applied for the blood damage prediction.

O80

METHOD FOR FEASIBILITY ASSESMENT AND OPTIMIZATION OF ROTARY BLOOD PUMPS

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Objectives: Implantable rotary blood pump (RBP) designs are pushed close to the technically feasible limit by anatomic restrictions and a maximum allowed local blood temperature increase. Exploring the strongly related fluid-dynamic, electromagnetic and thermal pump performance for the entire design parameter space with simulations only is resources demanding. The aim of this study was to develop a method which combines analytic and numerical models efficiently to optimize blood pump designs especially in the early development stage.

Methods: Starting with an initial pump geometry and resulting performance data of Computational Fluid Dynamics (CFD) simulations in five operating points, the hydraulic characteristics and efficiencies were modelled over the specified operating range. The corresponding motor loss distribution was computed with a newly developed quasi-analytic electromagnetic tool for motors with large gaps. Based on analytic thermal correlations, the maximum blood temperature increase was estimated. The design improvement potential was investigated by conducting a sensitivity analysis on the design parameter space.

Results: First results were derived exemplary for a double-flow pump concept for Fontan circulation with an 18 mm diameter rotor driven by two radial flux four pole motors. The model system indicated a local blood temperature increase of over 2 K if speed and total flow are both above 4800 rpm and 6 L/min respectively. With a sensitivity analysis it was found that a combination of small changes in motor rotor and stator outer radius (+1.1mm) and magnet height (+0.6mm) ensures that thermal requirements are not violated.

Discussion: In this study, a method to assess feasibility and optimize RBP designs across the different physical systems was developed. In contrast to a time demanding iterative simulation procedure, our approach enables fast and interactive design optimization. Once fully validated in-vitro, this method may constitute a powerful tool to accelerate the design process of optimized RBP's.

SESSION FA2: VASCULAR TISSUE ENGINEERING

O81

IMPROVEMENT OF THE DURABILITY AND RELIABILITY OF IN VIVO TISSUE ENGINEERED VASCULAR TISSUES BY CHEMICAL MODIFICATION

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Objectives: We have reported that in vivo tissue engineered vascular tissues easily constructed in the subcutaneous tissues of the recipients functioned as superior grafts in the animal experiments. We also clinically applied them for the pulmonary arterial reconstruction of the child. However, since the formation of the vascular tissues depend on the conditions of recipients including high risk or immature patients, several kinds of pretreatments such as chemical crosslinking by glutaraldehyde (GA) or dehydration by ethanol (ET) were attempted to improve their durability and reliability. We actually use ET dehydration for the clinical application mainly to improve surgical handlings. In this study, we compared the effects of such treatments on the mechanical properties of the tissues.

Methods: In vivo tissue engineered vascular tissues constructed in the subcutaneous tissues of beagle dogs were separated to the three groups, raw tissue group with no treatments (RAW), that under 10-minute dehydration in 70% ET (ET) and that under 10-minute crosslinking in 0.6% GA (GA). We measured the burst pressure of the circular area with a diameter of 5 mm and suture holding strength with 5-0 polypropylene sutures *in vitro* both of which were performed in the wet conditions.

Results: Burst pressure of RAW group (2400+/-478 mmHg) was significantly lower than those of ET group (3979 +/- 493 mmHg, $p<0.05$) and GA group (4835+/-532 mmHg, $p<0.05$). Minimal burst pressure (RAW; 186 mmHg) was kept higher by ET (1008 mmHg) or GA (759 mmHg) treatment, which indicated that these treatments

might improve the reliability of the grafts. Suture holding strength of RAW group (325 +/- 42 mN) also tended to be increased by ET (526 +/- 78 mN) or GA (520 +/- 48 mN) treatment.

Discussions: ET treatment and GA treatment of in vivo tissue engineered vascular tissues could enhance their mechanical strength and might increase their reliability.

O82

TOWARDS THE GENERATION OF FULLY AUTOLOGOUS TISSUE ENGINEERED THREE-LAYERED VASCULAR GRAFTS

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Objectives: Tissue engineered vascular grafts are promising alternatives to autologous, xenogeneic or synthetic grafts which are either limited in availability, immunogenic or prone to thrombosis and infections. Blood-derived fibrinogen can be used to generate fibrin scaffolds, however, with a poor biomechanical stability. Recently, a compaction technique was developed that stabilized fibrin grafts considerably. Here, these grafts were populated with autologous vascular cells to mimic the structure of native vessels.

Methods: Fibrin grafts were fabricated using cryoprecipitated fibrinogen from blood plasma, thrombin and factor XIII and assessed for burst pressure and uniaxial tensile strength. For cellularization, adipose tissue-derived mesenchymal stem cells (ASC) or ASC pre-treated with myogenic differentiation factors (SMC_{diff}) were incorporated into grafts and cultivated with or without pulsatile flow for 10 days. Moreover, grafts were seeded with blood-derived endothelial cells (EC) onto the luminal side or with EC plus ASC onto the abluminal side for 4-12 days. Subsequently, cell viability, cell orientation and the expression of myogenic proteins were analyzed.

Results: Compacted fibrin grafts were sufficiently stable (0.17±0.04 MPa tensile strength and 370±38 mmHg burst pressure) for a bioreactor-based pulsatile perfusion resulting in 6.9±1.2% strain. Incorporated cells remained viable for 10 days and elongated significantly under dynamic conditions that also increased the expression of αSMA, calponin and smoothelin in both ASC and SMC_{diff}. Luminal seeding with EC resulted in a confluent and flow-aligned monolayer after 4 days of dynamic cultivation. Co-culturing EC and ASC onto the abluminal surface led to capillary formation for up to 12 days.

Discussion: By seeding the graft with cells of all three vessel layers, first steps towards the generation of tissue engineered vascular grafts similar to natural vessels were performed which may help to prevent thrombosis and infections and accelerate graft integration after implantation.

O83

COMBINATION OF PRO-ANGIOGENIC FACTORS TO PROMOTE ENDOTHELIALIZATION OF TISSUE-ENGINEERED VASCULAR GRAFTS IN SITU

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Objectives: Tissue-engineered small-diamenter vascular grafts are widely tested as a promising substitute for arterial bypass surgery. To promote endothelialization of vascular grafts *in situ*, pro-angiogenic factors such as vascular endothelial growth factor (VEGF) are frequently used. However, an overdose of VEGF can induce the development of tumor-like vasculature; thereby other bioactive factors are needed to support VEGF-driven endothelialization. Here we investigated how the incorporation of basic fibroblast growth factor (bFGF) and stromal cell-derived factor (SDF)-1α into the grafts affects vascular tissue regeneration in comparison with and in addition to VEGF.

Methods: One-layer vascular grafts (2 mm) with either VEGF, bFGF, or SDF-1α, and two-layer vascular grafts with VEGF incorporated into the inner layer and bFGF and SDF-1α incorporated into the outer layer were blended of poly(3-hydroxybutyrate-co-3-hydroxyvalerate) and poly(ε-caprolactone) using emulsion electrospinning. We performed structural evaluation, tensile testing, and implantation of grafts into rat abdominal aorta followed by histological and immunohistochemical (CD34, CD31, vWF, collagen I/IV, α-SMA) examination.

Results: All grafts consisted of randomly distributed fibers, interconnected pores and had similar mechanical properties. Two-layer grafts with all three molecules had a higher primary patency rate (100%) 6 and 12 months post-implantation. Further, both bFGF and SDF-1α were not major inducers of endothelialization compared to VEGF; instead, they supported VEGF-induced endothelialization of the luminal surface as demonstarted by CD31+ cells count. Finally, bFGF induced a formation of a smooth muscle cells layer in both one-layer and two-layer grafts as early as 3 months postimplantation.

Discussion: These findings show that an incorporation of bFGF and SDF-1α into small-diamenter vascular grafts in combination with VEGF provides a higher primary patency rate and therefore improves *in vivo* performance.

O84

DO TISSUE-ENGINEERED HEART VALVES NEED STEM CELLS?

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Background: Tissue-engineered heart valves are being developed with various type of cell sources. However, it is not unclear how implanted valve tissues change their histological structure. We are developing a novel tissue-engineered heart valve (biovalve) with a unique in-body tissue engineering. In this study, we investigated the feasibility and time-course histological change in large animal experiments.

Methods: We developed 3 types of biovalves (a conventional type, a full-root type and a valve with a metalic stent for transcatheter implantation). We created plastic molds for each kind of biovalves with 3D printer easily and quickly, and embedded them in the subcutaneous spaces of adult goats for 1-2 months. After extracting the molds with the tissue and removing the molds only, biovalve with tri-leaflets similar to those of the native valves were constituted from completely autologous connective tissues and fibroblasts. Five cases of conventional biovalves were implanted in the aorta under cardiopulmonary bypass (CPB), 10 cases of full-root type were implanted in the pulmonary artery under CPB , and 26 cases of stent-valve type were implanted with transcatheter technique into in situ the aortic and pulmonary valves (17 and 9, respectively).

Results: In each type, Biovalves were successfully implanted and showed smooth movement of the leaflets with a little regurgitation in angiogram, and the maximum duration reached to 30 months in full-root type and 19 months in stent valve type. Histological examination of the Biovalves showed the autologous cells covering the laminar surface of the valve leaflets and also getting into the connective tissues.

Conclusions: The biovalves can adapt their histological structure to the environment. It suggests that tissue-engineered heart valves do not necessarily need stem cells. The biovalves have a potential to be used for viable bioprosthesis and to keep better function and biocompatibility longer than current valve substitutes.

O85

DEVELOPMENT OF BIOCOMPATIBLE ARTIFICIAL VASCULAR GRAFTS WITH AUTOLOGOUS VASCULAR CELLS

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The artificial vascular graft has potential disadvantages that relate to use of a conduit, including lack of growth potential and thromboembolism for children.

A biocompatibly structured vascular graft, resembling the multilayered structure of a natural vessel, may accelerate to regenerate the physiological function and growth potential of similar to those of a natural vessel. In this study, we developed biocompatible vascular grafts incorporated with autologous endothelial cells (ECs), smooth muscle cells (SMCs) and fibroblasts (FCs) on a biodegradable polymer.

Biocompatible vascular grafts were constructed on tubular scaffolds (ID=5mm, Length; 6cm) in vitro. Tubular scaffolds were made of biodegradable polymers composed of a polyglycolic acid (PGA), and a copolymer of L-lactide and aprolactone. Canine vascular cells were isolated from their jugular veins, and grown in cell cultures. The grafts consisted of ECs confluent monolayer and homogeneously mixed SMCs and labelled FCs layer. The designed artificial ECM was a mixed gel of type I collagen glue.

Pre-implanted grafts were completely endothelialized by scanning electron microscopy (SEM). Grafts have been implanted bilaterally in canine carotid arteries without anticoagulant. These grafts were achieved at physiological perfusion pressures.

Eight arterial graft were patent at the projected implantation periods of 2 and 8 weeks. In hybrid grafts, about 300 mm in thickness at 2 weeks after implantation. However, At 8 weeks of grafts, no progressive thickening occurred further implantation. Rather, a significant time-dependent decrease was observed. No aneurismal changes were observed and good constructed neoartery was observed. At 2 and 8 weeks after implantation, a diameter of 2 and 8 weeks implanted graft was a little larger than pre-implantation, but no significant changes during the this periods.

Vascular cells incorporated into biodegradable artificial grafts may contribute to enhanced tissue regeneration process including antithrombogenicity and growth potential.

O86

A MODEL OF A HUMAN BLOOD VESSEL FOR IN VITRO STUDIES BASED ON THE BIOREACTOR WITH ENDOTHELIAL AND SMOOTH MUSCLE CELLS

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Objectives: The aim of the study was to develop a model of a human blood vessel for *in vitro*studies with endothelial cells (EC) and smooth muscle cells (SMC) cultured in the capillary bioreactor under dynamic conditions.

Methods: A hollow fiber cartridge with polysulfone membranes (16 cm^2) constitutes the basis of the human blood vessel model. The EC and SMC were seeded on the inner and outer surface of the capillaries, respectively. Cultures were conducted under physiological shear stress generated by the flowing culture medium. Separate cultures of EC and SMC in wells of the culture plates were used as a control. Microscopic visualization of cells was made after fixation in formalin using hematoxylin and eosin staining. The percentage of EC and SMC inside capillaries and on their outer surface was analyzes using the flow cytometry. Cells were stained using carboxyfluorescein diacetate succinimidyl ester dye and CellTrace™ Violet dye. Viability of cells was assessed using a propidium iodide (PI) test. All analyses were made after 72 h of the culturing.

Results: We obtained a continuous and uniform coverage of the outer and the inner surface of capillaries with SMC and EC, respectively. In the PI viability test a slightly decreased percentage of the viable SMC (93%) isolated from the bioreactor was observed compared to the percentage of such cells isolated from the culture wells at the same time (98%). An analysis of the viability of EC isolated from the bioreactor and from the culture wells have not shown differences (96% *vs.* 95% viable EC).

Conclusion: The newly developed model of a human blood vessel, utilizing endothelial and smooth muscle cells cultured under dynamic conditions may be used in *in vitro* studies concerning pathophysiology of selected diseases or biocompatibility of various biomaterials.

SESSION FA3: SYMPOSIUM: ARTIFICIAL LUNG SUPPORT

O87

RECAPITULATION OF PULMONARY DEVELOPMENT IN 3D ORGANOIDS GENERATED WITH LUNG DECELLULARIZED ECM AND EXPANDED PROGENITOR CELLS

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Objectives: Unlike other organs and tissues, the generation of lung surrogate models that accurately replicate pulmonary development has been difficult to achieve. Hence, based on the recent findings of our laboratory in the successful isolation and expansion of murine lung progenitor cells and ECM decellularization, we were able to create 3D organoids that recapitulate lung development with the generation of differentiated tissue structures.

Methods: Lgr5+ progenitor cells were separated by FACS after isolation from healthy murine tissue. These cells were cultured in Matrigel™droplets, originating large lung organoids with extensive cell expansion for at least 10 passages. After the decellularization of mouse lungs, we generated 5mm diameter discs that we seeded with the expanded lung progenitor cells up to three weeks, to determine their ability to differentiate into the different cell lineages found in the lungs *in vivo*.

Results: The differentiated 3D lung organoids were then retrieved for histological processing, sectioning and immunostaining. In these sections, we were able to observe Clara cells (Scgb1a1), ciliated bronquiolar cells (GluTub), alveolar type II cells (ProSPC), alveolar type I cells (Pdpn) and alveolar progenitors (CD104 and CD49f). The expression of all these markers where also confirmed by RT-PCR.

Discussion: Thus, we believe that this novel 3D lung model constitutes an interesting surrogate of pulmonary progenitor cell differentiation and development. It also provides a useful *in vitro* tool to study the regenerative potential of these cells and their future application in lung bioengineering.

O88

THE MINIMALLY INVASIVE LIQUID LUNG CATHETER: IN-VITRO RESULTS IN A MODEL ENVIRONMENT

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Application of assistive devices for CO_2 reduction in blood is a possible treatment for the recovery from severe lung diseases. Aim of this study was to develop a minimally invasive catheter device for this task, the so-called Minimal Invasive Liquid Lung (MILL). In contrast to ECMO therapy, the MILL catheter operates directly in the Vena Cava. A biocompatible liquid serves as sweep fluid for absorption of CO_2 from blood through the catheter's membrane.

Methods: A lab prototype for the MILL catheter was developed, that integrates both membrane module and propulsion unit. Pressure loss in the membrane module is compensated by the blood pump driven by an electrical motor as parts of the propulsion unit. Outside diameter of the propulsion unit is 8mm. Perfluorocarbon, serving as CO_2 sweep fluid, was pumped in a closed circuit and purged in an extracorporeal console. Tests were done in a simplified artificial Vena Cava test loop gathering pump characteristics at different rotational speeds and corresponding pressure drops in and around the catheter.

Results: The results show that the propulsion system can overcome the pressure difference in the membrane catheter and provide 0.7 to 1.2 L/min blood flow for sufficient membrane cross-flow. By measuring pressures at specific inlet and outlet positions of the device at different blood flows by variating the rotational speed of the pump up to 30000 rpm the characteristics of the system were determined.

Discussion: A catheter prototype was tested in a Vena Cava model and the characteristics - pressure drops and flow rate distributions - were measured. Based on the results design optimization will be done. In the next step, CO_2 mass transfer in the membrane module will be optimized and the test circuit will be extended to validate computational simulations and to derive geometric design specifications.

O89

A NOVEL NUMERICAL MODEL OF OXYGEN TRANSPORT AND AUTOREGULATION WITHIN THE CARDIOVASCULAR SYSTEM

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Objective: Extracorporeal membrane oxygenation (ECMO) is a lifesaver for many patients with a failing lung. Ensuring the delivery of the oxygenated blood to the whole body is the key to a successful treatment. Numerical simulations can be a powerful tool to gain more insight into the oxygen distribution inside the human body and to optimize cannulation strategies. The aim of this work was to develop a lumped parameter model (LPM) of the cardiovascular system, which, in contrast to other models, includes oxygen and carbon dioxide transport as well as the mechanism of autoregulation (vasodilation and vasoconstriction). These effects play a major role in ECMO applications and need to be taken into account in order to generate a comprehensive model, which is able to reproduce the behavior of the human body during ECMO treatment.

Methods: A previously published LPM was extended by modelling myogenic and metabolic autoregulation processes as well as oxygen and carbon dioxide gas exchange dynamics. Different ECMO cannulation strategies were implemented for different patients based on clinical data.

Results: The modified LPM is able to reproduce the dynamic behavior observed in the cardiovascular system. The flow, pressure and gas exchange results were verified by clinical data. The model describes not only the hemodynamic conditions, but also the oxygen saturation in the cardiovascular system.

Discussion: The model gives insight into oxygen transport in patients undergoing different types of ECMO treatment. This will help to optimize cannulation strategies and to facilitate decision-making in clinical applications. Moreover, the simulation times are very low, making it a valuable tool for the calculation of transient boundary conditions for 3-D simulations in order to achieve additional results with high temporal and spatial resolution.

O90

NOVEL DESIGN FEATURES FOR THE OPTIMIZATION OF EXTRACORPOREAL GAS EXCHANGE SYSTEMS

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Objectives: Artificial lungs have evolved remarkably during the past 60 years, making them safer, smaller and more reliable in the process. Nevertheless, contemporary cardiopulmonary bypass (CPB) systems still suffer from significant drawbacks, such as high priming volumes (particularly prominent in neonatal/pediatric applications), wall effect phenomena, and stagnation zones. Ultimately, the cumulative effect of these disadvantages has a notable impact on hemocompatibility and blood trauma occurrence.Decades of experience in the field of extracorporeal gas exchange systems have permitted the development of a product capable of realizing individual solutions for each and every one of the aforementioned weaknesses of conventional CPB systems.

Methods: The fusion of a novel capillary membrane oxygenator with an elastic shell grants discrete pumping abilities to the product, which, combined with an external pump drive, can operate as a standalone CPB system with minimal priming volume, capable of generating targeted secondary flows. Alternatively, if combined with a conventional roller pump, the oxygenator's innovative design features enhance the pump's pulsation, thus augmenting boundary flow and eliminating stagnation zones.

Results: In vitro investigations with water as well as porcine blood have been carried out to validate the oxygenator's gas exchange efficacy, using both the external pump drive and the roller pump interchangeably. Furthermore, hemolysis rate has been assessed as an indication of blood trauma.

Discussion: Experimental results so far corroborate the significance of the unique design features implemented in this novel CPB system, both in terms of gas exchange

performance, and blood trauma attenuation. Currently, new oxygenator prototypes with further improved fluid dynamic performance are being developed, alongside more sophisticated external pump drives.

O91(IL)

ISOLATED LUNG PERFUSIÓN IN LUNG TRANSPLANTATION

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Nowadays, only about 15% of donated lungs are used for transplantation and up to 20% of patients die while waiting for a lung transplant. Several strategies have been developed over the last decades to expand the pool of donor lungs. Recently, ex vivo lung perfusion (EVLP) has been shown to be a useful technique for preservation, assessment and reconditioning of donor lungs.

Since Steen et al. reported the first clinical transplantation of lungs from a non-heart-beating donor submitted to EVLP in 2001, others have shown the role of EVLP in organ donor pool expansion by reconditioning of previously rejected lungs.

At present, three different EVLP strategies have been shown to produce transplantable donor lungs and several prospective studies based on these techniques have recently been completed or are underway in Europe and North America.

Currently, clinical and experimental researchers are trying to address several unanswered questions about EVLP: the optimal EVLP method; role of EVLP in assessing or preserving standard donor lungs; impact of pre-EVLP cold preservation in recipient outcomes; which chemicals should be added in the perfusate?; is centralized lung procurement and evaluation needed?; EVLP programs cost effectiveness; role of inhaled gases or aerosolized drugs during EVLP; or which is the optimum ventilation strategy for EVLP?

EVLP continues to lead its progression, spreading rapidly across the globe. Although the best EVLP method still needs to be determined. Moreover, EVLP could be used as a platform for researching in lung Cryopreservation and lung bioengineering in the coming years.

O193(IL)

ECMO – CARDIAC INDICATIONS

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Extracorporeal Membrane Oxygenation (ECMO) is essentially known for respiratory support. Nevertheless cardiocirculatory support by ECMO increased lately by new, easy to handle, systems. After decades of circulatory support mainly performed postcardiotomy by cardiothoracic surgeons with nearly deleterious results nowadays a variety of cardiocirculatory diseases can be treated by ECMO with good results. Starting from acute coronary syndroms, refractory arrhythmic storms over myocarditis, drug overdoses and pulmonary embolism to anaphylaxis and even malignant hyperthermia are indications for venoarterial ECMO support. Beyond these chronic or acute on chronic cardiomyopathies, primary graft failures or organ augmentation after thoracic transplantation are also accepted indications. Bridging patients to the next therapeutic step is one of the main goals in this context. More and more routine is achieved in short term ECMO support for cardiac interventions and perioperative during non cardiac surgery. Finally reanimation with ECMO (eCPR) gains in importance. Especially in these last situations peripheral or even percutaneous cannulation is performed. The awake patient with a cardiac indication for ECMO support is favored lately by many centers. Besides the indications and results of our supraregional ECMO center, a comprehensive overview regarding cardiac indications for ECMO is given. A complete elaboration of different indications, clinical realization and techniques with their key issues will be presented including recent developments, controversies and open questions.

SESSION FA4: SYMPOSIUM ON ACUTE KIDNEY INJURY: "TECHNOLOGICAL AND BASIC SCIENCE CLUES IN THE CRITICALLY ILL PATIENT WITH AKI"

O190(IL)

IMPLEMENTING BEST CLINICAL PRACTICES WITH MULTIORGAN SUPPORT

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Acute kidney injury (AKI) represents a clinical syndrome associated with incremental risk for death, acute and chronic kidney disease; and represents a mounting clinical challenge for healthcare professionals. Continuous renal replacement therapy (CRRT) use in ICU settings is rising, probably in response to similar trends in AKI, taken together with an ageing population burdened by high prevalence of multi-morbidity and high illness acuity. Numerous hallmarks of CRRT prescription are not standardized, nor are they supported from high-quality evidence. In spite of the publication of rigorous clinical practice guidelines focused on RRT for AKI that are intended to optimize the quality and reliability of CRRT, practice patterns and outcomes are highly variable. However, this latter issue has not been clearly translated into different clinical outcomes; such that conventional support treatment may be insufficient for adequate

management of some types of AKI. As a consequence, recent advances for the provision of CRRT for critically ill patients with AKI have been developed in order to consider other strategies focused on engaging targets, yet more studies are needed to better clear their clinical utility. Among non-conventional support treatments, some adsorptive devices allowing to eliminate inflammatory molecules which may play a main role as an adjuvant therapy for different clinical situations, such as sepsis and other disease states leading to a generalized inflammatory response, have been created. Nevertheless, there is a lack of evidence regarding blood purification techniques to routinely recommend their use and more studies are required in addition to the ongoing evidence to extend its clinical indications.

O191(IL)

INITIATION AND TERMINATION OF RENAL REPLACEMENT THERAPY IN THE CRITICALLY ILL PATIENT WITH AKI

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Acute kidney injury (AKI) occurs in up to 25% of patients in the intensive care unit, and approximately a 6% of them will require renal replacement therapy (RRT) during their ICU stay. Sepsis and septic shock is present in about 50% of ICU patients requiring RRT, and mortality approaches 80% in these cases. Once a patient requires RRT, several options can be considered: intermittent hemodialysis (IHD) (conventional and sustained low-efficient dialysis) and continuous RRT (CRRT).

While there is general agreement with respect to the dose prescription (i.e. 25 ml/kg/h) and anticoagulation (regional citrate), the issue of timing of initiation or termination is still not resolved. Traditional indications of RRT initiation (hyperkalemia, pulmonary edema) have been replaced by urine output criteria, dynamic evaluation of patient's condition and response to conservative measures.

In the past couple of years two important and well performed clinical trials have resulted in opposite results. The ELAIN trial evaluated 229 surgical and trauma patients, 32% with septic shock and showed reduced mortality when RRT was initiated early, within 8h of stage 2 AKIN. On the contrary, the AKIKI trial evaluated 621 ICU patients, 80% medical, 72% of which had septic shock and showed no beneficial effect of early initiation (wiithin 6h of AKIN3 vs traditional Indications). In addition, there are issues diffult to explain in the ELAIN trial: with only about 20h of difference in initiating RRT between groups, there is an astonishing reduction of 90d mortality from 54,7% to 39,3%, of time of mechanical ventilation, hospital LOS, and RRT days. We will have to await the results of the ongoing IDEAL-ICU clinical trial and see if it will shed more light in this critical issue of RRT prescription.

O192(IL)

NEW TARGET IN AKI: CHOLESTEROL RAFTS BLOCKADE

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Acute failure may be triggered by a vast amount of kidney insults. The role of proximal tubule reabsorption on glomerulo-tubular equilibrium is essential for renal physiology, but puts proximal tubule on the crosshair for toxic injury.

Proximal tubule apoptosis may be initiated by DNA damage (cisplatin toxicity), mitochondria (cyclosporine, tacrolimus toxicity), membrane (gentamycin), or endothelial reticulum (acetaminophen). However, after the first hit, and even if primary aggressor has disappeared, acute renal failure progresses though the extension phase.

The key for this amplification loop is the Fas/Fasl interaction on membrane bound cholesterol rafts. Fas/FasL complex formation induces rafts internalization and activation of the extrinsic pathway of apoptosis activation. This mechanism seems to be common to any toxic induced AKI, no matter which was the starting agent.

Cholesterol rafts blockade with cilastatin, a renal dehidropeptidase-I ligand, interferes with raft internalization, blocking the extension phase of AKI. ROS production, inflammasome activation, caspase 8,3 and 9 activation, citochrome C migration to citosol, Kim-1, ICAM-1, VCAM-1, TNFa expression and epithelial-mesenchymal transitions are all activated during the extension phase, and blocked by cilastatin.

Conclusion: Inhibition of cholesterol raft internalisation is the first common target to avoid most of known AKI.

SESSION FB1: SYMPOSIUM: TISSUE ENGINEERED VASCULAR GRAFTS

O92(IL)

ANIMAL MODELS FOR PRECLINICAL SAFETY AND PERFORMANCE EVALUATION OF VASCULAR GRAFTS

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Despite significant advances in interventional revascularization procedures, surgical revascularization therapies are

often indicated in the treatment of occlusive cardiovasculardiseases. Autologous vascular grafts are the preferred substitute material for small diameter vessel reconstruction because of favorable biomechanical properties and low thrombogenicity. However, in many patients the autologous approach is failing because of insufficient vessel quality. Small diameter prosthetic vascular substitutes, which are equivalent in long-term performance to autologous approaches, are currently not available. Synthetic grafts reveal inappropriate biomechanical properties and innate surface thrombogenicity. Various approaches and material modifications have been investigated to improve the performance of prosthetic materials but currently none of the clinically available conduits show sufficient patency rates after long-term application.

Development of new graft materials is of tremendous importance to improve the clinical outcome of vascular bypass surgery. To predict the performance of the device in humans and to assess its clinical potential appropriate animal models are necessary for device development and regulatory approval. However, there is no animal model available which fulfills all desired performance criteria for testing. To increase the validity of animal models comprehensive knowledge of comparative physiology is essential. Preclinical evaluation of tissue engineering approaches is challenging in animals and appropriate test settings have to be carefully selected.

O93(IL)

VASCULARIZATION OF TISSUE ENGINEERED CONSTRUCTS

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In natural tissues, the nutrition of cells and removal of waste products is facilitated by a dense capillary network which is generated during development. This perfusion system is also indispensable for tissue formation *in vitro* to generate tissues of clinically relevant dimensions. A main vessel structure needs to be implemented in such constructs for connection to a perfusion system *in vitro* and anastomosis to the host circulatory system *in vivo*.

So far, we concentrated on the establishment of a dense capillary network in a self-assembling approach employing human endothelial (hEC) and adipose tissue-derived stromal cells (hASC) as mural cells. Constructs were based on a carrier matrix of decellularized porcine small intestinal submucosa (SIS) with a three-dimensional hydrogel containing Matrigel™, collagen, and respective cells on top. hECs of different sources assembled in a network when co-cultured with hASCs in the presence of exogenous growth factors. The physical interaction of a subpopulation of hASCs with hEC network was visualized by staining for a-SMA. Lumen formation in the hEC network was demonstrated by accumulation of Texas-Red labeled dextran within hollow structures being a prerequisite for a connected and perfusable network. Casting of such hydrogel constructs on top of a decellularized biological vascularized matrix (BioVaM) with preserved mesenteric arterial and venous pedicles instead of SIS could lead to a connection of the preserved vessel bed and the network in the hydrogel finally resulting in a vascularized and perfusable constructs which offers the possibility for anastomosis to the host circulatory system during implantation.

O94(IL)

MECHANICAL TESTING OF VASCULAR GRAFTS - A REVIEW AND OVERVIEW

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For the success of vascular grafts, their mechanical behavior plays an important role. Standardized tests, as specified in international standards like ISO 10993 and ISO 7198 are the basis to guarantee a reproducible and safe product. Standard measurements provide results like tensile strength, elastic modulus, burst pressure and strain at break. At the development stage, where the material or the influence of micro- and nano-structures of the construct is evaluated or for the optimization of the production process, also other mechanical tests and methods are required. In most of the materials, some viscoelastic behavior is seen, where the load and speed of the wall movement affect their performance. This behavior is also of particular importance to mechanically mimic the native connected vessels, to minimize stress in the junction region and to prevent eventual intima hyperplasia formation.

Additionally to a literature research, in this work a focus is led on additional mechanical test and special requirements for testing small caliber vessels and vascular grafts. Factors influencing the measurement results will be discussed, like preconditioning, test parameters and specimen geometry. A method for testing dynamic and viscoelastic behavior, the Dynamic Mechanical Analysis (DMA), is going to be presented and some results of such measurements on electrospun vascular grafts are shown. DMA gives a better insight in the dynamic behavior of a structure and can show the influence of loading frequency, material stress and temperature.

In our measurements it was seen that dynamic loading cycles in the desired physiologic force range of the implanted vascular grafts are important to predict their in-vivo behavior. Due to viscoelastic material characteristics, considerable differences in the elastic modulus between

the standard quasistatic tensile test and a dynamic loading protocol were observed.

O95(KL)

TISSUE ENGINEERED VASCULAR GRAFTS (TEVG)

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Cardiovascular diseases are still the leading cause of death in developed countries. Revascularization procedures such as coronary artery (CABG) and peripheral bypass grafts, as well as access surgery mostly require a vascular graft. Despite intense research over many decades, no clinically suitable, shelf-ready, synthetic, vascular, small-caliber graft exists. Many approaches have been tried and are currently under investigation with promising results. These range from acellular and cell-based, stable or bio-degradable, synthetic scaffolds to biological or decellularized grafts, not forgetting self-assembly technologies for *in vitro* or *in vivo* TEVG.

We developed small-diameter vascular grafts made of slow degradable poly(e-caprolactone) nanofibres obtained by electrospinning and optimized by a factorial design approach. Fibre sizes, graft morphology, tensile stress and strain values were studied as a function of various parameters to obtain optimal vascular grafts for implantation after gamma sterilization. Consequently, these grafts were implanted as an abdominal aortic or carotid substitute in over 100 animals (rats and pigs) for periods up to 2-years showing no aneurysms, better patency, compliance and biocompatibility with faster endothelialization, less intimal hyperplasia and calcification compared to the clinically used ePTFE graft after long-term implantation in the rat aorta. Despite degradation, our graft maintains good mechanical characteristics, growth potential and tissue regeneration with specific cells, adequate angiogenesis and extra-cellular matrix formation. Thus, such a novel *in situ* tissue-engineered vascular graft using the body as bioreactor, may become better, shelf-ready, cheaper and clinically widely applicable for cardiovascular revascularization procedures and hopefully provide a better solution for our patients.

O96(IL)

AN ENGINEER'S CONTRIBUTION TO EFFICIENT VASCULAR REPLACEMENT GRAFTS

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Objectives: Cardiovascular scaffolds need to fulfil specific requirements, such as mimicing the extracellular matrix, match biomechanical properties and show high blood and cell compatibility. We developed techniques to fabricate tailor-made scaffolds, which address the as aforementioned requirements. In parallel, custom-made test benches were developed to assess specific properties of the scaffolds.

Methods: Scaffolds were electrospun from polycaprolactone (PCL) or blends of PCL/polylactide acid (PLA) with varying concentrations. Mandrel collectors were used to fabricated tubular scaffolds. Structured collectors allowed the fabrication of anti-kinking scaffolds. Scaffolds morphology was analyzed via scanning electron microscopy (SEM). Wettability was measured with captive bubble technique. Mechanical properties were assessed by tensile testing. Custom-made compliance as well as bending test benches were used to perform functionality testing. Blood and cell compatiblity were tested using a Chandler-Loop system and perfoming cell seeding studies with endothelial cells.

Results: Changing solution concentration or composition allowed for a variation of fiber diameter between 1 and 5µm. Wettability increased with increasing fiber diameter or increasing PLA concentration. Compliance increased with decreasing fiber size and decreasing PLA concentration. Structuring the mandrel collectors lead to an improved kinking behaviour. A 90° v-thread structure allowed for a bending up to 140° while the flow reduced to ~80% of its original value. Blood compatiblity tests revealed no influence of fiber diameter on the loss of platelets, whereas the addition of PLA significantly reduced the number of platelets. An endothelial cell seeding showed a significant improvement of the hemocompatibility.

Discussion: This study demontrates specific fabrication strategies as well as test systems to address common issue in the development of cardiovascular tissue engineering. Fiber diameter and compostion proved to be a powerful tool in adjusting the performance of cardiovascular scaffolds

SESSION FB2: MODIFICATIONS AND OPTIMISATION OF WELL-STABLISED TREATMENT OPTIONS IN RENAL FAILURE

O97

THE ANALYSIS OF THE DIALYSATE COMPOSITION AFTER FERMENTATION AND ELECTROCHEMICALLY MEDIATED SORBENT REGENERATION

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Objectives: The extracorporeal metabolites removal remains an acute medical problem, because hemodialysis is expensive, and peritoneal dialysis has low effectiveness.

To resolve this, a Wearable Artificial Kidney (WAK) is being developed; its main component, the Dialysate Regeneration Unit (DRU), may be based on enzymatic hydrolysis or on sorption with electrolysis. The paper studies the composition of a model solution of dialysate regenerated using these methods.

Methods: Constructed test bench simulates blood purification via peritoneal dialysis with dialysate regeneration. A thermostabilised flask with a model solution (peritoneal dialysis solution, pH=5…5.5) was used as a patient simulator. A 2ml solution containing urea 0.8g, creatinine 0.1g, uric acid 0.05g was added hourly using an infusion pump to simulate metabolites generation. The simulator was connected to the pump recirculating the solution through one of the two DRUs: the former represents complex sorbent unit with activated carbon "Causorb-212" 35g, urease 3g, ZrP 20g, ZrO2 20g; the latter represents electrolyser (graphite electrodes, total area 660±5cm2) between sorbent units (55±2g FAS activated carbon). For 8h a sample from the flask was hourly analysed for metabolites, pH, sodium, calcium, chloride ion using StatFax3300 biochemical analyser and AEC-01 electrolyte analyser.

Results: The enzymatic DRU removed urea 7g, creatinine 2g, uric acid 2g, and exhibited a rise in pH>8, while the ion concentrations changed by 15% at most. The electrochemical regenerator removed urea 2g, creatinine 0.4g, uric acid 0.4g; pH was levelled at 7, ion concentrations changed by less than 10%.

Discussion: Urease usage in WAK prototypes is popular, but electrolysis with sorption has lower effect on the ion composition and pH. However, it is less effective in removing urea, but more appropriate for WAK as the metabolites elimination rate approximates the rate of their generation, while consumables are cheaper.

O98

HIGH FLUX MIXED MATRIX HOLLOW FIBER MEMBRANES FOR BLOOD PURIFICATION

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Introduction: Current hemodialysis (HD) therapy removes small and non-protein bound toxins but cannot effectively remove middle-sized and protein-bound uremic toxins (PBUTs). This can lead to high mortality of patients with the end-stage renal diseases since the PBUTs are associated with high cardiovascular mortality. The application of convection via hemodiafiltration (HDF), combined with adsorption can significantly improve the removal of these toxins. In this work we present the development of a high flux mixed matrix membrane (MMM) which can achieve this combination.

Objectives: We aim to develop MMMs having superior removal of middle molecules and PBUTs. We therefore optimized the fabrication conditions in order to obtain hollow fiber MMMs with high membrane permeance, no albumin leakage and optimal accessibility of the sorbent particles.

Methods: Two homogenous polymer dope solutions, without activated carbon (AC) for an inner layer and with AC for an outer layer, were spun under different conditions. Studies on the membrane morphology, ultrafiltration coefficient, pore size, and toxin removal were carried out with microscopy and membrane transport experiments.

Results and Discussion: The fabricated hollow fiber MMMs have a relatively small diameter of the inner layer and under convective mode, have superior water permeance, higher sieving coefficient (SC) of PBUTs, and very low SC of bovine serum albumin (BSA). In fact, the PBUT removal with these MMM is much higher than the removal obtained with commercial HD membranes under the same experimental conditions.

O99

LOW FOULING MEMBRANES FOR LONG TERM DIALYSIS THERAPY

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Objectives: Most of dialysis membranes currently on the market are prepared by blending hydrophobic polymer, such as polyethersulfone (PES), with hydrophilic additives such as polyvinylpyrrolidone (PVP) for achieving optimal blood compatibility. However, membrane sterilization protocols could compromise the stability of PVP and the shear stress during dialysis sessions could lead to PVP elution from the membranes, resulting in altered membrane transport characteristics, fouling performance and hemocompatibility. Especially in the case of prolonged dialysis (*i.e.* portable/wearable artificial kidney systems), this can be a major drawback. Here, we investigate the development of new membranes suitable for longer dialysis treatment times, based on blending of PES with co-polymers to avoid hydrophilic additive elution and compromise of the membrane biocompatibility.

Methods: Polyethersulfone (PES) and co-polymer SlipSkin™ with excellent hemocompatibility were blended to obtain flat and hollow fiber membranes. Membranes were prepared by immersion precipitation and

characterized by scanning electron microscopy, water permeance and fouling resistance experiments. Furthermore, the membranes' long-term performance, blood biocompatibility and toxin removal using model solutions and human plasma were studied. Commercial flat and hollow fiber membranes were used for comparison.

Results and Discussion: The new blend membranes have high porosity with asymmetric morphology and water permeance in low ultrafiltration range. They have high creatinine removal (4000 mg/m^2 after four hours), very good fouling resistance (flux recovery ratio after protein solution of 82%) and good biocompatibility (low platelet and leukocyte adhesion and no complement activation) showing great potential for hemodialysis application. The investigation of removal of middle molecules and long-term performance is currently in progress.

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O100

CONDITIONALLY IMMORTALIZED PROXIMAL TUBULE EPITHELIAL CELLS DO NOT POSSESS TUMORIGENIC POTENTIAL SUGGESTING A SAFE USE IN RENAL REPLACEMENT THERAPY

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Objectives: Novel renal replacement treatments, such as a bioartificial kidney (BAK), hold great promise for the improvement of hemodialysis. The aim of this study was to evaluate the tumorigenic potential of conditionally immortalized human proximal tubule epithelial cells (ciPTEC) for safe use in BAK.

Methods: The ciPTEC line was characterized for loss of contact-inhibition and for anchorage-independent growth. The expression of temperature-sensitive SV40 large T antigen (SV40T), used for conditional immortalization, and its effect on cell cycle distribution were also addressed. ciPTECs were examined for apoptosis-resistance and for invading ability in Matrigel™ extracellular matrix. Genomic stability was determined using targeted locus amplification (TLA) technology. Tumorigenic potential was evaluated in athymic nude rats after injecting 10^7 cells subcutaneously.

Results: Focus formation assay showed that ciPTEC maintain contact-inhibition after 4 week culture (<1% foci compared to >50% by control HeLa cells; $p<0.001$). Cell cycle analysis confirmed this as >85% ($p<0.001$) of cells were present in G0/G1. Anchorage-independent growth of ciPTEC indicates that cells do require anchorage for growth (<1 colony per field, compared to 15 colonies for HeLa; $p<0.001$). SV40T expression was downregulated by >80% ($p<0.001$) after culturing cells at non-permissive temperature. Apoptosis analysis suggested that cells are not apoptosis-resistant. Only 7% of ciPTECs were able to migrate through extracellular matrix. The TLA analysis showed that transgenes integrated in the intronic regions of six genes in ciPTECs, including the EEA1 (Early endosome antigen 1), whose expression and function were not affected. The in vivo study showed that ciPTECs did not form tumors when injected subcutaneously in athymic nude rats.

Discussion: CiPTECs do not show typical cancer cell-like behavior in vitro, nor tumorigenic potential in vivo, suggesting a safe use in BAK and encouraging pre-clinical testing

O101

A LUMPED PARAMETER MODEL OF VASCULAR PERIPHERIES FOR CKD PATIENTS: A STEP TOWARDS MULTISCALE MODELLING

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Objectives: Microvascular impairment has been reported in CKD patients, especially in patients undergoing hemodialysis. To study these phenomena, we already develop a computational model allowing the description of fluid homeostasis at the microscale and a lumped parameter model of the vascular system. The intention is to approach the problem at different scales and in this view the here presented description of peripheral districts.

Methods: Starting for a previous lumped parameter model of the vasculature, we improve the peripheral districts description including: (i) a rheology of blood in small vessel strain rate dependent using Casson's model, (ii) a better lymphatic description, (iii) mechanical effect of fluid filtration, myogenic and metabolic controls along with the shear stresses effect, integrating different literature information.

Results: Tests performed on a single periphery both with constant and variable flow rate (based on data from the previous entire model) results in: (i) fluid accumulation within the interstitial space if the contribution of lymphatic system is not considered; (ii) highlighting the effect of peripheral controls in response to different input flow rate; (iii) estimating factors involved in fluid balance at the microvascular level, such as hydraulic and oncotic pressure for both capillaries and interstitium.

Discussion and Conclusion: This work highlights the key role of both lymphatic system and peripheral vascular

controls. Accounting for those contributions, the lumped parameter model allows estimating values of the input variables of the microscale model. Such information are difficulty retrieved clinically and their estimation is not simple due to the complexity of the phenomenon; however this type of analysis is essential to study microvascular impairment in CKD patients. In conclusion, this work represents a step towards a multiscale model of the vasculature for CKD patients.

O102

Abstract withdrawn

SESSION FB3: KIDNEY ARTIFICIAL REPLACEMENT AND APHERESIS: WERE WE ARE

O103

DATA FROM THE WAA REGISTER – UP DATE OF PATIENTS 21 YEARS AND OLDER

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Objective: The electronic registration through a web-page has been possible, at no cost, since 2002. So far 36 centres from 17 countries have entered data. An up date of results including change over time will be reported.

Methods: Electronic registration of each apheresis procedure includes demographic data and treatment procedures as well as to some extent outcome data. Application and data catch is made at the www.waa-registry.org supported by the World Apheresis Association (WAA).

Results: A total of 87147 procedures (12853 patients) have been reported up to January 18, 2018. Data was missing of the age of the patients in 159 procedures (46 patients). A total of 12048 patients (94%) were in the range 21-94 years. They had performed 82354 procedures, respectively. Most patients were treated with stem cell collection (42%) adding collection from donors (9.7%), plasma exchange by centrifugation (30%) or filtration (2%), photopheresis (2.7%), lipid apheresis in 179 patients.

The extent of work-load in the units for these children was most pronounced for centrifugation (35%), lipid apheresis (27%), cell collection (13%), and photopheresis (11%). Side effects were graded as mild (in 2.4%), moderate (3.3%) or severe (0.3%); one patient with plasma cell leukemia died due to myocardial infarction during the apheresis, a plasma reaction was present in parallel, thus it is unclear if the apheresis contributed or not. The most common diagnoses treated were mainly oncological diseases and haematological.

The distribution of the treatments over the years will be reported.

Discussion: Approximately 94% of apheresis is performed on adults. Most of these patients suffer from malignant diseases.

O104

PATIENTS WITH WORSE CARDIAC CONDITION RESPOND MORE TO THE HEMODIALYSIS PROCEDURE

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Objective: During haemodialysis (HD), the patient is exposed to the extracorporeal blood line including the dialyzer. In addition there appears a change in substances and fluid volumes both of which may influence the patient's circulation. The aim of this study was to investigate if the heart is relieved or burdened by such dialysis by following the change in troponin T and pro-BNP before and after HD.

Methods: Twenty patients on chronic HD were randomized to a prospective cross-over study of three modes of HD: (a) a dry-stored dialyzer (F8HPS, Fresenius, steam sterilized) with a low blood level in the venous chamber (DL), (b) the same dialyzer as above, but with a high level in the venous chamber (DH), and (c) a wet-stored dialyzer (Rexeed18L, Asahi Kasei Medical, gamma sterilized) with a high blood level (WH). Pro-BNP and troponin T (as markers for cardiac strain) were measured before HD and at 180 min of HD. The values were adjusted for the effect of fluid dilution or concentration.

Results: The start values of pro-BNP at start correlated with troponin T (rho=0.34, p=0.008, n=59). The difference in pro-BNP after 180 min of HD was larger if the start value was higher (rho=0.935, p<0.001). The troponin T value at start correlated with the change in troponin (rho 0.407, p=0.002) and pro-BNP (rho =0.374, p=0.005)

during HD. The change (in %) in troponin T during HD correlated with the change in pro-BNP (rho=0.577, p<0.001).

Discussion: These data indicate that patients with a worse cardiac background are more afflicted by each single HD. These data emphasize the importance to clarify the reasons for cardiac involvement during each HD.

O105

THE EX-VIVO EXPERIMENT OF EXTRACORPOREAL LUNG AND RENAL ASSIST DEVICE

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We developed a new system of CO_2 removal comprising acid infusion, membrane lung, and a continuous renal replacement therapy console at a low blood flow. To evaluate the new system, we conducted an ex vivo experiment using swine blood. We prepared a liter of aliquoted swine blood adjusted to pH 7.25 and pCO_2 65 mm Hg and mixed them with each concentration of acid (0, 10, or 20 mL of lactic or hydrochloric acid [1 mol/L]). These were immediately delivered to the system in a single pass, then blood gas samples were collected at each point of the circuit. The amount of CO_2 eliminated by the membrane lung was calculated from gas analysis across the membrane lung. The new system removed 35 ± 0.1 mL, 57.5 ± 1.3 mL, and 94.1 ± 0.6 mL of CO_2 (with 0, 10, and 20 mEq/L of lactic acid) and 32.8 ± 0.1 mL, 45.7 ± 1.2 mL, and 75.7 ± 0.8 mL (with 0, 10, and 20 mEq/L of hydrochloric acid), respectively. The levels of lactate and chloride ions for acid-base equilibrium were restored after continuous hemodiafiltration. The amount of CO_2 eliminated by the membrane lung was more than twice compared with non-acid controls. Thus, we revealed that this easy-to-setup CO_2 removal system was safe, effective, and removed CO_2 at a low blood flow.

O106

COMPARISON OF PERITONEAL TRANSPORT SYSTEM BETWEEN HEALTHY AND PERITONEAL DIALYSIS TISSUES: CONCLUSIONS FROM SPATIALLY DISTRIBUTED MODEL

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Background: Clinical studies on fluid and solute transport characteristics of tissues involved in peritoneal dialysis show functional and structural modifications of the two local transport barriers, capillary wall and interstitium. As no such studies are available in healthy individuals it is often assumed that parameters obtained in *in vivo* animal studies represent the function of healthy human tissues.

Objective: To compare local transport parameters (LTP) measured in healthy animal tissue (HT) vs. estimated from clinical studies in patients on peritoneal dialysis (PDT), and predict the overall peritoneal transport characteristics such as diffusive mass transport coefficient (KBD) and osmotic conductance for glucose (OsmCond) using spatially distributed model (SDM) of peritoneal transport.

Methods: LTP for fluid and glucose transport across the capillary wall and interstitium of HT were selected from physiological studies in animals. The LTP for 20 patients undergoing 6 h dwell studies at Karolinska Institutet were estimated using SDM. These local parameters were applied to predict overall KBD, hydraulic conductivity (HC), reflection coefficient, OsmCond, and penetration depths for glucose and fluid, for HT and PDT using SDM.

Results: As compared to PDT, HT is more permeable, except for lower glucose diffusivity and reflection coefficient in the interstitium; fluid and glucose penetration into tissue are lower in HT; and HC is higher, overall reflection coefficient lower, and OsmCond slightly higher in HT. The predicted ultrafiltration rates at the beginning of peritoneal dwell with glucose 3.86% fluid were 17.9 and 16.1 mL/min, and glucose KBD were 9.0 and 6.6 mL/min, for HT and PDT, respectively.

Conclusion: In spite of substantial difference in local transport characteristics between HT and PDT, HT provided predictions compatible with the range of values observed in PDT, although HT is more permeable for small solutes.

O107

EVALUATION OF THE DISTRIBUTION OF HEALTH AND EXPERIENCE IN QUALITY OF LIFE IN APHERESIS - DATA FROM THE WAA REGISTER

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Objective: The World Apheresis Association registry contains data from 14 countries and more than 30 centers. So far more than 87 000 apheresis procedures were performed

in more than 12000 patients. The aim of this study is to evaluate the distribution of health and experience in quality of life in those patients where an estimate was made.

Material and methods: This study focuses on 10 step graded evaluate of the health condition (scale from: bedridden unable to eat up to a level of athletic competition) and self assessment of quality of life (scale from: worst ever (0) up to best ever (10)). Data were compared in relation to various apheresis procedures and if it was the first or subsequent apheresis.

Results: Health condition estimates at the moment of apheresis were made in 39442 procedures. Of those who performed plasma exchange with centrifugation (n=15787) due to their disease 10% were bedridden, unable to come out off bed while for those who used plasma filtration (n=1018) the percentage was 27%. During the first procedure these figures were 16% versus 30%. Self estimates of quality of life were graded zero or 1 in 1.6% of patients during the first estimate; At the first contact those with plasma exchange graded like this to a percentage of 4.3%.

Conclusion: Many of the patients in apheresis have a poor health condition and quality of life, especially at the start of therapy. More differentiated data will be reported.

O108

DIALYZER CLEARANCE IN TWO-PHASE BLOOD: DEPENDENCE ON SOLUTE CELL MEMBRANE PERMEABILITY

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Objectives: During hemodialysis small solutes are exchanged between plasma and dialysis fluid, but also between plasma and erythrocytes. The classic theory of transport in hemodialyzers allows to estimate the dialyzer clearance, but does not account for the exchange between plasma water and erythrocytes intracellular fluid. We applied a mathematical model to assess the impact of this exchange to the calculation of the effective dialyzer clearance for solutes with different permeability across the cellular membrane.

Methods: The model describes the transport of solute in a counter-current dialyzer with one-phase flow in the dialysate channel, and two-phases, plasma and erythrocytes water, in the blood channel. The one-dimensional approach to solute distribution in the cross-section of the channels was assumed. The model calculated dialyzer clearance (K_D), as the sum of plasma and erythrocytes clearances, for urea (high cell membrane permeability), creatinine (low permeability), and a generic solute M (intermediate permeability). K_D was compared with the single-phase dialyzer clearance K_{th}, calculated as a function of effective blood flow.

Results: The formula for K_{th} agrees to the model's estimation of K_D for urea when total blood water flow ($Q_B = Q_P + Q_{Er}$) is used, and for creatinine when only plasma water flow (Q_P) is used. Neither flow can be used for solute M, for which K_{th} either overestimates or underestimates K_D. The best approximation was obtained with $Q_B = Q_P + 0.75Q_{Er}$.

Discussion: The formula for K_{th} works for solutes whose kinetics in blood can be approximated with a single-phase fluid, either because of the fast equilibration between blood phases (urea) or the lack of transport between plasma and erythrocyte fluid (creatinine). For solutes with an intermediate permeability across the cell membrane the problem cannot be solved using such simple assumptions, but our results suggest an approximate theory is possible.

SESSION FB4: SYMPOSIUM: FIBRONECTIN, CELL ADHESION AND TISSUE COMPATIBILITY OF BIOMATERIALS-SYMPOSIUM HONOURING GEORGE ALTANKOV

O109(IL)

FIBRONECTIN CONFORMATION AND CELL CULTURE ON PIEZOELECTRIC SUPPORTS

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Objective: Electroactive supports based on poly(vinylidene fluoride), PVDF, and copolymers based on vinylidene fluoride, can be produced with a variety of structures from flat films to 3D configurations. Depending on processing conditions, the polymer chains can crystallize in the electroactive b phase that, once polarized, presents piezoelectric properties. These supports allow subjecting cells in 2D or 3D environments to electromechanical stimulation that can be used to drive cell differentiation to a particular lineage.

Methods: Electroactive flat supports were produced by casting from a solution or by deformation of PVDF previously crystallized in a phase (which is not electroactive). Macroporous 3D scaffolds can be obtained by liquid-liquid or solid-liquid phase separation form a solution. Electroactive microspheres were produced by electrospray. An intermediate structure between 2D and 3D environments was prepared by adhering PVDF microspheres to a PVDF flat film or in nanofibrilar electrospun mats.

Results: The electroactive material surface can present a positive or negative distribution of electric charge that can be modulated by its mechanical deformation. It has been shown that not only the crystalline phase, but also the presence of electric charge on the surface has an important effect of the amount and conformation of fibronectin adsorbed on the cell culture substrate, and consequently cell adhesion. Pre-osteoblasts culture on flat substrates under oscillatory deformation proves the effect of the modulation of the electric charge on cell proliferation and viability. Substrate topography combined with electric charge highly affected the response of mesenchymal stem cells with respect to expansion and preservation of pluripotency when cultured in basal medium.

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O110(IL)

CELL ADHESION AND THE BIOCOMPATIBILITY OF MATERIALS

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Objectives: Cell adhesion on biomaterials is a crucial event for the fate of cells and related to the surface properties of biomaterials. Conventional implant materials can be tailored regarding physical surface properties, such as wetting behavior, charge density and topography. Each of these parameters controls adsorption of proteins and spreading of cells. Particularly the latter is a strong regulator of signal transduction and gene expression, which is connected with survival and growth of cells and their differentiation.

Methods: Adhesion studies with primary cells, such as fibroblasts, mesenchymal stem cells and cell lines like C2C12 myoblasts and HaCaT keratinocytes were carried out on different model materials like organosilane-modified anorganic substrata, polymer membranes based on acrylonitrile copolymers, polyetherimides and other polymers or on multilayers made of biogenic polyelectrolytes. While cell adhesion was investigated by different types of microscopy subsequent growth and differentiation of cells was studied by a variety of methods.

Results: Cell adhesion is a multistep process that starts with attachment of cells controlled by physical surface properties. A general finding is that hydrophobic substrata block cell adhesion due to conformational changes of adsorbed proteins, but also the hydrophilic nature of the cell glycokalyx coat. By contrast more hydrophilic materials promote cell adhesion because of strong protein adsorption with little conformational changes. In addition matrix formation, like fibronectin polymerization is supported, which paves the way for signal transduction events that support cell growth and differentiation.

Conclusion: The presentation will highlight some aspects of almost three decades of collaborative research of the author with Prof. Dr. George Altankov presenting some major achievements on understanding cell adhesion and function on artificial materials and ways to engineer substrata to promote colonization and healing of implant materials by the desired type of tissue cells.

O111(IL)

INSIGHTS FROM CELL-BIOMATERIAL INTERACTION TO ADVANCED TISSUE ENGINEERING

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Objectives: Cell-biomaterials interaction is a multistep paradigm which starts with the adsorption of adhesive proteins. Their recognized by the cellular integrin receptors triggers the biological part of cell adhesion for studies on which the author spent much time in the last three decades. Adhesion comprises of complex biomechanical and signalling events, resembling the natural cell-ECM interaction. Tissue engineering (TE) strives to mimic the natural cell-ECM interaction with scaffolds containing healthy tissue-derived cells intended to replace the injured tissue. A common obstacle however is the limited number of donor cells requiring their propagation *in vitro* leading to de-differentiation. Contemporary TE approaches solve this obstacle using mesenchymal stem cells (MSCs) that might be grown almost unlimitedly in undifferentiated state, consequently switched to differentiation. MSCs fate depends on a complex spatiotemporally signals and to control it requires engineering of analogous microenvironment. An example is our attempt to mimic the fibrillary organization of ECM - the leading concept in our two recent projects, STRUCTGEL and FIBROGELNET.

Methods: Fibrinogen containing PLA nanofibers (NFs) were electrospun in random and aligned configuration on gel slides providing for assembly of 2D or 3D constructs after seeding with MSCs. Cell morphology was evaluated via immunofluorescent for vinculin and actin while cell movements via time-laps microscopy. Alizarin red and Alcian Blue staining were used to follow the respective

osteogenic and chondrogenic differentiation while the corresponding genes activity was quantified by qPCR.

Results: MSCs respond on NFs organization acquiring irregular stellate-like shape on random and elongated on aligned NFs. Alignment promoted also directional cell movement. qPCR showed prevailing osteogenic response of MSCs on 3D aligned NFs, while 2D random arrangements supported their chondrogenic differentiation.

Conclusions: Collectively, the results of these projects highlighted the impact of NFs organization on MSCs functionality providing openings for broad TE application.

O112(KL)

ENGINEERING THE CELLULAR MICROENVIRONMENT WITH BIOMATERIALS, GROWTH

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Cells reside within the extracellular matrix (ECM), a complex 3D mesh of proteins and other macromolecules that provide anchorage support for cells but also instruct them with relevant signals that trigger different processes, such as cell migration and (stem) cell differentiation. During this talk, we will show examples of how different physical properties of the ECM play a key role in controlling cell behaviour, and how to recapitulate these aspects of the natural ECM by designing materials with application in cell engineering and regenerative medicine. Our examples will include viscoelastic properties and topography. We will discuss the importance of the presentation of growth factors – key signalling molecules that control cell development and hence regeneration – tethered to the ECM, and in crosstalk with integrins. In a futuristic approach, we will show how to engineer living interfaces based on bacteria that can control stem cell behaviour by providing, in a temporal controlled manner, adhesive molecules and growth factors to stem cells.

O113(IL)

ENGINEERING SUBSTRATES TO ENHANCE CELL-MATERIAL INTERACTIONS

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The understanding of cell/protein/biomaterial interactions is critical to the engineering of substrates for numerous biomedical and biotechnological applications and to the success of implants. The final biological response induced by implants is strongly influenced by its surface physicochemical properties that are intrinsically intertwined.

Surface topography is not the only variable controlling the biological response. Among other factors, surface energy has been determined as a very influential property in the biological response of these surfaces, specifically in the early events that occur when proteins adsorb and cells are recruited and adhere to the substrate. Another factor that is important for successful cellular interaction is the ability of adhering cells to remodel adsorbed and secreted matrix proteins, which may be supported by the material's surface properties. However, the mechanisms that underscore such topographical and physicochemical responses are still poorly understood.

Moreover, bioactive surface treatments allow biomaterials to ameliorate their integration into the body and accelerate the healing of damaged tissues. The immobilization of selected biomolecules on the inert biomaterial is supposed to create a cell instructive microenvironment on the surface by mimicking the extracellular matrix (ECM). Specifically, surface modifications presenting distinct chemical functional groups and/or topographies are effective strategies to enhance biomolecule immobilization and cell-material interactions.

The aim of this talk is to discuss the material-biosystem interactions, with an emphasis on establishing correlations between surface properties of modified metal surfaces and their *in vitro* biological response with particular focus on dental and cardiovascular applications.

SESSION FC1: SYMPOSIUM: WEARABLE BIOCOMPATIBLE DEVICES/ORGANS

O114(IL)

BIOMEDICAL TRIALS OF WEARABLE ARTIFICIAL KIDNEY

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Aim: Wearable artificial kidney (WAK) has potential to improve renal replacement therapy and to reduce its cost. The work is devoted to WAK development and its trial. Prototype of a peritoneal dialysis-based WAK was tested in vivo on animal model.

Materials and methods: The test was carried out on a 15 kg dog. The acute kidney injury was caused by injecting into the blood stream X-ray contrast. During trials blood samples were taken twice a day and dialysate samples - every hour before and after regeneration unit of WAK.

Results: During trials, WAK performed continuous peritoneal dialysis with dialysis fluid regeneration. In the second experiment creatinine and uric acid were eliminated from dialysate with rate of 0.3 mg/h, urea was eliminated with rate of 0.15 g/h, 350 ml of ultrafiltrate was removed. At the end of the experiment clinical blood analysis results stabilised.

Conclusion: The WAK revealed several problems in design that should be carried into consideration and is still a very promising direction of development.

O115(IL)

NOVEL PAEDIATRIC ROTARY BLOOD PUMP SPUTNIK

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Background: Due to the growing number of VAD implantation among a pediatric population and limitation of the pediatric VADs on the market, novel pediatric rotary blood pump is needed for the mechanical support of the heart.

Aim: The aim of this work was to design, prototype and study interaction of the Sputnik paediatric rotary blood pump (Sputnik PRBP) with cardiovascular system.

Methods: Computational fluid dynamics (CFD) studies were used to calculate head pressure-flow rate (H-Q) curves at rotor speeds ranging from 10,000 to 14,000 and comparing flow patterns at various points of the flow rate operating range (1, 3 and 5 L/min) for operating pressures ranging from 75 to 80 mmHg. In this study, a mock circulatory system (MCS) allowing simulation of physiological cardiovascular characteristics was used to investigate the interaction of the Sputnik PRBP with the cardiovascular system.

Results: At the inlet and outlet of the pump, when going to the operating point of 3 L/min, zones of stagnation become minuscule. The shear stress distribution was calculated along the pump volume. The volume in which shear stress exceed 150 Pa is less than 0.38% of the total pump volume at flow rates of 1, 3 and 5 L/min. During MCS study PRBP behavior was tested in the speed range of 6,000 to 15,000 rpm. Decreased contractility can be expressed in a stroke volume decrease approximately from 18 to 4 ml and ventricle systolic pressure decrease approximately from 92 to 20 mmHg. The left ventricle becomes fully supported at a pump speed of 10,000 rpm.

Conclusion: The proposed PRBP showed potential for improved clinical outcomes in paediatric patients with a body surface area (BSA) greater than 0.6 m^2 and weight greater than 12 kg.

O116(IL)

LASER CROSS-LINKING MECHANISM OF CARBON NANOPARTICLES IN A PROTEIN MATRIX FOR THE CREATION OF SCAFFOLDS

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New synthetic scaffolds have been used in tissue engineering that stimulate the proliferation of cells in the process of tissue formation. There are many works describing the production of cell scaffolds using laser methods and carbon nanoparticles. The present work is devoted to the description of laser structuring of carbon nanoscaffolds in albumin and collagen protein matrixes. These scaffolds provide cell proliferation. Cellular scaffolds were created from filamentary carbon nanoparticles - nanotubes. A quantum-mechanical approach was used to describe the mechanism of nanoscaffolds formation. The interaction of the carbon nanoscaffold with molecules of organic substances (proteins) was described using the molecular dynamics method. Pulsed and continuous lasers with a wavelength in the near infrared range were chosen to structure protein structures with a carbon nanocube. The laser structuring processes of single-walled carbon nanotubes (SWCNTs) of two types (armchair, zigzag) - were studied. The process of laser radiation energy absorbtion by defective sections of SWCNTs wass considered. Nanotubes with defects of type 1V (one vacancy of the carbon atom), 2V (two vacancies), SW (defect of communication rotation), mixed type 1V+SW were investigated. The process of binding nanotubes in a liquid protein matrix was demonstrated. In a liquid matrix, nanotubes can move relatively freely. It was determined that nanotubes with defects of 2V, 1V, SW and SW+1V absorb laser energy by ~ 50% more than other parts of SWCNTs. The absorption coefficients were calculated for the incidence of laser radiation with a stress vector directed along the nanotube axis and perpendicular to it. The nonuniform temperature distribution in the laser binding of SWCNTs was determined. The change in energy during the formation of C-C bonds in time (within 8 ps) varies in the range -7.43-7.36 eV/atom. An atomistic model of carbon nanoscaffolds with protein molecules was constructed. The electron charge density distribution and the interaction energy were determined for laser formation of cellular scaffolds from SWCNTs and proteins. Cellular scaffolds can be used to

repair cavities of connective tissues. For example, they can be colonized osteoblasts and chondroblasts and transplant into a defect of bone and cartilaginous tissue.

O117(IL)

NOVO BIOMIMETIC BIODEGRADABLE SCAFFOLDS PROMOTING VASCULARIZATION FOR DE-TISSUE FORMATION AND IN VIVO RECOVERY OF ITS MORPHOFUNCTIONAL CHARACTERISTICS

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Objectives: Our study aimed to develop methods of the fabrication of personalized cell-seeded carrier-matrices that mimic the architectonics of native tissues and to assess their potential for the clinical use.

Methods: To prepare biomimetic matrices, we applied laser-based rapid prototyping techniques (surface selective laser sintering, stereolithography, two photon polymerization, etc.) using biocompatible polymers (PLA, PGA, PCL and their copolymers) and CAD-models. The MSC-seeded scaffolds were tested in vitro and in vivo.

Results and Discussion: We revealed that the fabricated scaffolds induced the osteogenic cell differentiation in vitro. Then they were implanted into a cranial defect in a mouse to assess the bone formation. We showed that by week 10 there was the calcium deposition on the scaffolds at the defect site and the new bone tissue were formed. Moreover, the ingrowth of blood vessels from the surrounding tissues was noticed. These results are important for the development of new strategies in reconstructive therapy which include the personalized approach.

This work was supported by the Russian Science Foundation (18-15-00401).

O196(KL)

TISSUE ENGINEERED URETHRAL SUBSTITUTION: RECENT TRENDS AND OUR RESULTS

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Objective: This work aims to review recent advances and perspectives in tissue-engineered urethral reconstruction and to show our achievements in this field.

Methods: We analyzed papers, which discuss urethral reconstruction using tissue-engineered constructs and are accessible in PubMed, Scopus, and Web of Science, and particularly focused on using both acellular and recellularized constructs in humans and animal models. In our own experiments, to fabricate a construct, we used a matrix consisted of reconstituted collagen reinforced with glycolide and L-lactide fibers. Material structure and its mechanical properties were studied using nanoindentation, distribution map construction, and scanning electron microscopy. Its cytotoxicity was assessed via Live/Dead staining and MTT-assay. Cells and their spheroids were characterized using immunocytochemical and histological staining, flow cytometry, laser scanning confocal microscopy, and scanning electron microscopy.

Results and Discussion: Strictures and abnormalities of the urethra are still considered as complex urological problems. In such patients, the most effective treatment option is urethroplasty (anastomotic or substitution). Substitution urethroplasty implies widening the urethral lumen using flaps or grafts (e.g., buccal mucosa, foreskin, retroauricular or penile skin). Unfortunately, conventional approaches are less effective in case of longer and/or recurrent strictures. This requires development of novel treatment techniques such as implantation of the tissue-engineered urethra. However, one of the major challenges in growing any tissue-engineered organ is finding a proper material for its scaffold. In our experiments, we chose a hybrid matrix from collagen and glycolide and L-lactide fibers. It was seeded with spheroids from buccal epithelial cells. Epithelial cell in spheroids could save their phenotype and form epithelial lining on a matrix surface. The developed construct successfully passed preclinical trials (rabbits); and we have initiated its clinical trials (NCT03205670). Thus, this tissue-engineered construct is promising; and after ending trials, its use can be easily translated into clinical practice.

SESSION FC2:SYMPOSIUM: THE VAD COORDINATOR MOSAIC: CURRENT PICTURE OF THE VAD COORDINATOR'S WORLD

O118(IL)

FORMAL PREOPERATIVE EVALUATION OF VAD CANDIDATE DEXTERITY

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Introduction: The success of patients supported on ventricular assist devices (VAD) depends on their ability to manipulate the external components. Dexterity and other factors such as hand-eye coordination and depth perception play a role in determining how difficult it is for patients to perform these tasks and how VAD coordinators teach these skills.

Problem statement: There is no formal way to evaluate patient dexterity prior to VAD implant.

Approach: The rehabilitation members of the VAD team at a busy urban implanting center performed a thorough literature review to determine a formal set of tools with measureable results to objectively provide the team with an assessment of dexterity.

Results: The team complied a set of assessment tools to measure patients\' performance when manipulating shapes manually. These results assist the team to understand patients\' limitations and provide targeted strategies when educating patients postoperatively. The assessment set was polited on a group of patients then the team met to discuss implementation. The therapist were trained on the deployment of these tools and the documentation of the results.

Discussion: VAD coordinators are frequently the members of the team responsible for educating patients on device management. Most VAD coordinators are nurses with no formal therapy or adult learning education yet they are creating the structure for VAD patient education. Using formal tools to identify patient issues provides VAD coordinators with evidence based information to tailor education for individual needs.

O119(IL)

IMPROVING LVAD APICAL INFLOW CANNULA INGROWTH BY SINTERING

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Objective: Today inflow cannulae in left ventricular assist devices (LVAD) are sintered to ensure myocardial ingrowth in order to prevent thrombus formation at the apical penetration site. Studies, for instance the ADVANCE trial, compared the incidence of thromboembolic complications in the formerly polished pump of the HeartWare HVAD and the sintered version. This clinically important factor, however, is only a surrogate for inflow cannula thrombus development.

Methods: Available pumps in situ at autopsy or heart transplantation were investigated, quantifying thrombus formation at the inflow cannula in polished (A: 18 HTX, 25 died) and sintered (B: 28 HTX, 59 died) pumps. Average length at the penetration site was measured. At the transition of the sintered part to the polished tip circumferential thrombus formation was often observed.

Results: Demographic characteristics of the groups were similar. Incidence of thrombus formation at the myocardial penetration site was reduced to one third in group B. Comparing the average thrombus length, when seen, showed no significant difference (A: 6.4mm±4.5, B: 5.4mm±4.7, p: 0.385). After initial increase of thrombus load a decrease can be noticed in both groups. Long-term washout may be hypothesized. Of the sintered pumps 66% had thrombi at the transition. Average length was declining with prolonged support. Combining thrombus load at the apical penetration site and the transition leaves only 6% without thrombi.

Discussion: Sintering improved ingrowth as expected. The transition to the polished tip represents a new site for thrombus development, diminishing the advances of sintering. Thrombi at this site may be more critical due to poor anchoring. Incidence of thromboembolic events either manifest as pump thrombosis (EPPY A: .11, B: .20, p=.383) or stroke (EPPY A: .11, B: .25, p: .137) is higher in group B though not significantly.

O120(IL)

FRAILTY IN LVAD PATIENTS DIFFERENT ASPECTS

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Purpose: Dozen measuring instruments have been developed over the years to objective measure frailty (Dent et al., 2016). Most measuring instruments are mainly concentrating on the physical aspect of frailty while frailty is being defined by several more factors like social network, adherence in therapy, cognition, quality of life etc. (Boers 2010).

Previous research proves that an inadequate social support system or the presence of symptoms of depression or anxiety have adverse consequences for the results after implantation of a Mechanical Circulatory Support (MCS) device (Magid (2016), Cicoline (2016)& Overgaard(2012)).

Methods: Sandua (2013) describes 5 dimensions looking at which factors in frailty have an important role in MCS patients: physical, psychic/emotional, social, cognitive and spiritual next to physical frailty. Every dimension has different aspects.

This study investigates if there is a measurement instrument to examine frailty in MCS patients and if so, which ones.

Result: Literature study proves that such a measurement instrument doesn't exist.

Sometimes frailty has been made comprehendible by measurement instruments validated for (heart) transplantation (knowing: CHRISS, SIPAT, TERS, PSSS STAI, BDI-II and MCSDS.

Benchmark research shows that there isn't a measurement instrument to survey frailty.

Especially in the Netherlands and Belgium instruments have been used validated for heart convalescence (knowing; MMS, LDST, MPSSS, ESSI, KvL-H, PHQ-9, GAD-7 and BAI).

Only three of the five dimensions have been made comprehendible.

Conclusion: Only three of the five dimensions can be made comprehendible with the known measurement instruments.

Further study will be necessary in view of the need to make all aspects of frailty comprehendible.

A Delphi study has preference.

Frailty in MCS patients isn't static and changes too after implantation. That is the reason frailty has to be surveyed after implantation too. So that new or better interventions can be made.

O121(IL)

OUTCOMES OF MECHANICAL CIRCULATORY SUPPORT IN WOMEN IN A SINGLE CENTER

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Approximately, half of the 6 million adults living with heart failure (HF) in the United States are women, and yet they are less often enrolled in research studies involving HF medications or mechanical circulatory support. Notably, women are less likely referred for advanced therapies, to be listed for heart transplant, and to be implanted with durable left ventricular assist devices (LVAD) compared to men. Unfortuantely, these disparities exist despite studies demonstrating equivalent survival after LVAD implantation. Our aim was to research outcomes in women with end stage HF at a large tertiary care center after durable LVAD implantation to determine if outcomes were comparable to a contemporary cohort.

We retrospectively investigated all patients who received a durable VAD for destination therapy (DT) or bridge to transplant (BTT) at our institution from 4/2014 until 4/2017. Women who were lost to follow up, underwent VAD exchange, or underwent investigational device implantation were excluded from analysis.

Characteristics of the two groups analyzed were reviewed as the following: 1) One-year survival, 2) two-year survival of women 3) driveline infection, 4) stroke, 5) GI bleeding, and 6) hemolysis at one year. We then compared our data to the 8th Interagency registry for mechanically assisted circulatory support (INTERMACs) report. We found equivalent survival and outcomes for women compared to an entire cohort implanted with a durable VAD.

We recognize the importance of analyzing gender differences in outcomes on mechanical circulatory support. Further research should be performed on women using qualitative studies, lifestyle changes, employment issues to name a few.

O122(IL)

NEW PERSPECTIVES IN THE CARE OF THE DRIVELINE

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Aim: Evaluate the efficacy of the use of silicone spray on a patients with left ventricular assist devices of long-term skin reaction.

Description: One of the most frequent complications of ventricular assist device of long duration is infection in the exit site of the driveline. Preventive measures to reduce the risk of infection include immobilization and healing of the same. There is not a consensus in the existing protocols about the cleaning of the outlet hole of the driveline; neither in the frequency of the change of dressings nor on the materials used in the process of healing.

The literature supports the use of antiseptics and occlusive dressings at the exit point of the driveline as an essential part of care. However, silicone has been used in the treatment of wounds as a physical barrier in the prevention of skin irritation in different scenarios, as well as in ulcers by pressure and in the maintenance of the peristomal skin.

It used silicone spray in 4 patients with skin reaction around outlet driveline and skin irritation decreased significantly after 8 Weeks. After 10 weeks of application, the lesions completely disappeared, providing comfort to the patient, and reducing the trauma and the pain related with frequent dressing changes.

Conclusion: Literature has reflected the use of silicone spray in other scenarios because of its protective and harmless properties for the skin, and could be considered its employment as a complementary element in the protocol of the conventional cure of the driveline, especially in those patients at risk, who have skin reactions, and so prevent complications.

O195(IL)

AMBULATORY COUNTERPULSATION AT HOME; BALLOON PUMPS OUTSIDE OF THE INTENSIVE CARE UNIT

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Purpose: The NuPulseCV intravascular assist system (iVAS) is an ambulatory counterpulsation device with a portable drive unit. This device permits patients to be discharged home. The purpose of this study was to assess the outcomes of patients in the NuPulseCV First-In-Human and Feasibility clinical trials who were discharged home following iVAS implantation.

Methods: Patients were prospectively enrolled in a single-arm evaluation of the iVAS as a bridge to transplantation or decision between April, 2016 to August, 2017. Study protocol permitted discharge home at the discretion of study physicians. Discharged patients were seen in clinic every 2 weeks and followed closely with daily tele-remote monitoring. This study examined the clinical characteristics and outcomes of patients discharged home on the iVAS device.

Results: The study included 32 patients implanted with the iVAS device but only 19 of the 32 were eligible, due to FDA limitations, to be discharged home. 8/14 eligible patients were discharged home on the iVAS device: age 56 ± 9 years, 71% Male, and 71% ischemic cardiomyopathy. Average duration of device support was 96 ± 42 days. Average days spent home on the device was 41 ± 29 days (43% of total time on support). 3 patients (43%) had five unplanned readmissions (1 stroke from paroxysmal atrial fibrillation, 1 device alarm requiring driveline revision, 1 chest pain, 1 UTI, 1 seizure related to previous seizure disorder) at 25 ± 2.5 days after discharge. All patients were discharged home following readmission. No device infections were seen.

Conclusion: In this feasibility phase of the NuPulseCV study, we demonstrated that patients can safely be discharged home with good quality of life. A larger study is needed to evaluate the outcomes of iVAS patients who are discharged to home on device support.

SESSION FC3: VADS: NEW METHODS

O123

ELECTROCARDIOGRAM-SYNCHRONIZED ROTATIONAL SPEED MODULATION SYSTEM CAN REDUCE THE RECIRCULATION DUE TO AORTIC INSUFFICIENCY IN LEFT VENTRICULAR ASSIST DEVICE SUPPORT

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Purpose: Aortic Insufficiency (AI) is a worrisome problem in left ventricular assist device (LVAD) support. Progressive AI can cause to increase recirculation from LVAD to LV. Our previous study suggested that high rotational speed of LVAD can lead to increasing LVAD-LV recirculation. We have previously developed Electrocardiogram-Synchronized Rotational Speed Modulation System (ESRSM), which can change the rotational speed synchronously to ECG cycle. The aim of this study was to reduce the LVAD-LV recirculation by controlling the rotational speed with ESRSM.

Methods: Eight goats (45±2 kg) underwent LVAD (EVAHEART) implantation. Cardiac dysfunction was induced by continuous infusion of beta-blockade (esmolol). The AI model was established by placing a temporary inferior vena cava filter in the aortic valve. Hemodynamics was evaluated in three levels of AI (none, mild, severe) with the three driving modes of the ESRSM. The Co-pulse mode raises rotational speed in systolic phase, the Counter-pulse mode does in diastolic phase, and the Continuous mode maintained rotational speed to be constant (normal control). The each driving modes were set to maintain the same systemic flow. Recirculation rate which indicates the percentage of LVAD-LV recirculation to LVAD output was calculated as the index of AI.

Results: Continuous mode was driven with 1825 rpm (mean), and mean systemic flow was 2.1 L/min. The rotational speed needed to maintain the same flow was 2113 and 1563 rpm in Co-pulse mode, and 1488 and 1813 rpm in Counter-pulse mode (systolic and diastolic phase). The mean rotational speed of each modes was 1746 and 1704 rpm (Co-pulse and Counter-pulse mode, respectively). Recirculation rate in Counter-pulse mode was significantly lower than Continuous mode in mild and severe AI. It was indicated that the recirculation was reduced by lower mean rotational speed. ESRSM has the potential to reduce the recirculation due to the AI.

O124

EXPERIMENTAL INVESTIGATION OF RIGHT-LEFT FLOW BALANCE CONCEPTS FOR A TOTAL ARTIFICIAL HEART

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Objective: A total artificial heart (TAH) must ensure the fluid balance between the pulmonary and systemic

circulation to avoid lung damage. The required flow difference can vary, so the TAH has to respond dynamically to changes. The *ReinHeart TAH* has only one actuator that ejects the blood alternately from the right and left pump chamber. This coupling makes it difficult to control the right and left flow independently.

Method: In an experimental study, using an active mock circulation loop, four concepts to handle the right-left balance with the *ReinHeart TAH* were investigated. Three concepts are based on mechanical design changes to achieve a static flow difference. In combination with these static concepts, a dynamic concept was studied influencing the movement of the actuator by changing systole-diastole-ratio in order to respond to dynamic changes. For every concept variation, 270 measurement points were recorded to investigate the influence of circulation filling volume, heart rate, bronchial shunt flow and lung resistance.

Results: The blood pressures in the lung was used as main indicator to evaluate the right-left balance. The investigated variations of the right pusher plate geometry all result in high lung pressures which could cause lung damage. In comparison, the concept of a flexible pump chamber shows lower lung pressures, but these pressures can still damage the lungs. Reducing the size of the right pump chamber result in a proper lung pressure range. By choosing a suitable systole-diastole-ratio the right-left balance can dynamically be influenced with a positive effect on the lung pressures.

Conclusion: With a combination of a proper designed smaller right pump chamber as a static part and the variation of the systole-diastole-ratio as a dynamic part the right-left balance in the *ReinHeart TAH* can be properly controlled.

O125

EFFECT OF IMPELLER VIBRATIONAL EXCITATION ON ENHANCING ANTITHROMBOGENIC PROPERTIES OF A CENTRIFUGAL BLOOD PUMP WITH A MAGNETIC BEARING

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Introduction and Objectives: Mechanical circulatory support devices have been widely used in patients with heart failure. However, thrombus formation inside a blood pump remains a serious problem. We propose a method for physically enhancing antithrombogenic properties of a blood pump. The purpose of this research was to evaluate the effect of the impeller vibrational excitation on enhancing antithrombogenic properties of a centrifugal blood pump with a magnetic bearing.

Methods: A thrombogenic test using porcine blood anticoagulated with trisodium citrate was conducted. A magnetically levitated centrifugal blood pump without inlet and outlet was used. We compared four models that have an excitation frequency of 0, 70 and 300 Hz and an excitation amplitude of 10 and 50 μm, respectively. The pump was filled with blood added with calcium chloride to adjust ACT of approximately 200 s and operated at a rotational speed of 2000 rpm. When a measured motor torque increased, the pump was stopped and the blood was flushed with PBS. A hemolysis test was performed using a mock circulation loop with anticoagulated porcine blood to confirm whether hemolysis occurs by the vibration excitation. The pump was operated at a flow rate of 5.0 L/min and a rotational speed of 2000 rpm. Plasma free hemoglobin was measured and compared in each model.

Results: In the thrombogenic test, blood coagulation time, which is defined as the time when the differential value of the torque increased, tended to increase with increasing the vibrational frequency. In the hemolysis test, there was no significant difference in the concentration of plasma free hemoglobin in each model.

Conclusion: We confirmed the impeller vibrational excitation with an excitation frequency of 300 Hz and an excitation amplitude of 10 μm has the potential to prolong the clotting time of thrombus formation inside the blood pump.

O126

AN ADAPTIVE STARLING-LIKE PHYSIOLOGICAL CONTROLLER FOR ROTARY VENTRICULAR ASSIST DEVICES

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Objectives: Rotary ventricular assist devices (VADs) operated clinically under constant speed control (CSC) cannot respond adequately to changes in cardiac demand, resulting in sub-optimal VAD flow regulation during daily life. Starling-like control (SLC) for VADs mimics the healthy ventricular flow regulation and automatically adjusts VAD speed to meet varying cardiac demand. The use of a fixed control line (CL - relationship between preload and VAD flow) in SLC limits the flow regulating capability of the controller, especially for extreme circulatory states. Adaptive SLC (ASLC) overcomes this limitation by adapting the CL to meet a diverse range of circulatory conditions. This study assessed

ASLC, SLC and CSC in a mock circulation loop under a variety of simulated conditions.

Methods: Exercise, sleep, fluid loading and hypertension were induced by varying simulated heart rate, ventricular contractility, vascular resistance and circulating volume. The controllers were assessed on ability to maintain haemodynamics within a predefined range of mean aortic pressure (MAP) between 65 and 110 mmHg, left ventricular end-diastolic pressure between 6 and 10 mmHg, and VAD flow between 2.5 and 10.5 L/min.

Results: By appropriately adapting the CL, ASLC maintained haemodynamics within the predefined range during exercise, sleep and fluid loading. During hypertension, MAP rose above the defined level to 144 mmHg with ASLC, which was an improvement over SLC (MAP 168.3 mmHg) and CSC (right ventricular suction). SLC and CSC could not maintain the predefined haemodynamics for any of the simulated conditions.

Discussion: This study demonstrated the inadequacy of CSC and SLC to deal with extreme circulatory conditions. The improved flow adaptability of ASLC allowed it to maintain haemodynamics within the predefined range over a wider variety of simulated conditions than SLC and CSC, including exercise and sleep which occur daily in the lives of VAD outpatients.

O127

ULTRASONIC SENSOR CONCEPT TO FIT A VENTRICULAR ASSIST DEVICE CANNULA

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Objectives: Future left ventricular assist devices (LVADs) are expected to respond to the physiologic need of patients; however, they still lack reliable pressure or volume sensors for feedback control. In the clinic, echocardiography systems are routinely used to measure left-ventricular (LV) volume. Until now, echocardiography in this form cannot be integrated in LVADs due to its computational complexity. The aim of this study was to demonstrate the applicability of a simplified ultrasonic sensor to fit an LVAD cannula and to show the achievable accuracy in vitro.

Methods: Our approach required two ultrasonic transducers only, because we estimated the LV volume with the LV end-diastolic diameter commonly used in clinical assessments. In order to optimize the accuracy, we assessed the optimal design parameters considering over fifty orientations of the two ultrasonic transducers. A test bench was equipped with five talcum-infused silicone heart phantoms, in which the intra-ventricular surface replicated papillary muscles and trabeculae carnae. The end-diastolic filling volumes ranged from 180 to 480 mL. This reference volume was altered by ± 40 mL with a syringe pump.

Results: Based on the measurements acquired by the two US transducers, the LV volume was estimated well. However, the accuracies obtained are strongly dependent on the choice of design parameters. Orientations towards the septum perform better as they interfere less with the papillary muscles. The optimized design is valid for all hearts. Considering this, the Bland-Altman analysis reports the LV volume accuracy as a bias of ± 10% and limits of agreement of 0%—40% in all but one heart.

Discussion: The simplicity of traditional echocardiography systems was reduced by two orders of magnitude in technical complexity, while achieving comparable accuracy to 2D and 3D echocardiography. Hence, our approach exploits the established benefits of echocardiography and makes them applicable as a volume sensor for LVADs.

O128

DEVELOPMENT OF A MINIATURIZED FLOW METER USING A STRAIGHT CANNULA OF A BLOOD PUMP

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Objectives: To monitor a physiological condition of a patient having an artificial heart, it is important to measure a blood flow rate continuously and noninvasively. The purpose of this study is to develop a miniaturized flow meter using a straight cannula of a blood pump.

Methods: The developed flow meter utilized a straight cannula of a blood pump. The length of the flow meter was 40 mm. The outer and inner diameters were 14 and 12 mm, respectively. Two thin-wall parts were formed as measurement areas, A and B, by manufacturing outer side of a cannula. The wall thicknesses of measurement areas A and B were 50 and 160 μm, respectively. Measurement area A had micro-deformation in a flow path inside the cannula to measure a flow rate. Measurement area B did not have micro-deformation and measured only a static pressure for a pressure compensation. A strain gauge was adopted as a sensor. The first gauge, attached to the measurement area A, measured sum of a static pressure and a flow rate. The second gage, attached to the measurement area B, measured a static pressure. The flow rate was determined by subtracting the output of the two gauges. In a measurement test using a mock-up circulation loop, the measurement performances of the developed flow meter were evaluated under continuous flow and 1-Hz pulsatile flow conditions.

Results: In the measurement test, the measurement error between the developed flow meter and a commercial flow

meter was less than 15 % at a flow rate of 5 L/min. In the pulsatile flow condition, time delay was less than 0.25 sec.

Conclusion: We confirmed that the developed miniaturized flow meter could accurately measure not only the continuous flow but also the pulsatile flow continuously and noninvasively.

SESSION FC4: SYMPOSIUM: A LIFE FOR SCIENCE - IN HONOR OF JÖRG VIENKEN'S 70TH BIRTHDAY

O129(IL)

ALL ABOUT ALBUMIN - IN 15 MINUTES

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Human serum albumin (HSA) is the most abundant protein of the human body. It is central for the maintenance of the colloid-oncotic pressure, acid-base regulation, and is the most important antioxidant of the body. Moreover, HSA is needed for the transport and storage of most non-water-soluble drugs and metabolites in the blood and extracellular space. Given the many functions it is astonishing that clinicians just have the serum concentration available but nearly no information about the functional status of the molecule to diagnose and guide their therapies. Research is increasingly stepping in with a number of albumin-related biomarkers and tests evaluating the functional and structural status of the molecule. Among them are various binding assays like the drug-binding side-specific Albumin Binding Capacity (ABIC), the fatty acid-binding capacity by Electron-spin resonance (ESR) and the assessment of the oxidation and glycation status. Mounting evidence suggests a close correlation of albumin-dysfunction with the course and outcome of various diseases such as liver and kidney failure or septic multiorgan-failure. Clinically, the dysfunction can be improved by albumin infusions or extracorporeal albumin-cleansing methods like albumin dialysis MARS and albumin exchange approaches like plasma exchange. In the future, the better understanding of HSA in the context of various organ dysfunctions and clinical syndromes can guide clinicians in their diagnostic and therapeutic efforts.

O130(IL)

ON PRIORITIES IN SUBSTITUTIVE AND REGENERATIVE MEDICINE – PRAISE FOR AN UNRESTFUL CHAP

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In the last three decades, directly or indirectly, Prof. Joerg Vienken has promoted the advancement of substitutive and regenerative medicine in continuous and active fashion. Still today, his critical reviews of the current state-of-the-art and the limits of the therapeutic treatments offered to uremic patients are a reference for both physicians and technologists. In time, they have fostered the improvement of materials and therapies used for the treatment of uremic disorders. In his activity as a scientist, he has always been very open-minded and able to sort out of a large amount of information those issues most critical to patients' well-being clearly indicating the way to steer research in the field of substitutive and regenerative medicine in the most sustainable and efficient fashion.

In this presentation, some of Prof. Vienken\'s contributions will be briefly recalled. His capacity to analyze the limits of current therapies and to identify key problems will be used as a reference approach for analyzing in critical fashion the current dominant lines of research and allocation of resources in the field of substitutive and regenerative medicine.

O131(IL)

INFECTION PATHWAYS IN CENTRAL VENOUS CATHETERS

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Objective: Objective of this study are designs to limit infections in central venous catheters. A number of therapies rely on vascular access, functioning over long time spans. There are two pathways for infections: the extra luminal one and the intraluminal. The former starts at the site, where the catheter exits the body. Usually a sulcus forms at the exit site, permitting microbes to grow and creep along the outside into the body. The intra luminal path of an infection is likewise an adverse event, leading to a biofilm inside the catheter or to thrombosis or the combination of both. These events likewise limit the functional life of the catheter.

Methods: One design is proposed to solve the infection problem at the exit site: the catheter is equipped with a thin sleeve. It is attached to the catheter distal of the exit site and penetrates the skin. This sleeve is expandable and a continuous force is applied, which slowly pulls the sleeve out of the body, counteracting the invading microbes. Another design is proposed to solve the intraluminal infection problem: instead of the current method to infuse a lock solution ahead of a resting period of the catheter, the lumen is equipped with a balloon, which is blown up and takes the role of the lock solution – to keep the lumen clear of fluid.

Results: The method using the expandable sleeve has been developed and four devices were implanted in two goats. An infection free time of over 500 days was achieved. The intraluminal balloon has been investigated in vitro only.

Discussion: Jointly with a catheter fabricating company a grant proposal has been submitted to the German Ministry of Research to develop a clinical product.

SESSION FD1: IFAO SYMPOSIUM

O132(IL)

ESAO-IFAO SESSION: BRIDGE TO RECOVERY STRATEGIES FOR FAILING HEART WITH VAD OR/AND REGENERATIVE

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Mechanical circulatory support with a continuous flow left ventricular assist device (LVAD) plays an important role in the treatment of end-stage heart failure.

Since 2011, 4 types of implantable continuous flow (CF) LVADs have been covered by national health insurance as BTT and destination therapy is under clinical trial in Japan. According to Japanese national database, the J-MACS registry, more than 680 CF LVADs have been implanted during the last 6 years, with 1 and 2-year survival rates of 93% and 90%, respectively. Because of severe shortage of donor, duration of LVAD support exceeded 3 years in 60% of transplanted patients and we are still struggling with adverse events during support.

In Osaka University 190 CF LVADs were implanted since 2005 and 3 years survival was 86%. We also witnessed cardiac recovery during long term LVAD support which enabled LVAD explantation in 2 patients after myoblast cell sheet implantation and 8 patients after medical treatment alone. Recurrence of heart failure was not seen in any of those and we consider an implantable LVAD as a new platform for cardiac recovery.

In conclusion long-term LVAD support in Japan may have survival benefit equivalent to heart transplantation and it also provides us a unique platform for aggressive medical and cell therapy aiming at cardiac recovery in end-stage heart failure patients.

O133(IL)

MYOCARDIAL RECOVERY DURING MECHANICAL SUPPORT; DOES THE HEART RECOVER BY MECHANICAL UNLOADING

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In chronic heart failure the heart undergoes a series of biochemical, structural and functional changes, referred to as myocardial remodeling. These changes are driven by hormonal changes and pressure and volume overload of the failing ventricle. This remodeling is beneficial in the short term but causes over years an irreversible damage to the ventricle. Medical therapies can slow this process but not reverse it. Sporadic reports have indicated that mechanical support by Left Ventricular Assist Devices (LVADs) in end-stage heart failure might reverse this remodeling process, called reversed remodeling. In some cases this reversed remodeling allowed to explant the LVAD. During LVAD support the heart is unloaded by the assist device. This normalizes the volume and pressure overload of the ventricle. On the other hand due to increased cardiac output and blood pressure the activation of the hormonal axes is also normalized. Looking at the differential changes between the left, unloaded ventricle, and the right ventricle we might appreciate the relative contributions of the mechanical unloading and hormonal normalization. A better understanding of these contributions might improve myocardial recovery rates in the future.

SESSION FD2: BIOMATERIALS: TISSUE INTERFACE & SURFACE MODIFICATION

O134

BIOMIMETIC FUNCTIONALISATION OF PLLA WITH ACRYLATE BRUSHES

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Objectives: Poly L-Lactic acid (PLLA) is an established biodegradable polymer used in biomedical engineering. However, inefficient adsorption of key biological factors, such as the extracellular matrix component fibronectin (FN), hinders its use as a cellular microenvironment. Poly (ethyl acrylate) (PEA), on the other hand, has been shown to induce the organisation of FN into physiological-like fibrils upon adsorption, exposing binding motifs critical for cell adhesion and differentiation. Here, we aim to polymerise functional PEA brushes on PLLA by using a surface-initiated atomic transfer radical polymerisation (SI-ATRP) technique.

Methods: PLLA samples were aminolysed prior to initiator immobilisation and polymerisation of EA brushes via SI-ATRP. Surface characterisation of the samples was performed alongside characterisation of bulk polymer properties. The biological performance of the modified surfaces (PLLA-*b*PEA) was investigated in terms of fibronectin adsorption and C2C12 cell adhesion and differentiation.

Results: We developed and optimised an SI-ATRP technique to produce materials that retained the bulk physical characteristics of PLLA, i.e. Young's modulus in the MPa range and similar degradation rates, while forming functional PEA brushes on their surface. These formed a nanometric coating (< 10 nm) with wettability and chemical composition similar to bulk PEA controls. The brushes triggered FN organisation into nanofibrils, which specifically exposed the PHSRN synergy domain compared to untreated PLLA. Moreover, the FN nanofibrils on PLLA-*b*PEA facilitated the formation of larger numbers of mature focal adhesion plaques and supported higher levels of myogenic differentiation of C2C12 cells.

Discussion: This work outlines the production of a biodegradable PLLA-*b*PEA system able to induce the fibrillogenesis of FN and, in turn, to drive cell fate. This opens new avenues for the incorporation of functional cell microenvironments on implantable biomaterials, harnessing the ability of FN nanofibrils to bind growth factors.

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O135

RIBOFLAVIN MEDIATED UV-CROSSLINKING OF EXTRACELLULAR MATRIX CONDUITS TO IMPROVE VASCULAR GRAFT CHARACTERISTICS

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Introduction: Naturally-derived materials have been proposed as an alternative source to create small diameter vascular grafts. Although, the extracellular matrix (ECM) supports various cell functions, the required decellularization process, to remove cellular antigens and to reduce immunogenicity often leads to a decrease in mechanical strength of the material. Furthermore, preservation induced collagen exposure on the luminal surface mediates platelet adhesion and may favours graft occlusion without further graft modification steps.

Methods: In this study, placental arteries with an inner diameter of 2 mm, were decellularized using either Triton X-100 or SDS. After decellularization, UV-irradiation in combination with riboflavin (vitamin B2) was used to crosslink the collagenous ECM fibers of the small diameter vascular grafts and heparin molecules were covalently cross-linked to the matrix to further improve mechanical strength and hemocompatibility of the decellularized grafts. Graft characteristics and biocompatibility with and without UV-crosslinking (UV-CL) were studied *in vitro* and *in vivo*.

Results: The UV-CL ECM-grafts showed significantly improved mechanical strength and complete smoothening of the luminal graft surface compared to untreated grafts. Cell seeding using human endothelial cells and human fibroblasts confirmed no cytotoxic effects of the UV-CL treatment. Short-term orthotopic implantation of ECM and UV-CL ECM grafts (n=28 +/- UV-CL) in a rat model showed similar performance of both graft types. Histological examination revealed undisturbed cell migration and matrix degradation of both UV-CL ECM-grafts. By using a myograph system functional graft remodeling was detected in all grafts indicated by contractile responses to increased levels of potassium chloride.

Conclusion: UV-crosslinking is a preferable tool to improve graft characteristics of decellularized matrix grafts.

O136

SURFACE STRUCTURING AND SURFACE MODIFICATION OF DRUG ELUTING BALLOON CATHETERS

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Drug-Eluting Balloon (DEB) catheters for coronary and peripheral intervention are conventional semi-compliant balloons covered with an anti-proliferative drug which is released into the vessel during inflation of the balloon. But, the loss of drugs before catheter reaches the application position due to inefficacy of coating techniques made life threading effects and limits its application in modern drug delivery practice. Anti-bacterial coatings helps to reduce thrombosis and restenosis which were induced during catheterization. Therefore, various surface modification techniques were used to fix drugs on the surface to improve therapeutic effects.

Polymer balloon catheter tubes made from PE, TPU and PVC were mounted on a rotational stage and surface structured (half-moon structure) with laser ablation to get cages for drug molecules. Thereafter, the polymer surface was pretreated with a low-pressure plasma process and dip coating with heparin solutions was performed. Finally, drug diluting of heparin was determined made by High pressure liquid chromatography (HPLC). Otherwise, the catheter tubes were

dip coated with chitosan glutamate to reach anti-bacterial surface properties. To improve the adhesion of the chitosan molecules, the polymer surface was pretreated using an atmospheric plasma-assisted deposition process. Under consideration of ISO 20473, the anti-bacterial performance of the coatings was proved by investigations of the activity of the bacterium P. aeruginosa in the eluent.

Surface chemistry of the uncoated and coated catheter tubes was investigated with photo electron spectroscopy (XPS) and contact angle measurements. After atmospheric plasma treatment, the amount of oxygen on the surface in increased and this improves chitosan molecule adhesion. Low pressure plasma treatment allow the formation of amine functional groups on the surface and increase the amount of adhered heparin molecules. The adhesion forces of different coatings were investigated using Atomic Force Microscopy in tapping mode (tm-AFM).

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Materials

O137

MODIFICATION OF ELECTROSPUN FIBROUS POLYVINYLIDENE FLUORIDE MATS WITH

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Objectives: This study aims to assess the effect of polyaniline (PANI) on the piezoelectric modulus of polyvinylidene fluoride (PVDF) electrospun fiber mats.

Methods: For PANI synthesis, 0.15 M aniline diluted in 0.1 M hydrochloric acid was carefully mixed with 0.125 M ammonium persulfate (APS) in deionized water (amount-of-substance ratio 4:5 aniline to APS). Both solutions were kept at 0-5° C during preparation. Electrospun PVDF fiber mats were placed in the solution during PANI synthesis for 4, 6 and 8 h. After drying, pure and PANI-modified PVDF mats were mechanically tested in compression from 1-20 N at 1, 5 and 15 Hz while their induced electrical values were measured.

Results: Modified mats showed color differences after PANI treatment. PVDF mats remained nearly white at 4 h, turned greenish at 6 h and were completely green at 8 h. Scanning electron microscopy showed an increase in PANI salt accumulation on fibers. Mean conductivity was 7.2E-6 S/cm (8 h) and a decrease in internal resistance was observed. All measurements of piezoelectric modulus were compared to the literature value of PVDF (d_{33} = 3.3E-11 C/N). In comparison, piezoelectric modulus for PVDF mats was higher ($d_{33(1N/1Hz)}$ = 1.6E-10 C/N) and increased with higher load frequency ($d_{33(1N/15Hz)}$ = 2.7E-10 C/N). With constant load frequency, the modulus decreased with increasing force ($d_{33(20N/1Hz)}$ = 4.4E-11 C/N). The modulus of PANI-modified mats was close to the literature value ($d_{33(1N/1Hz/4h)}$ = 2.6E-11 C/N), but decreased with longer treatment time ($d_{33(1N/1Hz/8h)}$ = 1.3E-11 C/N). However, deviations in modulus between different load frequencies and forces decreased with higher PANI modification.

Discussion: The study showed that piezoelectric modulus depends on load and load frequency due to the nonlinear behavior of PVDF fibers. PANI modification increased conductivity of PVDF mats, leading to a more precise value of piezoelectric modulus.

O138

3655HOW THE OXIDE LAYER FORMATION OF MAGNESIUM STENTS IS INFLUENCED BY BLOOD SERUM

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Objectives: Hydroxyapatite (HA)-like plaques are the origin of many cardiovascular diseases. Magnesium is used as resorbable implant material for stents in cardiovascular applications. In physiological fluids, magnesium degradation leads to a HA-layer on the stent surface. Nevertheless, magnesium has a promising in vivo outcome. This study examines the mechanism behind the successful implantation of magnesium stents and transfers these findings into recommendations for improving stent material development.

Methods: We immersed 15 stents made of magnesium based alloy in simulated body fluid (SBF) which is the currently used method to evaluate degradation behavior. We also immersed 15 stents in fetal bovine serum (FBS) for 6, 16, 24, 48 and 72h. Subsequently, we analyzed the oxide layer with Raman-spectroscopy.

Results: The stents immersed in FBS degrade much slower than stents immersed in SBF. The FBS treated stents show $Mg(OH)_2$ precipitation on the surface and no HA-like products for at least 48h. On the contrary, the SBF leads to an oxide layer that consists of HA-like precipitation that can be detected after 6h of immersion.

Conclusions: The deceleration effect of FBS on magnesium degradation has an influence on the oxide layer formation, which forms $Mg(OH)_2$ that does not induce plaques. The currently used method to evaluate the degradation behavior of magnesium implants needs to be tailored to the intended application.

SESSION FD3: VADS: CLINICAL I

O139

A NEW 2D ECHOCARDIOGRAPHIC APPROACH TO EVALUATE THE MEMBRANE AND VALVE MOVEMENT OF THE BERLIN HEART EXCOR VAD CHAMBER IN PEDIATRIC VAD PATIENTS

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Objective: The use of Berlin Heart EXCOR VAD (BH) is a validated therapy to bridge pediatric patients to heart transplant. Serial echocardiographic (ECHO) assessment of VAD patients is necessary to support patients\' management. This work aims at developing an innovative strategy to evaluate the BH device functioning by ECHO and its interaction with the native heart in a pediatric population.

Methods: ECHO evaluation of BH membrane movement, inflow and outflow valves was performed in 2D, 2D-color doppler, M-mode and M-mode color doppler in order to assess the functioning of the device by direct positioning of the ECHO probe on the BH cannulas and membranes.

Results: 37 BH on 15 different patients were analyzed. 6 BH were placed as RVAD and 31 as LVAD. Results evidenced that 13 (20) inflow (outflow) valves presented a mild regurgitation, while 4 (3) inflow valves presented a moderate regurgitation. In two cases (5%) we observed severe valve regurgitation with back flow in the left ventricle/right atrium. In both cases, the BH chambers were substituted. The M-mode and the ECHO of the membranes and valves permitted to appreciate the beat phenomenon to assess if the native heart and the BH are working in opposite or in the same phase. The membrane ECHO permits to evaluate minimal changes in membrane movement to assure the completely empty-completely fully work modality.

Conclusions: Systematic ECHO assessment of BH chamber might support the BH programming and the diagnosis of device malfunctioning.

O140

EARLY DIAGNOSIS OF PUMP THROMBOSIS BASED ON TIME-FREQUENCY ANALYSIS OF LOG- FILES OF THE HEARTWARE HVAD VENTRICULAR ASSIST DEVICE

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Objectives: Pump thrombosis in the setting of Ventricular Assist Device therapy is a major and severe complication. No clinical standardized methods are available to capture the early build-up stage of the pump thrombus, preventing the development of therapeutic strategies to limit its progression and associated complications. We developed a novel algorithm based on time-frequency analysis of the HeartWare HVAD log-files allowing detection of pump operating dysfunctions correlating with degenerative processes associated with the thrombus build-up stage.

Methods: We retrospectively analyzed pump motor power consumption (PMPC) in 17 HVAD patients who suffered pump thrombosis over 30 days before clinical manifestation of the thrombotic event. PMPC data were downloaded from the HVAD controller. Time-frequency analysis was run via custom made and in-built IgorPro6 (Wavemetrics®) procedures to evaluate circadian variation (CV) of the PMPC. Time series were processed by Wavelet decomposition (Morlet mother wavelet, scale range: $5x10^{-6}$ - $5.5x10^{-4}$ Hz). CV was detected as power (magnitude square) in the wavelength time-frequency domain concentrated in the band $1.16\pm0.3x10^{-5}$ Hz. CV was defined as prevalent at a specific time point if power in the circadian band was greater than 50% of the total signal power (subtract by its DC component) for at least 5 days in a row.

Results: We detected loss/instability of CV of the PMPC 13±7 (mean±SD) days before clinical manifestation of the thrombotic event in 82% of the patients.

Discussion: Monitoring of CV of the PMPC might serve as an effective prognostic marker of pump thrombosis. This study opens the perspective for the development of a dedicated processing unit for real-time analysis of CV of the PMPC with ad-hoc alarm system. Such a system might be integrated on-board of the HVAD controller to advance prompt diagnosis and medical management of pump thrombosis.

O141

STANDARDIZED MECHANICAL CIRCUALTORY SUPPORT GUIDELINES: THE COORDINATORS PERSPECTIVE

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Introduction: Mechanical Circulatory Support (MCS) therapy's success has given rise to an increase in number of MCS Programs; thus variation in the care of MCS

patients exists. While consensus statements on the delivery of care exists, few resources are available in discussing widely accepted guidelines. This study attempted to gauge the interest of MCS Coordinators in the US regarding the development of standardized guidelines for clinical decision making and therapy advancement.

Methods: A 10-question survey was created to establish interest in the development of standardized guidelines for two separate series of topics, clinical practice and job responsibilities. Participants consisted of members of a VAD Coordinator profession online discussion board.

Results: 54 MCS Coordinators submitted; responses with 94.44% (51) respondents favorable to the development of standardized guidelines in that it would be beneficial to their practice, 38.89% (21) said they would adapt them to their current practice and another 53.70% (29) said they would use the guidelines to develop their programs' policies and procedures. Topics of most interest by participants were related to driveline management 81.13% (43), patient selection 73.58% (39), community education 75% (39), MCS staffing ratios, and Job responsibilities each with 65.38% (39) and deliverance of patient education 65.38% (34).

Discussion: MCS therapy has rapidly grown in popularity, thus, standardized guidelines are necessary to mainstream uniformity while allowing for individual selection factors for MCS implanting centers. This study demonstrated that MCS Coordinators would favor standardized guidelines to assist in the management of common issues that are faced. Professional organizations can act as a catalyst for this development by connecting clinicians, engineers, and industry members together for the advancement of MCS therapy.

O142

BERLIN HEART EXCOR AND HEART TRANSPLANT: A SUCCESSFUL ASSOCIATION

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Objectives: We describe our experience with the Berlin Heart Excor (BHE) as a brigde-to-transplant therapy. BHE is a mid-term ventricular assist device for both right and left support. Used as a bridge-to-transplant strategy, it allows to optimize the patient condition.

Methods: Since 2005 16 BHE were implanted. 14 patients were male and the median age was 59.5 years-old. 8 were for left support (L-VAD) and 8 for biventricular support (Bi-VAD). In 7 patients the underlying pathology was non-ischemic dilated myocardiopathy, in 6 was ischemic dilated myocardiopathy, in 2 was acute myocardial infarction and in 1 was graft vascular disease. In 10 patients the transplant was contraindicated due to high pulmonary vascular resistance and the device was implanted for reversing it. 1 patient was at the INTERMACS 1 level, 10 patients at the INTERMACS 2 and 5 patients at the INTERMACS 3.

Results: The 30-day survival was 81.6% (13 patients). The median time of assistance was 95 days. The most important complications were: major bleeding (68.6%), kidney failure (56.3%), hepatic failure (50%), stroke (43.8%), cannula site infection (31.3%) and aseptic sternal dehiscence (11.1%). 11 patients reach the transplant (6 L-VAD and 5 Bi-VAD), with 2 deaths due to septic shock, 2 deaths due to intracranial hemorrhage and 1 death due to multiorgan failure related to post-operative bleeding. 10 of the 11 patients transplanted were discharged home, with only 1 death, in the L-VAD group, because of a septic shock from a mediastinitis. All the patients with pulmonary hypertension as the indication for the device implantation who reach the transplant were discharged home. 2 patients died in the follow up due to non-cardiac causes (urinary sepsis and cancer).

Discussion: Even though the high risk and the technical difficulties of transplants in patients with BHE, results are encouraging both in the uni and biventricular support.

O143

RELATIONAL CHARACTERISTICS BETWEEN INTERVAL VENTRICULAR ASSIST DEVICE SPEEDS AND ADVERSE EVENTS, LENGTH OF STAY AND 30-DAY READMISSIONS: A DUAL CENTER EXPERIENCE

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Objective: Ventricular Assist Device therapy (VAD) has been a treatment option for Advanced Heart Failure. This study examined the relationships of interval VAD speeds, Adverse Events (AE), Length of Stay (LOS) and 30-day Readmissions (RE).

Methods: Two VAD implanting centers retrospectively analyzed 151 patients (n=117 males, or 77%) from 9/2012 through 8/2017 compared group differences in interval VAD speeds, LOS, AE and 30-day RE. Patients were supported with either the Heart Mate II (HMII n=111) or

Heartware (HVAD n=40) device. Independent Samples T-Test was used for statistical analysis.

Results: Thirty day RE were found in 23% of implants [HMII n=26; HVAD n=10]. No differences were found in 30-day RE, Bleeding or Infection to either speed sets [(t(144)=-0.07; p=0.947) and (t(144)=-0.14; p=0.889); (t(149)=1.64; p=0.104) and (t(149)=1.62; p=0.108); and (t(149)=0.05; p=0.963) and (t(149)=-0.03; p=0.977)]. However, statistical significance in Clotting was found with both speed sets [(t(144.43=7.20; p=0.000) and (t(148.02)=7.76; p=0.000)]. HMII 30-day RE had longer LOS [(Mean=28.73 +/- 21.09 days); (t(109)=2.27; p=0.025)] with higher DC speed association to post-operative bleeding [(Mean=9174.36 +/- 243.57 revolutions per minute (rpm)); (t(93)=2.09; p=0.039)].

Discussion: This is the first study comparing VAD speed sets, AE, LOS and 30-day RE. Both speed sets found to have no bearings on 30-day RE, LOS, Bleeding or infection, yet did affect Clotting. LOS statistically affected 30day RE. Further multi-center studies are warranted to look at these relationships closer.

O144

PUMP THROMBOSIS AND INTRAVENTRICULAR LVAD CANNULA POSITIONING

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Introduction: Malpositioning of Left Ventricular Assist Devices (LVADs) is an important risk factor for pump thrombosis caused by disturbed inflow conditions and intraventricular flow patterns. Routinely acquired computer tomography (CT) and X-Ray data can be used to define pump position parameters and to find correlations to pump thrombosis.

Methods: Retrospectively patients implanted with a Heartmate II or HVAD (n=115) were analyzed. A pump thrombosis group (PT) and a propensity-score-matched control group (NT) assigned. The position of the inflow cannula was analyzed in X-Ray and CT-scan data sets. Parameters defining the inflow cannula (IC) were defined in respect to cardiac landmarks. In CT data a short axis and three-chamber view was reconstructed and the IC direction deviation to the apex-to-mitral axis measured.

Results: In the patient cohort 15 patients (age: 60.3±8.1 y, male n=13, HMII/HVAD n=7/8, BMI: 26.6 kg/m^2) experiences a pump thrombus. In the CT short-axis view a shorter distance of the IC to the ventricular wall was measured in the PT-group for both pump types. (0.8±0.8 vs. 1.2±0.5cm; p=0.03). Further a larger deviation of the inflow orientation from the mitral valve was found in the PT group was compared to NT patients (angle α: PT -22.0±4.7° vs. NT -1.2±7.5°; p= 0.006). For the HVAD in frontal X-Rays the projected pump area correlated well with this angle (ρ =-0.922; p=0.003) and the short pump diameter was significantly different in the groups (PT 41.3±4.8 mm vs NT 34.9±6.0 mm, p=0.026). In the lateral view for the PT group the areas of the pump body were smaller (PT 2006±77 mm² vs NT 2138±132 mm², p=0.042).

Conclusion: Risk parameters from both X-Rays and CT data were identified that contain information about a possible malposition of the pump that could lead to pump thrombosis. A more frontal posterior inclination of the HVAD pump might imposes some risk of pump thrombosis.

SESSION FD4: VADS: CLINICAL II

O145

MCS/VAD TECHNOLOGY: ACUTE AND INTENSIVE CARE NURSE'S ATTITUDES AND KNOWLEDGE

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Objectives: The care of patients requiring mechanical circulatory support (MCS) by ventricular assist device (VAD) therapy is challenging and complex. Existing research of nursing knowledge and skills of MCS patient care management has focused on advanced practice nurses and VAD coordinators but not the bedside nurses. The purpose of this study was to explore factors that influence competencies among intensive care unit (ICU) and progressive care unit (PCU) nurses that deliver direct care to hospitalized patients with VADs.

Methods: An exploratory, cross-sectional design was carried out over a 6-month period using convenience sampling. Inclusion criteria consisted of full-time ICU or PCU RNs (i.e. staff, preceptor, or charge RNs) with direct patient care responsibilities for VAD patients. Data were collected by using an online survey to various professional organizations where the VAD nurses were known to be members. Study participants completed demographics and work-related questionnaire as well as the diffusion of

MCS innovation in Nursing Appraisal Scale. Data were analyzed with SPSS 22.0 software.

Results: Bedside nurses reported a high level of knowledge about the use of VAD technology with a greater general knowledge noted to be among ICU nurses as compared to non-ICU nurses. A greater rate of adoption of VAD use was noted among ICU nurses. To acquire VAD competency, the nurse most often communicated with the VAD team and VAD experts. ICU nurses were most apt to subscribe to professional journal and seek information regarding VAD care.

Conclusion: The results indicate a need to perform more research on this population to explore the relationship between various aspects pertaining to the bedside nurses and VAD outcomes. These results only affirm that those that deliver hands-on care should be included in education and collaboration of a dynamic feedback.

O146

DESENSITIZATION PRIOR TO HEART TRANSPLANTATION IN PATIENTS ON VENTRICULAR

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Objectives: Temporary use of left ventricular assist devices (LVAD) as bridge-to-transplant has been associated with formation of antibodies directed against human leukocyte antigens (HLA). We present two cases of successful desensitization. Both patients were on biventricular assist devices and on the urgent transplant waitlist.

Methods: The first patient had a history of antraciclin-related dilated cardiomyopathy and severe heart failure. We implanted a **biventricular Berlin Heart Excor** as bridge-to-transplant until VHC infection was resolved. Meanwhile, the patient developed HLA-allosensitization. Desensitization was performed through plasmapheresis, gamma globulins and rituximab, reaching a successful reduction of the antibody count. The patient was then listed for urgent transplantation. Global donors were potentially accepted without preoperatory crossmatch needed.

The second case was a previously seronegative patient. She presented a postcardiotomy biventrivular failure and an **ECMO** was implanted. Later on, the mechanical assist device was changed for a biventricular centrifugal **Centrimag**. During this process, she presented sensitization with a PRA of 57% and high count of antibodies. After desensitization was performed through plasmapheresis and gamma globulins, the antibody count diminished, but didn't negativize. Thus, compatible virtual Crossmatch was needed preoperatively.

Results: The first patient was successfully transplanted and had a satisfying postoperatory evolution. At this moment, eight biopsies have already been performed and yet only a 1A-1R cellular rejection has been described.

The second patient has also had a satisfactory transplant and postoperatory evolution with a 1A-1R cellular rejection on biopsies.

Discussion: The rise in the use of LVADs is increasing the prevalence of previously sensitized patients who are on the urgent transplantation list. Therefore, desensitization strategies become very important and should always be individualized. Likewise, sensitization may justify urgent transplantation list inclusions.

O147

AORTIC VALVE REPLACEMENT TECHNIQUES DURING SIMULTANEOUS LEFT VENTRICULAR ASSIST DEVICE IMPLANTATION: CONSIDERATION OF A NEW OPTION

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Objective: Aortic Stenosis (AS) and Aortic Insufficiency (AI) found together prior to Ventricular Assist Device (VAD) Implantation poses a surgical conundrum. It's imperative to create a plan to decrease post-operative risk and improve outcomes. No literature exists addressing combination AS/AI in this population.

Methods: Retrospective data was gathered on VAD implants in our center, between 9/2012 and 2/2018 (n=41, 31 males). Four males required plans for AV disease during implantation of the VAD. Median age at the time of concomitant surgeries was 71.5 years (ranging between 63 to 77). Three patients had non-ischemic cardiomyopathy (CM) and one with mixed CM.

Results: One patient (Pt) with Moderate (Mod) AI and another with Severe AS/Mod AI, both underwent AV Replacements (AVR) prior to VAD implant utilizing 25 and 27 mm aortic valves (AV). Another Pt with Mod AI, had unsuccessful interventions to the AV including a Park stitch, pericardial patching and AV closure. The last Pt with Severe AS/Mild to Mod AI underwent Rapid Deployment Aortic Valve Replacement (RDAVR)

immediately prior to VAD implantation, a first in its kind. Mean Cardiopulmonary Bypass time (CPBT) in the AVR group: 179 minutes (mins) and mean Cross Clamp Time (XCT): 76.5 mins. CPBT in the multiple interventions Pt: 346 mins with XCT of 131 mins. CPBT in the RDAVR Pt: 119 mins with XCT of 35 mins. Right Heart Failure and Mortality occurred in the Pt who underwent multiple interventions, (25%; n=1). Device days ranged from 8 to 1291 days.

Discussion: AV disease is uncommon yet requires a surgical plan at VAD implantation. The RDAVR technique is a viable option for combination AS/AI to decrease XCT, CPBT and AE. Further research is needed for applicability to larger populations as another possible surgical option.

O148

OUTFLOW GRAFT OBSTRUCTION IN CENTRIFUGAL CONTINUOUS FLOW VADS (CCFVAD) – DETECTION, TREATMENT AND POSSIBLE CAUSES

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System thrombosis is a known complication during VAD support. In contrast to pump thrombosis outflow graft thrombosis is usually an evolving process. Diagnosis of thrombosis or other kinds of obstruction (kinking, twisting) is complex because similar flow change patterns result from decreasing viscosity or right heart failure.

Objectives: In Aug2014 to Feb2018 476 patients received implantation of cCFVAD systems (347 HVAD, 124 HM3). Together with ongoing patients earlier implanted, an average of 243 patients were on support in this period (195 HVAD, 48 HM3, mean support 679 days). There were 39 cases (33 HVAD, 6 HM3) of outflow graft obstruction (OGO).

Methods: Presence of OGO can be assumed if progressive flow depletion is accompanied by decreasing pulsatility of pump flow in contrast to high blood pressure pulsatility. Usually aortic valve opens regularly and LVEDD is increased.

To verify OGO angioCT is routinely used for localization of the bottleneck. Interpretation may be difficult due to metal artifacts. Final assessment has to be by angiography. A pressure gradient indicates the position of the obstruction. The shape of the contrasted area reveals the type of obstruction.

Results: Reasons for obstruction with HVAD were graft-thrombosis (n=13, .012EPPY), obstruction by accumulated material between GoreTex graft implanted additionally around the bend-relief and outflow graft (n=17, .015EPPY) or kinking (n=3, .003EPPY) treated by stenting. Rare graft twisting or protector mobilization (n=6, .038EPPY) occurred only with HM3, requiring surgical correction. HM3 obstruction by accumulated material between bend relief and graft n=1.

Discussion: Circumstances promoting thrombosis inside or around the outflow graft are not completely understood. Lysis therapy in the case of pump thrombosis seems to carry the risk of unexpected OGO by mobilization of neo intimal lining inside the outflow graft. Diagnosis of graft thrombosis implies carotid protection while stenting.

O149

WEANING IN CHILDREN WITH LEFT VENTRICULAR ASSIST DEVICE SUPPORT: A SINGLE CENTER EXPERIENCE

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Recent adult studies have shown the possibility of Heart recovery in LVAD patients. We reviewed our experience in LVAD children selected for weaning.

Outcomes and serial echocardiographic data were reviewed in 31 LVAD children (2007-2018) including: Left ventricular ejection fraction (LVEF), LV end-diastolic and end-systolic diameters (LVEDD, LVESD), global LV longitudinal strain (GLS), right ventricular fractional area change (RVFAC), TAPSE, grade of mitral regurgitation. Patients were considered for the off pump test for weaning if LVEF≥45%.

Four (13%) children were eligible for LVAD weaning. Median age was 31 months (IQR 27.5-54.75), median weight was 14.1 kg (IQR 11.75-15.9), with a median duration of support of 188.5 days (IQR 130.5-231.5). Myocardial biopsies and virus assessments excluded myocarditis in all four, with three of them confirming a genetic diagnosis. Patient 1: had a 25cc Berlin Heart (BH) and underwent an off-pump test during right heart catheterization but failed because of worsening of LVEF and hypotension during the test. After 210 days of LVAD support, he underwent heart transplantion. Patient 2: after 21 days of support this patient was successfully weaned with a LVEF of 50%, a GLS of -20%, a RVFAC of 49% and a RVFWLS of -25.9%. All these

parameters remained stable at seven months follow-up. Patient 3: after 296 days of support with a 15cc BH the LVAD was explanted, but he died due to neurological complications. Patient 4: after an off-pump trial and cardiac catheterization, the patient underwent was weaned for 6 days only, then required a new LVAD support and is still on support.

Recovery in LVAD children is possible with potentially a greater capacity of reverse remodeling, even though the reported rate of cardiac recovery is very low. It remains difficult to characterize patients who may have the potential for optimal and stable cardiac recovery.

O150

INTRAOPERATIVE AUTOLOGOUS BLOOD PREDONATION BEFORE CPB FOR PREVENTION OF BLEEDING INDUCED BY CPB BLOOD INJURY IN CASES WITH PREOPERATIVE ANEMIA

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Objectives: During CPB, blood injury is induced by hemodilution, the contact with the device itself and etc. only to increase bleeding in need of blood transfusion. Though homologous blood transfusion might be effective for uneventful postoperative course, some complications may have been reported. On the contrary, intraoperative autologous blood predonation could possibly be performed in elective CPB operations.

Methods: We analyzed the major factors of homologous blood transfusion in the 25 consecutive cases, with intraoperative autologous blood predonation except those with concomitant preoperative autologous blood donation, out of consecutive 350 elective valvular heart operations without concomitant procedures.

Results: Based on the criteria of blood transfusion, homologous blood was not transfused in 18 cases, but was in 7 cases only after CPB. The homologous transfusion was not correlated with body weight, CPB dilution or duration, or preoperative hematocrit level, but was found to correlate with age (r^2=0.28, p=0.04), bleeding output (r^2=0.19, p=0.04), and predonation blood volume (r^2=0.43, p=0.01).

Discussion: Even in cases with difficulty in preoperative blood donation, suitably much intraoperative blood predonation may reduce the necessity for homologous blood transfusion in CPB operations, which could preserve coagulation factors enough for hemostasis.

SESSION SA1: WORKING GROUP HEART: DEBATE SESSION – VADS, THE HOLY GRAIL FOR HEART FAILURE TREATMENT?

O151(IL)

SHOULD / WILL MECHANICAL SUPPORT RENDER HEART TRANSPLANT A TREATMENT OF THE THE PAST? CON

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Introduction: Patients with advanced heart failure seem to do better treated with heart transplants. However the scarcity of donors, long waiting times, and an increasing number of unstable patients have favored the development of mechanical circulatory support. ¡

Methods: We reviewed our series of heart transplants and compared life expectancy and long-term adverse events with published data about destination therapy (DT).

Results: From August 1988 to April-2018 571 heart transplants were performed in our center. 44% of them were previously heart operated. Mortality was globally 45.4% after a mean follow-up of 7 years,. In-hospital mortality was 16.5% If we focus on the last 10 years, survival is: 79% at 1 year and 73.3% at 5 y. Global mortality due to graft rejection was observed in 6.7% of the cases. Besides rejection, tumours were another important source of complications with a global number of 87 cases (87/571). Neurological incidence was 0.027 cases/patient-year and infections incidence 0.21 cases/patient-year. Dyalisis was definite in 1.7% of the patients.

One-year survival is 75% in DT but these results drop to 50% if a right ventricular device is needed. Right ventricular failure and infections account for 20% each. Thrombosis is slightly decreasing with the new devices but certainly the Acheeles'heel is bleeding, as 81% of patients under DT are exposed to major bleeding. Neurological issues are one of the main causes of death as well.

Finally, regarding quality of life, 90% of transplanted heart patients are independent whereas 40% of DT patients have serious limitations in their routines according to INTERMACS data.

Conclusions: According to the decreasing but still high number of complications related to VAD mechanical devices, heart transplant still seems to be the best option for these patients.

O152(IL)

SHOULD / WILL MECHANICAL SUPPORT RENDER HEART TRANSPLANT A TREATMENT OF THE PAST? PRO

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Introduction: as of today, heart failure patients that are transplanted appear to have generally better outcomes than patients that receive long term mechanical circulatory support (MCS). However, MCS technology and patient management are advancing, and outcomes are improving, so the question that will be debated is: will the outcomes from MCS match or better those of transplantation at some point in the near future?

Discussion: MCS has evolved through multiple generations: first generation pulsatile devices; second generation continuous flow devices with mechanical bearings; and third generation fully levitated devices. Alongside this, alternative MCS approaches have been developed that do not contact the blood and in development are pumps with novel flow mechanisms that aim to reduce blood trauma.

Through these successive generations survival rates have improved from less than 20% at 2 years to 83% which is on par with transplantation. Adverse event (AE) rates are improving but remain high. Interestingly, the profile of the AEs has changed as the technology has changed providing insights into both the root causes and potential solutions. Further technical improvements that address these AEs appear feasible.

Management is also a significant factor, with results for the same device varying significantly both temporally and between centres. Device peripherals and control algorithms have a role to play here, with innovations such as TETS, remote monitoring and smart pump control potentially improving device management for both patients and clinicians.

Surgical implantation of devices is already significantly less traumatic than heart transplantation and will become even less so in the future.

In summary it is feasible that devices will soon be able to match outcomes of transplantation with less invasive procedures, however, MCS devices for the foreseeable future will still require peripheral equipment that is ultimately less convenient for the patient than a transplanted heart.

O153(IL)

IMPROVING CLINICAL OUTCOMES FOR HEART FAILURE PATIENTS

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Objectives: 2-year survival of patients with a left ventricular assist device (LVAD) increased up to 80% in the last decades. However, despite clinical advancements and novel devices, adverse event rates impair the success of the therapy. These adverse events may be related to shortcomings in terms of pharmacologic treatment and/or stirred by the non-physiological flow patterns and the interaction between artificial substrates and blood in rotary pumps.

Methods: Based on a literature review, problems of LVAD therapy from the clinical and engineering point of view will be highlighted. Shortcomings of the clinical therapy, patient management and the interaction between the pump and blood as well as the cardiovascular system will be derived. Novel concepts and approaches will be discussed with the potential to improve therapy with mechanical circulatory support.

Results: Although the ISHLT has broad guidelines for the outpatient care of patients on mechanical circulatory support – LVAD patient selection, intraoperative and postoperative management strategies still vary significantly from center to center, thus representing a major influence factor in outcomes. Previous studies of VAD patient care have suggested the evaluation of patient factors, strict hypertension management, frequent monitoring of the driveline exit site for signs of infection and anticoagulation quality by point-of-care INR monitoring to reduce adverse events in LVAD therapy.

Newest LVAD technology indicates benefits in terms of thrombus formation, however, disabling strokes and bleeding complications remain a major problem. To further improve clinical outcomes breakthroughs in terms of material science, automated pump adaptation, remote monitoring and pump design or even alternative pumping principles may be required.

Discussion: Better patient management, including strict adherence to guidelines with currently used pumps and the implementation of novel technologies indicate potential to substantially improve treatment with mechanical circulatory support towards an alternative to heart transplantation.

SESSION SA2: NUMERICAL SIMULATION: VADS AND HEARTS - SPECIAL PROBLEMS

O154

CAN WE USE THE NEW INFANT JARVIK 2015 IN PATIENTS LESS THAN 8KG? A SIMULATION STUDY

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Objective: The objective of this work is to study test the feasibility of implanting the Infant Jarvik 2015 in patients lower than 8kg.

Methods: The Infant Jarvik 2015 LVAD was tested in a hybrid simulator of the cardiovascular system reproducing specific patients haemodynamic for different patients weight (2-8kg). For each weight, we tested the sensitivity of the pump to different circulatory parameters (pheripheral resistance, left ventricular elastance, right ventricular elastance, heart rate and heart filling characteristics) repeating for each experiment a pump ramp (10000-18000rpm).

Results: The increment of the pump speed causes a decrement (increment) of the left (right) atrial pressure, an increment (decrement) of the arterial systemic (pulmonary) pressure, an increment of the right ventricular pressure, a decrement (increment) of the left (right) ventricular volume, a decrement of the left ventricular cardiac output, an increment of the LVAD output and an increment of the right ventricular cardiac output (total cardiac output).

Suction was observed for lower weight patients and for higher pump speed in the case of vasodilation, left ventricular recovery, bradycardia, right ventricular failure and left ventricular hypertrophy, while backflow was observed only in the case of left ventricular recovery at lower pump speed.

Conclusions: the use of a hybrid circulatory model permits to test the use of innovative VAD in extreme condition and the sensitivity of the pump to different circulatory parameters. The simulator could be a valid alternative to animal experiments especially in extreme conditions. In this specific application, we verified that the Infant Jarvik 2015 could be suitable for the implantation in patients lower than 8Kg because of the stability of the device respect to the cardiocirculatory changes in terms of low frequency of suction and backflow phenomena and because of the capability of the device in maintaining an adequate patients haemodynamics.

O155

THE RESPONSE OF DIFFERENT VAD PRESSURE SENSITIVITY TO EXERCISE PHYSIOLOGY: EVALUATION WITH A COMPUTATIONAL MODEL

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Objectives: Continuous-flow VADs have proven to restore patients' hemodynamics at rest condition but their capability to properly support hemodynamics during exercise is an open question. It is known that hemodynamics change dramatically during exercise, thus changing the working condition of the VAD itself. Aim of this work is to investigate which type of VAD pressure-flow characteristics better responds to these changes.

Methods: A computational cardiorespiratory simulator was used to reproduce the exercise hemodynamics in heart failure condition. Two VADs were connected and tested: VAD1 with a pressure sensitivity (PS: average change of flow per change of pressure difference) of 0.21l/min/mmHg and VAD2 with a PS of 0.08l/min/mmHg up to 10l/min mean flow. For each VAD the basal speed was set at rest to assure a full support of 4.5l/min. Then a bicycle exercise of 80Watts was simulated and the cardiorespiratory system was left evolve to a steady condition.

Results: Exercise induces changes in the cardiovascular system that in turn affect the pressure drop across the VAD so that pump flow increases. But for VAD1 flow increases more (from 4.5 to 6.6l/min) than for VAD2 (from 4.5 to 5.7l/min). VAD1 better unloads the left ventricle (ventricular flow 1.0l/min with VAD1 and 1.8l/min with VAD2) and reduces left atrial pressure (20mmHg with VAD1 and 21mmHg with VAD2). VAD1 has positive effects on energetic parameters: left ventricular power increase is +150% with VAD1 and +240% with VAD2.

Conclusions: A VAD with higher PS can better sustain exercise physiology. This is a desirable feature especially for patients with a poor residual left ventricular function, for whom the increase of cardiac output at exercise mainly depends on the VAD flow increase itself.

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O156

CONGENITAL ANATOMICAL ANOMALIES AND THEIR INFLUENCE ON THE BLOOD FLOW HYDRODYNAMICS – COMPUTATIONAL FLUID DYNAMICS (CFD) INVESTIGATIONS

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Objectives: The primary objective of this research was to analyze the impact of the congenital cardiovascular anatomical anomalies on the blood flow determined by means of the numerical analysis (CFD). The investigated patient-specific anomalies included fenestrations and segmental duplication of the aorta with a lack of the brachiocephalic artery. Since

some fenestration types are claimed to be a reason of the aneurysm formation, it was decided to verify such an assumption by analyzing their impact on the flow velocity, vorticity, intensity and wall shear stress distribution.

Methods: Several patient-specific arterial models were reconstructed basing on the DICOM image sets deriving from the angiographic Computed Tomography examinations. The major part of the reconstruction process was performed in the SolidWorks software. Ansys Mesher was used to generate the volumetric meshes with prism elements embedded in the inflation layer. The transient numerical analyses (Ansys CFX) enabled simulation of 5 full cardiac cycles, where the time-variant boundary conditions were taken from the literature.

Results: It was proven that depending on the anatomical anomaly location, the blood flow is altered in a specific manner. For instance, elevated wall shear stress in the vicinity of the basilar artery fenestration indicates that this anomaly might be a possible reason of the aneurysm formation. Similar phenomenon could be observed for the segmental aorta duplication. The left vertebral artery fenestration did not lead to nonphysiological flow parameters.

Discussion: The elevated levels of shear stresses near fenestrations prove that those anomalies cannot be neglected during the vascular treatment planning. Due to rarity of those anomalies, it is impossible to gather unambiguous empirical material for the statistical risk analysis by clinical trials. Since the numerical analyses results are in conformity with the data found in literature, it was proven that CFD can serve as reliable source of information.

O157

NON-INVASIVE CARDIAC STRESS TESTS: A 0D MODELLING APPROACH

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Objectives: Cardiac stress testing is a major diagnostic tool in evaluation of heart disease. A variety of methods exist including dynamic and isometric exercise or pharmacological stress testing. These tests are used to assess changes in haemodynamic parameters and to unmask possible symptoms under non-resting conditions.

However, there are many contra-indications for stress tests including acute myocardial infarction within 48 hours, unstable angina, severe symptomatic aortic stenosis and others. Furthermore stress tests are often invasive, like for example a catheter-based pressure drop measurement. The goal of this study was the development of a numerical model predicting hemodynamic conditions under stress only from hemodynamics at rest.

We are presenting a non-invasive cardiac stress test for patients with congenital heart disease like coarctation of the aorta or with acquired valve disease like the aortic valve stenosis.

Methods: The non-invasive cardiac stress test models the change in heart physiology and the change in pressure drop under stress conditions. The assumed change in heart physiology is based on a quantitative systematic literature review including 87 studies with a total of 2740 subjects.

The normalized pressure drop at stress is calculated according to a polynomial relationship between the normalized pressure drop and the normalized peak systole flow rate. The polynomial coefficients are based on a set of 88 pressure drops simulated at different flow rates using CFD.

Results: The model was implemented in python as a stand-alone tool with user-interface. Six different stress conditions including dynamic exercise and pharmacological stress, each with three stress levels were realized within the software.

Discussion: A test with seven patient-data-sets showed promising results. After the validation with a larger patient cohort the model can possibly replace invasive clinical routines like catheter-based pressure drop measurements under stress.

O158

INFLUENCE OF THE REMAINING HEART ACTIVITY ON THE FLOW WITHIN A VENTRICULAR ASSIST DEVICE: A COMPUTATIONAL STUDY

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Objective: Computational Fluid Dynamics (CFD) is a common-used tool to evaluate the biocompatibility of Ventricular Assist Device (VAD). The operation point of the device is mostly treated steady when simulating the flow. But, many VAD patients have a remaining heart activity, which results in a pulsatile inflow condition for the VAD. We want to show the influence of this condition on the developing flow.

Methods: We carried out a Large-Eddy Simulation (LES) with a pulsatile boundary condition. An intraoperatively recorded flow rate from a heart failure patient was used to simulate the flow within our axial continuous-flow VAD. The pulse waveform ranges from (3.6…7.6)*l*/*min* and one second of flow was simulated with a rotational speed of the rotor of 7900 rpm.

Results: The *h-q*-curve shows a hysteresis loop, which leads to a significantly higher pressure head at the same flow rate and decreasing pulse amplitude. Same results holds for the hydraulic efficiency. The turbulent kinetic energy (TKE) is much higher during the entire systole, but composes itself as quickly as the volumetric flow rate at diastole. In the gap vortex region, the TKE increases after systole and remains on a very high level. A transport equation for the hemolysis index was calculated to estimate the blood damage while pulsatile flow. With increasing flow rate, the production of hemolysis decreases down to a minimum, from where it then rapidly increases until peak of systole with a reversed progression afterwards.

Conclusion: The results show a significant impact of the pulsatile boundary condition on turbulent flow features, which are influencing the blood damage prediction. The hydraulic characteristics also behave differently, which cannot be accessed when simulating a stationary operation point. We conclude, that these effects should not be neglected, while VAD designing and blood damage prediction.

O159

PULSATILE FLOW IN VADS: CFD ANALYSIS OF VELOCITY FIELDS AROUND THE PRESSURE- FLOW LOOP

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Objectives: VADs are commonly designed in steady state for either a specific operating point, or a specific gradient of the pressure-flow curve. However, due to the heartbeat, which is still apparent even with severe heart failure, the flow through a VAD is pulsatile. The pulsatile flow means that over a cardiac cycle the VAD experiences a range of flow rates, and so also the pressure varies. However, due to inertia of the blood the pressure-flow relationship does not follow the steady state curve but rather forms a closed loop. The aim of this study was to investigate the velocity field within the VAD during pulsatile flow.

Methods: Computational Fluid Dynamics was used to calculate the flow within two popular VADs: the HeartMate II and the HVAD. In order to calculate the unsteady flow it was necessary to simulate at least two cardiac cycles and therefor a relatively large timestep was used: 0.001 s. This is too large for studying the rotor-stator interaction and therefore the frozen rotor method was used to approximate the rotation of the impeller.

Results: The transient simulation results revealed large differences in the pressure fields but smaller differences in velocity fields. These velocity field differences included variations in the size of recirculation zones, such as those in the diffuser region of the HMII, throughout the cardiac cycle.

Discussion: These preliminary results suggest that although, with pulsatile flow, any given flow rate has two different pressure heads, depending on whether the flow is accelerating or decelerating, there is very little difference in the velocity field between the two. This implies steady state calculations may well be sufficient for VAD design optimisation. That said, the pulsatile flow calculations are likely to be important for more advanced modelling such as washout or blood damage calculations.

SESSION SB1:BONE REGENERATION

O160

INJECTABLE CHITOSAN-HYDROXYAPATITE HYDROGELS PROMOTE THE OSTEOGENIC DIFFERENTIATION OF MESENCHYMAL STEM CELLS

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Objectives: A new generation of materials for bone tissue regeneration are injectable hydrogels which have the ability to adapt to different shapes of defect. Chitosan-based hydrogels support chondrogenic differentiation of mesenchymal stem cells (MSCs). However, the addition of hydroxyapatite into chitosan matrices stimulates MSCs differentiation into osteoblasts and further formation of new bony tissue.

Methods: The lysozyme-induced degradation of Cht/HAp hydrogel was studied for 28 days at 37 °C by monitoring swelling behaviour, dry weight loss, molecular weight, polydispersity index and microstructure. The osteogenic differentiation of encapsulated MSCs was evaluated by immunofluorescent imaging of osteogenic markers Runx2, collagen type I (COLL I), osteocalcin (OCN), and by colorimetric quantification of alkaline phosphatase activity (ALP). The deposition of late osteogenic markers (calcium phosphates) was detected by Alizarin red and Von Kossa staining.

Results: It was found that Cht/HAp hydrogel is highly stable during 28 days of enzymatic degradation under different lysozyme concentrations (1.5 μg/mL and 500 μg/mL), despite being physically crosslinked. The expression of osteogenic markers (ALP, Runx2, COLL I and OCN) and calcium phosphates deposits were found at 7 and 14 days of cell culture.

Discussion: Hydrogels derived from natural polymers are not often stable under physiological conditions and they undergo rapid degradation. As cell carriers, hydrogels need to be stable during cell encapsulation and differentiation.

The expression of osteogenic markers found at 7 and 14 days of cell culture suggested good osteogenic potential of prepared Cht/HAp hydrogel. The deposition of calcium phosphates indicates extracellular matrix mineralization. Additionally, MSCs are homogeneously dispersed through entire Cht/HAp hydrogel during cell culture, which is crucial for complete bone healing. Obtained results could indicate the potential of Cht/HAp hydrogel to be used as a stable three-dimensional carrier for MSCs proliferation and differentiation into osteoblastic cell line.

O161

SCAFFOLDS FOR BONE REGENERATION

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Objectives: Mesoporous bioactive glasses (MBGs) are a new family of bioceramics intended for bone tissue regeneration purposes. The aim of this work is to study the capability of macroporous scaffolds made of MBGs for regenerative purposes in a model that mimics osteoporosis. To evaluate the potential effects of antiresorptive drugs locally delivered, zoledronic acid (ZOL) was loaded within the scaffolds and their effects compared with drug free implants.

Methods: MBGs cylindrical macroporous scaffolds with and without ZOL were manufactured by robocasting. The *in vitro* behavior was evaluated with osteoblasts and osteoclasts. Six 4-year-old female Merino sheep were included in the study. Six months before the implantation all sheep underwent a laparoscopic bilateral ovariectomy, as well as low-calcium diet and corticosteroids administration until the end of the study. Cylindrical critical size defects (8x13mm) were created in each sheep by drilling the cancellous bone and the scaffolds were implanted by press fitting. The bone samples containing the implants were harvested 12 weeks after the implantation and histologically analyzed.

Results and Discussion: MBG scaffolds without ZOL evidenced an excellent *in vitro* biocompatibility with osteoblasts and osteoclasts. On the contrary, scaffolds containing ZOL induced a significant decrease of osteoblast proliferation, partial inhibition of osteoclastogenesis and decrease of resorptive capability of differentiated osteoclasts. These results were confirmed by the *in vivo* studies. Despite of the osteoporotic scenario, MBGs scaffolds without ZOL stimulated the bone ingrowth with a high presence of osteoblastic border and trabeculae of 0.3 mm in thickness. On the contrary, ZOL loaded scaffolds resulted in a very poor bone ingrowth, trabeculae of lower quality (0.11 mm thickness) and high presence of inflammatory infiltration. These results evidence the high potential of MBG scaffolds but also the deleterious effect of the local administration of zoledronic acid for bone regeneration purposes in an osteoporosis scenario.

O162

AN INNOVATIVE BIOGLASS COMPOSITION:BM-MSCS INDUCTION TOWARD THE OSTEOGENIC LINEAGE

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Objectives: The development of biocompatible scaffolds in bone tissue engineering is a growing field. Bioactive glasses have gained great importance for their ability to enhance osteogenesis thanks to the release of specific ions during their degradation. Here we proposed an innovative bioglass (BGMS10), designed to combine a low tendency to crystallize to high bioactivity, osteoconductivity and osteoinductivity. In this context, a cellular model based on human bone marrow-derived stem cells (BM-MSCs) was used to evaluate the osteoconductivity and osteoinductivity of BGMS10.

Methods: BGMS10, a glass belonging to the Na_2O-K_2O-CaO-MgO-SrO-P_2O_5-SiO_2 system, was produced by a melt-quenching route [1] and sieved to obtain granules (grain size 250 μm<x<500 μm). BM-MSCs, isolated from 3 donors, were thawed, expanded and seeded on BGMS10. At each time point (1h, 24h, 3days, 7 and 14 days) Crystal violet staining was performed to investigate BM-MSC colonization. Then, differentiation was induced by specified growth factors; a 2D cell culture served as control. The differentiation potential of MSCs on BGMS10 was evaluated by Alizarin Red S and Masson's trichrome.

Results: Preliminary investigations on BGMS10 demonstrated its ultra-high crystallization temperature (~932 °C) and its bioactivity in a Simulated Body Fluid solution. BM-MSCs adhered to BGMS10, colonized it in 7 days and differentiated after 14 days of induction. The differentiation rate was higher on the glass compared to the 2D control. Also the 3D control, i.e. the BGMS10 with no growth factors, showed a differentiation towards the osteogenic lineage, thus suggesting the possible role of the material in inducing cell differentiation.

Discussion: The cellular model highlighted the osteoconductive ability of the new bioglass. Based on these promising results, it will be interesting to evaluate in an animal model the performance of BGMS10.

O163

LASER WELDING INVESTIGATION OF SUBCHONDRAL BONE AND HYALINE CARTILAGE WITH NANOCOMPOSITE SOLDE

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Objectives: In surgical practice, often there are damages of an hyaline cartilages (HC) on a subchondral bones (SB) in a joints. Laser welding can be used to treat such damages. Welds are tight and small. Laser solders are used to improve a welds tensile strength. To date, about 10 different components are used in laser solders. We propose the laser device and the solder based on bovine serum albumin (BSA), multiwalled nanotrubes (MWCNTs) and indocyanine green (ICG).

Methods: Laser solders based on BSA (25%), MWCNTs (in the range 0.01-1%) and ICG (0.1%) were used for laser welding of HC and SB. Laser radiation was focused in a beam diameter of 1.48 mm. Laser radiation power varied in the range from 0.1 to 5 W. Temperature feedback based on the matrix IR temperature sensor and microcontroller unit was used.

Results: Investigation of the tensile strength of welds showed a significant increase (up to 0,8 MPa) if added MWCNTs to the solder. The solders absorption spectra have been studied. The denaturation temperature of BSA with CNTs in the solder were measured by differential scanning calorimetry (at 55-70 ºC). The 3D structure of the welds has been visualized by optical microscopy.

Discussion: MWCNTs adding to the solder has significantly increased the strength of the weld. Using of ICG, which has an absorption peak in the laser radiation generation region (808 nm), has reduced the radiation absorption by healthy tissues, and hence their overheating. The proposed method of laser welding with the nanocomposite solder and the laser device allows the creation of HC and Sb compounds.

O164

DIELECTRIC PROPERTIES OF POLYCAPROLACTONE-HYDROXYAPATITE/ BARIUM TITANATE NANOCOMPOSITE MEMBRANES

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Objective: The present study aims to examine the dielectric properties of hybrid nanocomposites consisting of polycaprolactone/hydroxyapatite/$BaTiO_3$. The examined system could be exploited as polarized bone substitutes, because of the development of a surface charge distribution.

Materials and Methods: Synthetic Hydroxyapatite was prepared by the aqueous precipitation method. The $BaTiO_3$ nanopowder (with size less than 100nm) and polycaprolactone (PCL) of MW 45000 were purchased by Sigma-Aldrich. The appropriate amounts of HAP and $BaTiO_3$ were mixed in an agate mortar and next were dispersed in a 10 % w/v PCL solution in dichloromethane in a bath sonicator for 30 min. Membranes were prepared using the solvent evaporation method by pouring the PCL/HAP/$BaTiO_3$ suspension into glass Petri dishes. Ten formulations with the filler materials at concentrations of 2, 6, and 10 phr were prepared. The dielectric characterization was performed by means of broadband dielectric spectroscopy in the frequency range 0.1Hz to 10 MHz at constant temperature 37^{o}C.

Results and Discussion: PCL dielectric spectra reveal the presence of at least three relaxation processes attributed to local re-arrangement of polar side groups, glass to rubber transition and interfacial polarization at the interface between hard and soft regions (crystal and amorphous). The addition of HAP and $BaTiO_3$ enhances systems heterogeneity and at the same time increases the real part of dielectric permittivity of the hybrids in the whole frequency range. Relaxation phenomena related to interfacial phenomena shift to lower frequencies. Furthermore, relaxation processes related to HAP are also recorded and assigned to dipolar orientation of hydroxyl groups and defects of hydroxyl ions.

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O165

ANTIBACTERIAL CAPABILITY OF 3D MESO-MACROPOROUS SCAFFOLDS ENRICHED WITH ZINC AND OSTEOSTATIN

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Objectives: Mesoporous Bioactive Glasses (MBG) are widely investigated for bone regeneration [1]. Their biological behavior can be improved by adding Zn^{2+} ions which are bactericide and osteogenic, and osteogenic peptides like osteostatin [2]. This study evaluates the bactericide capacity against *E. coli* and *S. aureus* of three MBG scaffolds: (80-x)%SiO_2-15%CaO-5%P_2O_5-x%ZnO (x= 0, 4, 5). The influence of osteostatin in the bactericide action of the scaffolds was also assessed.

Methods: MBG powders were synthesized by the sol-gel EISA method and conformed into 3D porous scaffolds by rapid prototyping [3]. Scaffolds were coated with 2.4 wt% of gelatin crosslinked with glutaraldehyde and characterized by XRD, FTIR spectroscopy, N_2 adsorption, SEM, EDX and Hg porsimetry. The release of ions from scaffolds to Tod Hewith Broth (THB) medium was measured by ICP. For the bacterial assays, scaffolds were incubated under stirring in THB with 10^6 CFU/mL concentration of *E. coli* and *S. aureus* (37 ºC, pH 7.4).

Results and Discussion: Scaffolds exhibited hierarchical porosity including ordered mesopores (3-4 nm), macropores (1-100 μm) and channels (1 mm). Moreover, MBG exhibited surface areas higher than 240 m^2/g and EDX confirmed ZnO contents close to nominal ones, i.e., 4.2 and 4.8 mol-%. After 4 days the Zn^{2+} concentration in medium was 5.5 ppm (4%ZnO-MBG) and 8 ppm (5%ZnO-MBG). A noticeable bacterial growth inhibition along the first hours in contact with the two Zn-containing scaffolds (with and without osteostatin) was observed showing the potential of these biomaterials for bone tissue engineering.

[1] Salinas et al. J. Non-Cryst. Sol. 2016,432,9

[2] Salinas et al. Biomater. Sci. 2013,1,40

[3] Sanchez-Salcedo et al. J. Mater. Chem. B, 2014,2,4836

SESSION SB2: BONE AND CARTILAGE TISSUE ENGINEERING

O166

EFFECT OF CAPACITIVELY COUPLED ELECTRICAL STIMULATION OVER GROWTH PLATES OF RAT CHONDROEPIPHYSIS EXPLANTS

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Objective: The growth plate is a cartilaginous layer regulated by endocrine, autocrine, and paracrine processes from the gestation period until the end of puberty where it ossifies joining the diaphysis with epiphysis. A disruption in in cell dynamics may lead to different pathologies that affect normal long bone development. Due to biophysical stimuli have directly influence in cell deformation, nutrient concentration gradients and stimulation of molecular synthesis, this work presents a novel framework to assess histomorphometrically the effect of external electric fields over growth plates of chondroepiphysis explants.

Methods: Bones were stimulated with 3.5 and 7 mV/cm, and for each of these electric fields, two exposure times were tested for 30 days (30 minutes and 1 hour). Histologies were done to elucidate the chondrocyte morphology and immunohistochemistry assays were performed to visualize COL type II and type X activity.

Results: It was evidenced that electric fields increased the pre-hypertrophic and hypertrophic zones compared with controls. In addition, an electric field of 3.5 mV/cm applied for 1 hr maintain stable the growth plate zones. It was also evidenced that electric fields stimulated chondrocytes to maintain stable the columnar cell density and its orientation during culture. Additionally, it was shown that electrical stimulation induces chondrocytes to enter in a pre-hypertrophy state in the center of the chondroepiphysis.

Discussion: These findings allow to enhance the *in vitro* procedures either inducing changes in growth plate morphology or stimulating chondrocyte molecular synthesis to modify the morphophysiology of chondrocytes.

O167

NOVEL SURFACE COATINGS AS BIOCOMPATIBLE RESERVOIRS FOR BMP-2 FOR BONE REGENERATION

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Objectives: This study was aimed to fabricate various layer-by-layer (LbL) systems using glycosaminoglycans (GAGs) with capability to bind BMP-2 specifically in order to control osteogenic differentiation of cells by biocompatible release systems.

Methods: Heparin, chondroitin sulfate and their oxidized forms as polyanions were combined with chitosan and collagen I as polycations to form various multilayer coatings on model materials with getting advantage of the intrinsic cross-linking formed between oxidized GAGs and

polycations to improve multilayer stability and affect the release of BMP-2. The myoblast cell line C2C12, which can differentiate into osteoblasts was seeded on 5 μg/mL BMP-2 loaded multilayers. Cell viability was investigated by Qblue assay; adhesion using immunohistochemical staining, osteogenic differentiation by alkaline phosphatase (ALP) assay and alizarin red-S staining. In addition, studies on release of BMP-2 were done by ELISA.

Results: C2C12 cells cultured directly on the top of multilayers showed that particularly BMP-2 loaded multilayers made of oxidized GAGs promoted an osteogenic differentiation that was nearly comparable to the positive control, when 5 μg/mL BMP-2 was added directly to the medium. Interestingly, the BMP-2 had synergistic effect on cell adhesion and spreading. BMP-2 in oxidized chondroitin sulfate multilayers was successfully loaded to the layers, sustainably released over time and affected cell differentiation more than the soluble BMP-2.

Discussion: The results show that oxidized GAGs forming intrinsically cross-linked multilayers are useful as reservoirs for sustained release of BMP-2 in which the intrinsic cross-linking affected BMP-2 release, improved multilayers stability due to the resulting stiff surface compared to the native ones, supported cell adhesion, proliferation and subsequent differentiation. This can pave the way for coating implants and scaffolds for repair and regeneration of bone fractures.

O168

BORON INDUCES FATE DECISION OF MMSCS VERSUS OSTEOGENIC LINEAGE

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Objectives: Boron (B) plays a key role in metabolism and it has been reported that is involved in bone mineralisation. However, its use for Tissue Engineering has been limited to bioactive glasses. Its mechanism of action is unknown to date. The objective of this work is to evaluate for the first time B effects on mouse Mesenchymal Stem Cells (mMSC). We analysed mMSC behaviour by examining both differentiation potential along three different lineages (osteogenic, adipogenic and myogenic) or analysing its capability to induce sustained self-renewal, culturing cells in absence/presence of differentiation factors. Multiple phenotypic features including cell morphology, gene/protein expression and functional differentiation were examined.

Methods: PLLA spin casted films were functionalised with fibronectin (20 μg/ml) prior cell culture. We have tested two boron concentrations (0.59 and 1.47 mM) as additive in the culture medium. Cell morphology and myogenic/osteogenic/adipocyte commitment were assessed by immunofluorescence and qPCR. In cell western was used for determination of key proteins involved in MSC fate and intracellular signalling.

Results: Boron effect on mMSC using basal and differentiation media was evaluated. Adipogenic and myogenic commitment markers showed minimum levels after 15 days of culture under basal conditions. However, osteogenic markers presented greater expression only using boron in basal media. mMSCs stimulation using differentiation media showed an increase in osteogenic and a proportional decrease in adipogenic markers only in boron presence. Interestingly, besides enhancing osteogenic commitment, boron presence inhibits adipocyte formation even in the presence of adipogenic-defined media.

Discussion: We report that boron direct osteogenic differentiation in mMSCs in absence of defined factors in the culture media. Furthermore, in the presence of defined media, boron maintain its effect enhancing osteogenesis and inhibiting adipogenesis. We propose boron as a novel bioactive molecule to direct osteogenic mMSC differentiation.

O169

PARALLEL BINDING OF AUTOLOGOUS BMP-2 AND VEGF ENVISIONING A VASCULARIZED BONE TISSUE ENGINEERING APPROACH

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Objectives: Reconstruction of large bone defects still remaining a major clinical orthopedic challenge, since the repair of bone defect comprises not only the process of new bone formation, but also the formation of new blood vessels - angiogenesis[1]. Bone morphogenetic proteins (BMPs) and vascular endothelial growth factor (VEGF) are involved in cell differentiation and bone vascularization to develop viable osseous tissue[2,3]. Accordingly, herein it is hypothesized that the synergistic effect of autologous BMP-2 and VEGF, parallel bound over a single nanofibrous substrate, can lead to a successful osteogenic and angiogenic differentiation of human bone marrow mesenchymal stem cells (hBM-MSCs).

Methods: Specific antibodies for BMP-2 and VEGF were immobilized over an electrospun nanofibrous mesh, in a parallel pattern design. The BMP-2 and VEGF derived from platelet lysate (PL) were captured to the biofunctional nanofibrous substrate. The unbound protein solution was quantified by ELISA. The osteogenic and angiogenic potential of this engineered biofunctionalized system was

assessed by culturing hBM-MSCs during 21 days, without exogenous induction.

Results: The antibodies against BMP-2 and VEGF were immobilized parallel in at the maximum concentration of 4 μg/mL each, over the same nanofibrous substrate. Biochemical performance of hBM-MSCs cultured on the engineered biofunctional system confirms the biological activity of bound BMP-2 and VEGF. The quantification of angiogenic and osteogenic transcripts revealed that hBM-MSCs respond according to the growth factor bound to the engineered biofunctional system. The immunolocalization of osteocalcin and CD31 confirmed the osteogenic and angiogenic phenotype of the differentiated hBM-MSCs.

Discussion: The biofunctional nanofibrous substrate is capable of efficiently capture BMP-2 and VEGF from PL. The proposed system containing BMP-2 is able to promote the osteogenesis of hBM-MSCs, as well as the bound VEGF is able to stimulate angiogenesis. The synergistic effect of bound growth factors enables the development of a vascularized bone tissue engineering approach

O170

BIODEGRADABLE MEDICAL DEVICES

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Cartilage is a dense connective tissue with limited selfrepair properties. Currently, the therapeutic use of autologous or allogenic chondrocytes makes up an alternative therapy to the pharmacological treatment. The design of a bioprinted 3D cartilage with chondrocytes and biodegradable biomaterials offers a new therapeutic alternative able of bridging the limitations of current therapies in the field. We have developed an enhanced printing processes-Injection Volume Filling (IVF) to increase the viability and survival of the cells when working with high temperature thermoplastics without the limitation of the scaffold geometry in contact with cells. We have demonstrated the viability of the printing process using chondrocytes for cartilage regeneration. An alginate-based hydrogel combined with human chondrocytes (isolated from osteoarthritis patients) was formulated as bioink-A and the polylactic acid as bioink-B. The bioprinting process was carried out with the REGEMAT V1 bioprinter (Regemat 3D, Granada-Spain) through a IVF. The printing capacity of the bioprinting plus the viability and cell proliferation of bioprinted chondrociytes was evaluated after five weeks by confocal microscopy and Alamar Blue Assay (Biorad). Results showed that the IVF process does not decrease the cell viability of the chondrocytes during the printing process as the cells do not have contact with the thermoplastic at elevated temperatures. The viability and cellular proliferation of the bioprinted artificial 3D cartilage increased after 5 weeks. In conclusion, this study demonstrates the potential use of Regemat V1 for 3D bioprinting of cartilage and the viability of bioprinted chondrocytes in the scaffolds for application in regenerative medicine.

O171

MECHANICAL STIMULATION MONITORING TOWARDS OPTIMAL TENDON TISSUE RECONSTRUCTION

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Objectives: Subject to loads during movement, tendons are permanently under the effects of mechanical strains. Thus, mechanical stimulation appears as a necessary income to achieve tendon healing. How this stimulation acts on the cells and its activity is not clearly established. We propose to set an *in vitro* model to evaluate the potential of mechanical stimulation on the differentiation of stem cells and the evolution of cell-construct mechanical properties over time.

Methods: The scaffold was produced by electrospinning of ε-polycaprolactone over a rotary collector, forming a randomly oriented entangled fibril structure. Bone Marrow Stromal cells isolated from Sprague Dawley rats were cultured over the electrospun scaffold for 48h. After this period, mechanical stimulation was achieved for 12 days with a Bose Biodynamic™ Bioreactor. A force sensor of 22N allowed recording the generated stress over time. Cell morphology, matrix synthesis (Masson's Trichrome, Hydroxyproline) and differentiation (qRT-PCR) were evaluated.

Results: Submitted to a stress, cells constructs showed an increased viscoelasticity related to the extracellular matrix deposition compared to static control. Stimulated cells presented an oriented morphology. The increase of tenomodulin, tenascin-c and type I collagen demonstrated a clear differentiation of cells towards tendon tissue. Alignment of collagen fibers under mechanical stimulation is thought to be the main guide to increase the mechanical properties.

Conclusions: Our study emphasizes the importance of the use of mechanical stimulation as a factor for tendon differentiation. Recording the mechanical response of cells during the stimulation period allows a detailed knowledge about cellular activity and its response to the mechanical environment. This model can be adapted for any material by determining the range of stimulation and the cell response into the tissue-engineered construct.

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SESSION SC1: WORKING GROUP BIOARTIFICIAL ORGANS

O172(IL)

MULTILAYERED FIBER MATS WITH ANISOTROPIC PROPERTIES FOR LOAD-BEARING TISSUES

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Objectives: This project focuses the development of fabrication techniques for scaffolds intended to replace load-bearing connective tissues (e.g. tendons) or cyclic loaded organs (e.g. lung). The main task is to combine aligned and non-aligned fibers in an individual scaffold.

Methods: The fiber mats were fabricated by electrospinning on a rotation drum collector. A custom-made automated gap spinning collector was used to fabricate either multilayered or graded scaffolds. Mechanical properties were measured with tensile testing. Alignment was quantified by the degree of fiber orientation and was optically assessed by scanning electron microscope (SEM) images. Change in crystallinity was analyzed by measuring melt enthalpy via differential scanning calorimetry (DSC).

Results: The Fiber alignment range vary with increasing circumferential speed of the rotation drum collector from 0% (at 2m/s) to 90% (12 m/s). With increasing orientation the crystallinity and mechanical properties increased while strain decreased. The melt enthalpy was 17% higher at a circumferential speed of 12 m/s in comparison to a static setup. Gap spinning resulted in highly aligned fibers (< 90%) and non-aligned fibers (0%) on the surface of the collectors.

Discussion: The developed techniques are promising to overcome tensile load limitations caused by overall material properties of the polymer. Crystallinity and hereby mechanical properties could be increased by varying circumferential speed of the rotating drum collector. Gap spinning technique allowed for the combination of aligned and non-aligned fibers into multilayered and graded scaffolds. The fiber mats can be segregated into designated junction parts and cell-bearing structures (that allow for cell migration). For the near future, with melt electrospinning fiber morphology limitations and thereby related mechanical properties can be overcome.

O173(KL)

ON BIOREACTOR DESIGN FOR SUBSTITUTIVE AND REGENERATIVE MEDICINE

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Bioreactors are broadly used in substitutive (SM) and regenerative medicine (RM). In SM, cells are cultured in bioreactors to temporarily replace the complex metabolic functions of diseased organs. In RM, bioreactors are used for expanding stem/precursor cells to clinical mass, for promoting cell differentiation to a given phenotype, for guiding organization of different cells in hierarchical three-dimensional structures resembling the natural tissue or organ to be replaced, and as models for testing new drugs. The complexity of tissues and organs structure and functions, and the scarce information on physiology of healthy and pathological tissue, on isolated cell requirements and behavior, and on the presentation of biochemical challenges makes bioreactor design and scale-up/-down extremely challenging.

Batch static two-dimensional culture dishes are still the most used bioreactors, although metabolite concentration changes in space and time beyond the operator control. To overcome their limitations, bioreactors have been proposed in which medium/plasma is per(i)fused around or through cell-seeded 3D porous scaffolds. Research has mainly focused on scaffold architecture and surface properties, and the selection of cell types. Bioreactor design has often been approached by adding actuators and features to bioreactors borrowed from industrial applications adapted to host predetermined scaffolds and cells (i.e. building block approach) to challenge cells with mechanical, electrical and/or magnetic cues, seldom accounting for organ or tissue specificity in the distribution of matter and operation.

In this presentation, it will be discussed the complexity of bioreactor design and scaling for SM and RM that calls for bioreactor designs specific to tissue/therapy requirements. It will also be discussed how specific distribution of matter and operation is key to successful bioreactor design. Consistent approaches to hollow fiber membrane bioreactor design and bioreactor development for assisted reproduction will be illustrated as examples of complex and (relatively) simple solutions to complex therapeutic problems.

O174(IL)

BIOMIMETIC SURFACES WITH GLYCOSAMINOGLYCANS – FROM CONTROL OF CELL DIFFERENTIATION TO ANTI-INFLAMMATORY ACTIVITY

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Glycosaminoglycans (GAG) represent a group of polysaccharides providing high affinity binding sites to proteins

regulating adhesion, growth and differentiation of cells or that interact directly with specific cell receptors. Due their bioactivity, relatively high thermal and chemical stability, the presence of functional, charged groups allowing covalent or physical bonding and cross-linking, GAG represent interesting materials for biomimetic surface modification. The covalent binding of GAG to biomaterials was achieved here by oxidation of GAG to generate reactive aldehyde groups reacting with amino groups (i) and by thiolation (ii) that permits direct immobilization on gold or photochemical to vinyl groups. Protein adsorption and fibroblast adhesion studies showed that a lower degree of such functionalization did not impair the bioactivity of GAG. Beside covalent also physical immobilization of GAG with layer-by-layer technique was applied to generate multilayers using chitosan or collagen I as polycations. Such bioactive surface coatings made of GAG can be designed to support adhesion and differentiation of mesenchymal stem and other cells. They also allow the uptake and release of growth factors like BMP-2, which paves the way to use GAG as bioactive coatings on scaffolds and implants to repair defects in bone and cartilage. GAG-based surface coatings possess also an anti-inflammatory activity, which was evident by reduction of macrophages activation as key players during inflammation. Hence, GAG represent highly interesting materials to control inflammatory processes, wound healing and tissue regeneration after implantation of biomedical devices and tissue engineering scaffolds.

O175(KL)

NEVES N (1)

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(Invited talk at the Symposium in WG Tissue Engineering)

Among the various possible embodiements of Advanced Therapies and in particular of Tissue Engineering the use of temporary scaffolds to regenerate tissue defects is one of the key issues. The scaffolds should be specifically designed to create environments that promote tissue development and not merely to support the maintenance of communities of cells. To achieve that goal, highly functional scaffolds may combine specific morphologies and surface chemistry with the local release of bioactive agents.

Many biomaterials have been proposed to produce scaffolds aiming the regeneration of a wealth of human tissues. We have a particular interest in developing systems based in biodegradable polymers. Those demanding applications require a combination of mechanical properties, processability, cell-friendly surfaces and tunable biodegradability that need to be tailored for the specific application envisioned. Those biomaterials are usually processed by different routes into devices with wide range of morphologies such as biodegradable fibers and meshes, films or particles and adaptable to different biomedical applications.

In our approach, we combine the temporary scaffolds populated with therapeutically relevant communities of cells to generate a hybrid implant. For that we have explored different sources of adult and also embryonic stem cells. We are exploring the use of adult MSCs, namely obtained from the bone marrow for the development autologous-based therapies. We also develop strategies based in extra-embryonic tissues, such as the perivascular region of the umbilical cord (Wharton's Jelly).

This talk will review our latest developments of biomaterials and scaffolds in combination with stem cells for advanced biomedical devices and therapies.

SESSION SC2: WORKING GROUP UREMIC TOXINS: THE CHALLENGE OF PROTEIN-BOUND TOXINS

O176(IL)

NEW CONCEPTS FOR REMOVAL OF PROTEIN BOUND UREMIC TOXINS

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Introduction: In the coming years, due to the aging of the population and the low availability of donor organs there will be urgent need for bioengineered organs to assist, mimic or replace failing patient organs. The developed organs could be: Artificial: based on new biomaterials and novel designs or Bioartificial: combining biomaterials and biological cells.

Artificial and bioartificial kidney devices for removal of protein bound uremic toxins Hemodialysis is a widely available and well-established treatment for patients with End Stage Renal Disease (ESRD). The therapy requires patients to visit the dialysis centres 3-4 times a week, which is for these patients a great social and psychological burden. Major drawbacks of the therapy are the poor removal of middle-sized molecules and protein-bound uremic solutes and the non-continuous treatment, causing large fluctuations in water balance and uremic wastes of the patients. In this presentation, we will discuss various strategies for removing protein bound uremic toxins including:

Sorption based therapies and Mixed matrix membranes (MMM), which combine the benefits of diffusion and /or convection, provided by the membrane structure, and of adsorption, achieved by activated carbon particles dispersed through the membrane;

Application of a bioartificial kidney device. A key requirement there is the formation of a "living membrane" consisting of a tight renal cells monolayer with preserved

functional organic ion transporters, on suitable artificial membranes. The cell monolayer is used for active removal of the uremic solutes mimicking the function of the kidney proximal tubule.

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O177(IL)

TRANSPORTERS AS DETERMINANTS IN UREMIC TOXIN DISPOSITION

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In patients with chronic kidney disease (CKD) adequate renal clearance is compromised, resulting in the accumulation of a plethora of uremic solutes. These uremic retention solutes, also named uremic toxins, are a heterogeneous group of organic compounds that originate mostly from microbiome-mediated dietary protein breakdown. Further metabolism and passage through the intestinal epithelial cells and hepatocytes take place before the uremic toxins enter the systemic circulation. These processes are mediated by metabolism enzymes and transporters facilitating their membranal passage. The final removal of uremic toxins is determined by kidney function. For this, in addition to glomerular filtration, renal tubular secretion is an important determinant, especially for the protein-bound uremic toxins by shifting the binding and allowing active secretion of the free fraction. To facilitate this process, renal proximal tubule cells are equipped with a range of transporters that cooperate in basolateral uptake and luminal excretion. This presentation discusses the current knowledge on the disposition and removal of protein-bound uremic toxins. Many of the metabolism enzymes and transporters involved in uremic toxin handling have been characterized as mediators of drug disposition as well. This indicates that during uremia, drug disposition may be severely affected as a result of drug-uremic toxin interaction. In addition, CKD patients receive various drugs to treat their complications potentially resulting in drug-drug interactions, also for drugs that are non-renally excreted. This presentation will also deal with these pharmacotherapeutic aspects of CKD.

O178(IL)

PROTEIN-BOUND UREMIC TOXINS ORIGINATING FROM GUT MICROBIAL METABOLISM

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It is increasingly recognized that the gut is an important source of uremic toxins. Important representatives include p-cresyl sulphate (PCS), indoxyl sulphate (indS) and trimethylamine-N-oxide (TMAO). PCS and IndS are endproducts of microbial protein fermentation, while TMAO is an endproduct of microbial choline metabolism. Serum levels of these metabolites increase dramatically along the progression of CKD. With regard to PCS and IndS, not only a decreased renal clearance but also an increased generation contributes to the increasing circulating levels in CKD patients. Indeed, mounting evidence indicates that CKD promotes alterations in the composition of the gut microbiota and causes a shift towards a predominantly proteolytic fermentation pattern. In addition, the free fraction of PCS and IndS, both prototypes of the protein-bound uremic toxins, increases as kidney function declines, thereby further boosting the toxicity of these metabolites. PCS, indS and TMAO may contribute to inflammation, progression of renal failure and accelerated cardiovascular disease. This presentation will discuss key features of the gut-kidney axis and as such will provide clues to targeted therapy.

SESSION SD1: MISCELLANEOUS

O179

HAND FLEXIONS IN THE PROTOTYPE OF A PROSTHETIC SUPPORT DEVICE FOR PEOPLE WITH AGENESIS OF THE UPPER LIMB

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Objectives: The aim of this research is to present alternative controls that simulate the hand flexions in a prototype hybrid prosthetic device of the upper limb for people with hand agenesis so that they attribute comfort in the use, easy fixation and autonomy to carry out activities with the hand.

Methods: It began with the bibliographic basis in the themes of hand agenesis, muscle and musculoskeletal system of the upper limb, hybrid prosthetic devices. Next, we searched for and related the functions performed with the hands and the muscular contractions necessary to trigger the prototype of the device to perform a certain activity with the movement of opening and closing the hand. A hybrid prosthesis prototype was fabricated with Fused Deposition Modeling (FDM) and additive printing. Inside the enclosure was added controls of sensors driven by the movement of muscle contraction to perform different types of activities.

Results: The prototype hybrid hand prosthesis presents three functions in the sensor controls to perform a given hand activity: a) closure control and hand strength by means of amount of activation by muscular contraction; b)

command to fully open or close the hand by means of a muscular contraction; c) command to keep the hand closed without remaining with muscle contraction. The prototype has a rechargeable battery by micro USB and control on / off. The casing was made of biodegradable thermoplastic material.

Discussion: The prototype prosthesis has low cost by the additive manufacture of the casing presenting time reduction for custom configuration. The actuation of the sensor controls can be installed in parts of the human body, as instructed by health professionals of the user to have control in muscle contractions without the need for continuous effort accompanied by the rehabilitation program.

O180

MEMBRANE BASED MACROENCAPSULATION DEVICE FOR IMPROVED PANCREATIC ISLETS SURVIVAL AND FUNCTION

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Objectives: The efficacy of clinical islet transplantation is hindered mostly by lack of vascularization, inflammatory response and necessity of immunosuppression. Here, we develop a macroencapsulation device based on thin, microwell membranes, able to shield the islets from the host immune cells without compromising their endocrine function. We also investigate whether co-culture of beta cells with endothelial cells within encapsulation device could improve beta cell function. Moreover, we investigate the effect of micropatterned membranes on endothelial cell alignment and interconnection as a first step towards development of prevascularized device in vitro.

Methods: The membranes were fabricated using polyethersulfone by phase separation micromolding. The functionality of human islets encapsulated within the membranes was assessed by glucose induced insulin secretion test after 7 days of culture. Mouse insulinoma MIN6 cell aggregates functionality was compared to the encapsulated aggregates co-cultured with human umbilical vein endothelial cells (HUVECs) after 1 day of culture. HUVECs were cultured on micropatterned membranes and CD31 immunostaining was applied in order to investigate the effect of the patterns on HUVECs organization.

Results: The encapsulated human islets are viable and function over 1 week. Co-culture of HUVECs with MIN6 aggregates within our device improves beta cell functionality. Finally, by using micropatterned membranes we achieved interconnected HUVECs structures oriented in the direction of the patterns. Micropatterned membranes applied as a lid of the encapsulation device could support device controlled prevascularization.

Discussion: Our results indicate that the macroencapsulation device is a potential carrier for extrahepatic islet transplantation. By providing beta cell–endothelial cell contact mimicking native islet we can improve cell functionality within encapsulation device. In the future, the microstructure membranes can be used as a part of the encapsulation device allowing creation of organized prevascularized layer in vitro to improve the connection between the device and host vasculature after implantation.

O181

VARIATIONS OF CIRCULATING MIRNA IN PEDIATRIC PATIENTS WITH HEART FAILURE SUPPORTED WITH VENTRICULAR ASSIST DEVICE

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Objective: Circulating miRNAs (c-miRNAs) are promising biomarkers for prediction, diagnosis and prognosis also for patients with heart failure (HF). For this reason, the aims of this study were: 1) to examine the profile of c-miRNAs in children with HF; 2) to evaluate the effects of VAD on the c-miRNAs levels in these patients; 3) to validate, in vitro, the c-miRNA targets previously selected through miRWalk database.

Methods: Blood samples were collected from five children [13±6 (mean±SD) months, 17±2 LVEF%] with HF before and at 4hrs, 1, 3, 7, 14 and 30 days after VAD-implant. c-miRNA profile at the moment of VAD-implant and after 30 days of treatment was determined by NGS and qRT-PCR was used for validated, during time-course, the data on c-miRNA differentially expressed. miRNA mimic transfection on HepG2 cells were used for to validate putative miRNA targets selected using miRWalk database.

Results: In the screening phase, after NGS, N=13 c-miRNAs were found simultaneously modulated at 30 days after VAD-implant compared to pre-VAD. In the validation phase, the trend of only N=6 c-miRNAs were confirmed [miR-483-3p, miR-409-3p, miR-485-3p, miR-432-5p (down regulated); miR-150-3p and miR-375(up-regulated)]. Putative targets of selected c-miRNAs found are involved in the hemostatic process. The study in vitro confirmed a regulatory effect of miR-409-3p towards coagulation

factor VII(F7) (0.756±0.22 vs 1.13±0.25; p=0.022 miR-409-3p mimic vs control).

Discussion: In this pilot study in children with HF, circulating levels of N=6 miRNAs, potentially involved in the regulation of hemostasis event, changed after 30 days of VAD treatment. The mimic transfection study confirmed the down-regulatory effect of miR-409-3p towards F7.

O182

VISUALIZATION OF HEMODYNAMICS: SYNTHESIS OF ARTIFICIAL ERYTHROCYTES WITH ENCAPSULATED PIV-PARTICLES VIA MICROFLUIDIC SYSTEMS AND ELECTRO-SPRAYING

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Objectives: Visualization of hemodynamics often show a simplification of blood as a monophasic fluid. In this study, blood is considered as a multiphase fluid. The aim is to synthesize artificial erythrocytes (ArtErys), to visualize hemodynamics with Particle Image Velocimetry (PIV). The synthesized ArtErys are made of hydrogels which make them transparent and elastic. For PIV tracking, particles are encapsulated directly into the ArtErys and are not added to the plasma where they might affect the hemodynamics. Two methods of synthesizing ArtErys are considered - microfluidic systems (MFS) and electro-spraying (ES).

Methods: ArtErys are made of Agarose (0.3-0.7%). Spericals©, commercial available PIV particles (0.2%), are added to the Agarose solution. For the MFS and ES, different oils (e.g. paraffin) are used as disperse phase. The flow velocities of the oil and Agarose phases in the MFS range from 5-80ml/h and 5-40ml/h, respectively. The voltage for the ES method ranges up to 2kV/cm. The ArtEry size is determined with a light microscope. Viscosity, surface and interfacial tension between Agarose and the oils are measured.

Results: Viscosity tests showed that the ArtErys do not fuse with lower oil viscosities (paraffin 38mPas). The higher the Agarose concentration, the higher the interfacial tension between oil and Agarose becomes (e.g. 0.3%|25.1mN/cm; 0.7%|54mN/cm). There the ArtErys do not merge. The ArtEry size depends on the flow velocity of the oil (MFS) and the voltage (ES). The higher the flow velocity (80ml/h) and the voltage (2kV/cm), respectively, the smaller the ArtErys become, 20µm (MFS) and 50µm (ES).

Discussion: MFS and ES have been successfully implemented to fabricate ArtErys with encapsulated PIV particles. For further experiments, the index of refraction, mechanical properties and the ArtEry concentration are being considered.

O183

ASSOCIATION STUDY OF MITOCHONDRIAL GENOME BY AMPLICON SEQUENCING IN SEPSIS

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Introduction: Sepsis is a clinical syndrome of high mortality and morbidity and still has a lot of controversy in mechanism. Mitochondria are the core part of the cell oxygen metabolism and mitochondrial dysfunction may have a profound impact on sepsis and multiple organ damage. Mitochondrial single nucleotide polymorphisms, in Europe and in the Han nationality have been shown to affect the prognosis of sepsis, however, similar to many complex diseases, the exact effect of mtDNA variation on sepsis and how to influence is not clear. With the development of genome sequencing technology and biological information, it is possible to use the next generation sequencing (NGS) to deal with that.

Objective: To investigate the relationship between mitochondrial haplotypes and the prognosis of severe sepsis, and to screen the mitochondrial DNA single nucleotide polymorphisms associated with severe sepsis.

Methods: Peripheral blood DNA from 151 sepsis patients and 103 healthy people were obtained. Mitochondrial genome wide association study of sepsis was conducted based on the mitochondrial DNA barcode sequencing method. We compared the mitochondrial haplotype distribution in the disease and control group, and the relationship between haplotype and prognosis of disease. Single nucleotide polymorphisms associated with disease onset and prognosis were screened.

Results: Association analysis based on the mitochondrial DNA sequencing found 9 loci associated with sepsis and controls: A (OR=0.2186, p=4.06E-05), B (OR= 0.2271, p=0.001107), C (OR=0.2274, p=0.003112), D (OR=5.221, p=0.003419), E (OR=2.532, P=0.02615), F (OR=0.2478, p=0.02668), G (OR=0.2478, p=0.02668), H(OR=2.327, p=0.02913) and I (OR= 0.2256, p=0.03349). And 1 loci associated with in-hospital mortality of sepsis patients. J was associated with in-hospital mortality (OR=2.469, p=0.04966). There was no difference in the distribution of mitochondrial haplotypes among the groups.

Conclusions: mitochondrial SNP A/B/C/D/E/F/G/H/I are associated with sepsis, while J is associated with the in-hospital deaths in sepsis patients.

O184

CHARACTERIZATION OF POLY-SODIUMACRYLATE-CO-ACRYLAMIDE HYDROGELS FOR PIV BASED IN VITRO FLOW ANALYSIS

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Objectives: Transparent *in vitro* models of blood vessels are promising to analyze biological fluid flows with a high standardization and repeatability. In order to mimic *in vivo* conditions, model fluids and solids have to be matched with respect to their physical properties. Furthermore, their index of refraction (IOR) has to adjusted when using particle image velocimetry. This study aims to assess whether Poly-sodiumacrylate-co-acrylamide (PSAAm) hydrogels are suitable for fabricating *in vitro* models of native blood vessels, while matching the IOR of modeling fluids.

Methods: Formulations ranging from a total monomer concentration of 1 - 4 mol/L (sodium acrylate and acrylamide) and a crosslinker concentration of 1 - 4 mol% regarding the monomer concentration (N,N\'-Methylenebisacrylamide) were fabricated. The IOR was measured with a custom made light-transmission-refractometer and an Anton Paar - Abbemat 300 refractometer. Mechanical properties were obtained via compression-testing on a BOSE - test bench. The Swelling index for different saline solutions was calculated.

Results: Compressive moduli of up to 50 kPa, failure strength of up to 0.65 MPa and strains at break of up to 87% where obtained. With an IOR of 1.3329 the hydrogel model was nearly indistinguishable from the corresponding swelling solution (double-distilled water). The water content of the swollen hydrogels was up to 99 wt. %.

Discussion: PSAAm hydrogels are suitable to mimic the mechanical behavior of different tissues due to its composition and modeling fluid swelling-dependency. Optical and mechanical properties can be adjusted to mimic certain *in vivo* conditions. A solid based IOR matching for PIV applications with defined fluid properties can be achieved. The use of TPO nanoparticles showed promising results due to the utilization of UV-based rapid-prototyping fabrications methods. Further studies will assess the mechanical and optical properties of printed PSAAm hydrogels.

SESSION SD2: VADS: NEW DEVICES

O185

DEVELOPMENT OF AN ULTRA COMPACT DURABLE ECMO SYSTEM WITH BUILT-IN MONITORS AND CONTINUOUS USE EVALUATION IN CHRONIC ANIMAL EXPERIMENTS UP TO 4 WEEKS

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Objectives: ECMO system has been used for over days to weeks to treat patients with severe respiratory/circulatory failure, while device exchanges and complications due to its poor durability and thrombo-resistant property are still risks in long-term use. In addition, lack of portability and operability due to large and complicated apparatus are also problematic issues. We have been developing a durable ECMO system which can solve these problems. In this study, we developed a prototype of a compact ECMO system with built-in monitor functions and evaluated its durability and biocompatibility in a series of chronic animal experiments.

Methods: This system is consisted of a pre-connected blood circuit unit, a pump driver unit integrating with measurement instruments and a gas bomb unit. The circuit unit was consisted of a centrifugal pump (BIOFLOAT NCVC) with hydrodynamically bearings, a membrane oxygenator (BIOCUBE6000) and built-in sensor connectors. The entire blood-contacting surface of the circuit was treated with heparin bonding material (T-NCVC). Prototype of the driver unit was made as extremely compact (W290 x D205 x H260 mm, 6.6 kg). Veno-arterial bypass ECMO using the prototype system was conducted for 2 or 4 weeks using adult 7 goats (Body weight: 42 – 61 kg). Heparin was continuously administered to control ACT between 150-200 sec, except one case without continuous systemic anticoagulation.

Results: In all cases, the ECMO could run for scheduled periods without device exchange and each monitor was stably. 2.5 L/min of bypass flow rate could be maintained. After the experiments, thrombus formation was hardly observed in the each blood circuits including the built-in sensor connectors.

Conclusions: The ultra compact ECMO system was developed and demonstrated long-term durability, stability of monitor functions and thrombo-resistant property up to 4 weeks.

O186

A MECHANICAL CIRCULATORY SUPPORT SYSTEM AS DESTINATION THERAPY FOR FONTAN PATIENTS

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Objectives: The circulatory system of patients with a single ventricle (Fontan patients) fails eventually. Heart transplantation constitutes the only treatment option. However, heart transplantation is complex in these patients and outcomes are worse compared to other populations. Aim of

this project is to develop a blood pump to replace the missing pulmonary ventricle as a destination therapy.

Methods: Requirements for a pump in cavopulmonary position were defined in close cooperation of medical professionals and engineers. Pump concepts were developed and ranked based on these requirements. Two favorite concepts were further investigated using computational fluid dynamics (CFD) as well as electromagnetic simulations, and additive manufactured physical pump models to identify the hydraulic properties. Both pumps have two inlets and two outlets and can be surgically implanted in the junction between the caval veins and the pulmonary arteries.

Results: The pump concepts with contact bearings feature a single rotor (diameter 18mm) and dual motor architecture. Both pumps reach an operating point of 4.5L/min against 10mmHg at a pump speed of 2800 and 3100rpm respectively. Measured pump characteristics indicate flat slopes of -2 to -4 mmHg*min/L. CFD revealed a low blood trauma potential. Large gaps in the fluid path (>0.75mm) warrant a good washout over a wide operating range.

Discussion: Pump concepts to support the circulatory system of Fontan patients were developed, simulated and experimentally investigated. These pumps fulfill the requirement of a small size, high pressure sensitivity, and low blood trauma potential over the required operating range to support Fontan patients at rest and during physical activity. Large gaps in the fluid path may allow passage of floating thrombi through the pump. Both pumps can be adopted for fully magnetic levitation.

O187

A VALVELESS PULSATILE PUMP FOR THE TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Objectives: Effective treatment of patients with terminal heart failure and preserved ejection fraction (HFpEF) is an unmet medical need. The application of rotary blood pumps (RBPs), commonly used to support patients with heart failure and reduced ejection fraction (HFrEF), is rarely reported for HFpEF. The aim of this study was to investigate a novel valveless pulsatile device as a therapeutic alternative for the HFpEF population through numerical simulations.

Methods: In a numerical model of the cardiovascular system, four HFpEF phenotypes (hypertrophic cardiomyopathies, infiltrative diseases, non-hypertrophic HFpEF and HFpEF with cardiovascular comorbidities) were simulated and compared to a typical HFrEF case. The proposed device, which was modeled as being directly connected to the left ventricle, features a single valveless cannula as the inlet and outlet. Hemodynamics were collected for two different stroke volumes (30 and 60ml) with the pump driven in co-pulsation with the left ventricle.

Results: In all HFpEF conditions, the 30ml pump improved the cardiac output by approximately 1L/min, increased the mean arterial pressure (>12%) and lowered the mean left atrial pressure (>30%). These hemodynamic improvements were more pronounced with the larger (60ml) stroke volume. In the HFrEF condition these effects that were three times less in magnitude.

Conclusion: In this simulation study, the valveless pulsatile device improved hemodynamics in HFpEF patients by increasing the total stroke volume. The benefits in hemodynamics are achieved with a small device volume comparable to typical implantable RBPs. The device is specifically well-suited for HFpEF patients and may afford a promising treatment option for this patient population.

O188

PULSATILE BEHAVIOR AND EFFICIENCY OF AN UNDULATING MEMBRANE BASED LVAD

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Objectives: Heart failure affects roughly 40 million people globally. In developed countries around 6 to 10 % of adults over the age of 65 are affected by it. In the case of left-sided heart failure a left-ventricular assist device (LVAD) may be implanted to support the blood pumping capability of the heart. All currently approved LVAD systems are based on centrifugal pumping technology, either axial or radial. The high momentum of inertia of the rotating impeller prevents these systems from pumping blood in a pulsatile manner. Continuous blood flow is suspected to be at the origin of severe adverse events of the therapy, in particular gastrointestinal bleeding and stroke.

To improve the LVAD therapy, CorWave is developing an LVAD based on a low-inertia undulating membrane pumping mechanism which can provide pulsatile blood flow mimicking the native action of the heart.

The objective of this study is to investigate the pulsatile behavior of the CorWave LVAD.

Methods: To this end three different studies are necessary. First investigates the pulsatile behavior of the implant in a static environment. Second investigates the impact of a pulsatile environment on the implant in a continuous flow configuration. Third investigates the interaction of a pulsating implant in a pulsatile environment. The research is

carried out on dedicated hydraulic test benches and a mock circulatory loop.

Results: The acquired data provides insights on the transient state changes of the implant, the efficiency of the system and understanding on the operating conditions of the implant in dynamic environments.

Discussion: These results are crucial in determining the ideal operation and design points of the pump, as well as in general of any pulsatile LVAD. Driving the implant in these optimized conditions will allow for efficient pulsatile operation, all while ensuring hemocompatibility, thus significantly improving patient outcomes.

O189

DEVELOPMENT OF A NOVEL ENDOTHELIALIZED PULSATILE VENTRICULAR ASSIST DEVICE

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Objectives: We aimed at designing a pulsatile ventricular assist device (pVAD) with improved hemocompatibility by covering its luminal surface with endothelial cells and conducting corresponding in-vitro experiments and acute animal trials.

Methods: Blood propulsion was achieved through the actuation of a silicone membrane designed to minimize the mechanical stress on endothelial cells in the pVAD. A topography was introduced on the target surfaces to protect the cells from supraphysiological wall shear stresses. In-vitro tests were performed to confirm monolayer integrity after 5h of pVAD actuation. Operating conditions of the pVAD covered frequencies from 60 to 240 bpm and stroke volumes from 12 to 30 mL. For the acute animal trial ovine endothelial cells were harvested from saphenous veins, isolated and populated in-vitro, and finally transferred to the pVAD surface. Cellularized pVADs were deployed in 4 adult sheep and actuated for up to 5h.

Results: In-vitro pVAD actuation demonstrated reliability for several millions of cycles. The endothelialization protocols were successfully tested in-vitro, yielding an adherent monolayer of cells over several hours of pVAD operation. The acute animal trials successfully demonstrated pVAD functionality under all operating conditions. In-vivo, no sign of thrombosis was present on the membrane and the endothelial monolayer was preserved intact upon implantation and operation in all tested animals.

Discussion: The proposed approach for improved hemocompatibility of the pVAD was validated by in-vitro experiments and acute animal trials. Future work will focus on improved actuation strategies and long-term response of endothelial cells in-vivo.

POSTER SESSION PT01: KIDNEY & LIVER

P1

THE EFFICACY OF PLASMA EXCHANGE FOR THE BILIRUBIN REMOVAL IN PATIENTS WITH HYPERBILIRUBINEMIA

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Aim: It is believed that the hyperbilirubinemia is not the cause but the result of the liver failure. However, plasma exchange (PE) is performed for the bilirubin removal in patients with hyperbilirubinemia in Japan occasionally, and we sometimes find it clinically effective in the patient who underwent PE against hyperbilirubinemia. The aim of this study is to evaluate the relationship between the changes in blood bilirubin level before and after PE and the outcome of the PE-treated patients.

Methods: We retrospectively assessed the changes in blood bilirubin level before and after treatment of PE and 28 days mortality. We calculated the bilirubin removal rate and the rebound rate post-PE in ICU patients with hyperbilirubinemia who were treated between December 2006 and September 2017.

Results: Fifty-one PEs were performed in 14 patients during the study period. The SOFA Score was 12.2 ± 2.8 in survival group and 9.4 ± 3.1 in non-survival group. The platelet count and serum bilirubin concentration was 77×103 and 19.0 ± 9.6 mg/dL in survival group and 35×103 and 20 .5 ± 4.4 mg/dL in non- survival group. Bilirubin removal rate was 32 ± 7.4 % in survival group and 35 ± 14.5 % in non-survival group. While the rebound phenomenon was seen in both groups next day of the procedure, the rebound rate in survival group was significantly lower than that of non-survival group, 23 ± 10 % and 38 ± 16 %, respectively.

Conclusions: We can conclude that the lower rebound rate of blood bilirubin level after PE is predictive of favorable patient outcome. While the efficiency of bilirubin removal is not directly associated with outcome, PE should be considered for hyperbilirubinemia with the patients with relatively higher platelet count.

P2

IN VITRO ASSESSMENT OF DIFFERENT MATERIAL HAEMODIALYZER CLEARANCE IN HIGH- FLUX HAEMODIALYSIS AND ON-LINE HAEMODIFILTRATION

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Objectives: The aim of the study was to evaluate the clearance of different material hollow fiber haemodialyzers undergoing high-flux haemodialysis (HD) or on-line haemodiafiltration (HDF) in an *in vitro* set-up.

Methods: A pool of 625 ml of uremic plasma and 500 ml of erythrocytes was connected to a FMC 5008 device and HD or HDF treatments were performed. A blood, dialyzate, ultrafiltration and substitution flow of 400ml/min, 600ml/min, 10ml/h and 134ml/min (0 in HD) respectively were set in 1h experiment. FX-1000 Cordiax (PS), BG-2.1U (PMMA), Sureflux-2.1UX (CTA) and Polyflux-210H (PA) haemodialyzers were tested. Blood samples were taken at t=0', 10', 20' and 60'. Levels of β2-microglobulin, myoglobin, prolactin, α1-microglobulin and albumin were measured. A monocompartimental model was implemented to fit the clearance K (ml/min).

Results: HDF treatments showed the highest clearance values for all molecules as expected. β2- microglobulin clearances for PMMA, PS and CTA were KPMMAβ2-m=241±1, KPSβ2-m=241±5 and KCTAβ2-m=202±6 respectively (p>0.05). PMMA obtained the highest depuration values for all other molecules as well as a noteworthy albumin elimination (KPMMAMyo=199±3, KPMMAProl=148±37, KPMMAAlfa-1=49±11 and KPMMAAlb=22±3) as compared with the other dialyzers. CTA showed enhanced clearance as compared to PS (KCTAMyo=180±6 *vs*. KPSMyo=93±7, p<0.01, KCTAProl=112±2 *vs*. KPSProl=52±6, p<0.01 and KCTAAlfa-1=19±5

vs. KPSAlfa-1=5±4, p< 0.05). PA achieved the lowest clearance values for all treatments and molecules.

Discussion: In terms of *in vitro* depuration, CTA as well as PS should be considered as all-purpose haemodialyzers regardless of the chosen treatment. Despite the highest obtained clearances for PMMA, significant albumin absorption was present in HDF. PA should be reserved for low molecular weight toxins.

P3

THREE DIFFERENT TYPES OF NATIVE ARTERIOVENOUS FISTULA: TIMING OF CREATION AS AN INDEPENDENT PREDICTOR OF THE SUCCESSFUL MATURATION

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Background: Arteriovenous fistula(AVF) is a vascular access that guarantees the long-term survival and quality of life of patients on hemodialysis (HD).

Methods: Medical records for creation of an AVF in the patients with chronic kidney disease stage 5 were retrospectively studied for year 2016. Demographic variables, timing and location of the AVF creation, hemodialysis vintage, and the persistence of diabetes were included in the regression analysis for determination of the predictors of successful maturation of AVF.Three different types of native arteriovenous fistula were created: the distal (radial-cephalic), middle-arm (radial-cephalic) and proximal (brachial-cephalic). Primary trombosis of AVFwas defined as immediate failure of fistula within 72 hours of surgery.

Results: A total number of 341 AVF fistula were created in 257 patients. In195 (76%) patients only one AVF was createdand in 62 (24%) patients were created more than one AVF. The distal AVF was dominant location in 50.4% of created fistulas, followed by middle-arm locationin 34% and proximal in 15.6% of created fistulas. Prevent AVF fistulas were 15.8%. Successful maturation of AVF was presented in 69.8% of created fistulas. The number of successful AVF was significantly higher in prevent AVF compared to non-prevent AVF, (p=0,002). The number of successful AVF was significantly higher in the distal location compared to the middle-arm location (p=0.000). The independent predictor of the successful maturation of AVF was preventive creation of fistula (OR=1.22, 95% CI:1.07-1.39, p=0.002).

Conclusion: The timing of creation of AVF had an important role in the process of AVF maturation.Distal AVF is still the gold-standard access for hemodialysis.

P4

COMPARISON OF PLATELET ACTIVATION OF ELECTRON-BEAM AND STEAM STERILIZED MEMBRANES

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Objectives: Use of electron-beam sterilized haemodialysis membranes was associated with risk of thrombocytopenia in a study of 2011 (Kiaii et al, JAMA, October19,

2011-Vol306, No. 15). We investigated platelet activation of electron-beam and steam sterilized haemodialysis membranes.

Methods: Mini-dialyzers with membrane area 360 cm² were prepared from Baxter Revaclear400 (steam), WegoF14, or WegoF15 (electron-beam). They were tested in-vitro with 25 ml recirculating human whole blood. Samples were drawn after 0, 60, 90 and 120 minutes. Platelets were counted (cell counter) and platelet factor 4 (PF4) was analyzed by commercial ELISA. 5 independent experiments with 3 different mini- dialyzers in parallel were done. Polyvinylpyrrolidone was analyzed in aqueous extracts of the full dialyzers via an iodine complex and photometry at 470 nm.

Results: Results are given in % and starting value normalized to 100. Data shown represent mean (SEM) after 0/60/90/120 min. Platelet values of Revaclear 100(0)/39(9)/34(8)/37(7), of WegoF14 100(0)/28(7)/18(4)/23(4), of WegoF15 100(0)/19(3)/17(3)/23(3). PF4 values of Revaclear 100(0)/378(55)/501(70)/551(87), of Wego F14 100(0)/518(86)/659(93)/692(146), of WegoF15 100(0)/555(59)/675(80)/746(105). In extracts polyvinylpyrrolidone was highly increased in WegoF14 and WegoF15 as compared to Revaclear.

Discussion: Platelets decreased and PF4 increased in all cases. Compared to Revaclear, WegoF14 and WegoF15 showed stable trends of larger platelet drop and PF4 increase pointing towards stronger platelet activation. Differences were not significant except for PF4 after 60 minutes between Revaclear and WegoF15 (paired t-test on $p<0.05$). Based on elevated polyvinylpyrrolidone concentration in the extracts it is hypothesized that electron-beam sterilization caused material degradation which made the membrane more susceptible to platelet activation.

P5

EVALUATION OF PRE- AND POST-DILUTION CONTINUOUS VENO-VENOUS HEMOFILTRATION ON BIOCOMPATIBILITY SHINYA

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Objective: We investigated differences in biocompatibility between pre- and post-dilution continuous veno- venous hemofiltration (CVVH) focusing on leukocyte and platelet function.

[Patients and methods] The subjects were twelve septic shock patients who underwent CVVH for acute kidney injury (AKI) between January 2016 and September 2017. The first six patients received pre-dilution CVVH and then consecutive six patients received post-dilution CVVH. The blood flow rate and filtration flow rate for CVVH were set to 150 ml/min and 35 ml/min, respectively using polysulfone hemofilter. Leukocyte and platelet counts were determined at 0 and 24 h after CVVH. Serum interleukin (IL)-6 and IL-10 levels, and the expression rates of regulatory T cells (Treg) and monocyte HLA-DR, neutrophil phagocytic and sterilizing ability, and platelet P-selectin expression rate were determined at 0, 6 and 24 h after CVVH.

Results: Significant differences in patients' characteristics were not found between the two groups. Serum IL-6 was decreased during pre- and post-dilution CVVH over time. Serum IL-10 level was decreased during pre-dilution CVVH, whereas serum IL-10 level during post-dilution CVVH was not changed. The Treg and platelet P-selectin expression rates significantly increased at 24 h compared with 0 h during post-dilution CVVH. Neutrophil phagocytic ability at 24 h was significantly decreased compared to that at 0 h during post-dilution CVVH. No significant changes in leukocyte and platelet function were observed during pre- dilution CVVH.

Discussion: Compared with post-dilution CVVH, pre-dilution CVVH had significantly fewer changes in Treg, neutrophil phagocytic ability, and platelet P-selectin expression. Therefore, selection of pre-dilution CVVH, which has superior biocompatibility, may reduce the risk of CVVH-associated exacerbation of clinical conditions in septic shock patients with AKI.

P6

IMPROVEMENT OF VASCULAR ACCESS CREATION FOR HEMODIALYSIS IN REPUBLIC OF MACEDONIA

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Objectives: In order to achieve good vascular access outcome for hemodialysis (HD), the aim of our work was to increase the use of arterio-venous fistulas (AVFs) and reduce the use of central venous catheters (CVCs) in the 15 year period.

Methods: In the period 2003-2017, we performed 4412 AVFs, 978 tunneled catheters (TCs), 10668 femoral catheters (FCs), 377 jugular catheters (JCs), 601 subclavian catheters (Scs). We created AVFs in 4th-5th stage of renal insufficiency, few months before HD, Doppler mapping of blood vessels was mandatory; no cannulation of veins of both forearms; standard use of loupes 3-4 magnification;

artery and vein dilatation; vein preparation to avoid swing possibility, adventitia removal. Catheter insertion: single/dual catheters; temporary/permanent; femoral/subclavia of jugularroute (15/20/24cm lenght); Seldinger technique. Removal of catheter was related to bacteriemia, and/or to inadequate blood flow.

Results: We performed 4412 AVFs, 978 FCs, 377 JCs, and 601 SCs. The number of AVFs ranged from 199 (72%) in 2003 to 431 (88%) in 2017, for TCs from 62 (28%) in 2003 to 59 (12%) in 2017. We increased a number of JCs from 41 in 2015 to 111 in 2017, but reduced Scs from 67 in 2014 and 2015 to 32 in 2017.

Discussion: Creation of vascular access is time and money consuming procedure. Although end stage renal disease patients represent only 1,2% of medical care population, it is spent 8,2% expenditures. A percentage of 24-42% of all AVFs would require intervention to facilitate maturation. Additional 3 month period is needed for sufficiently developed AVF for cannulation. We achieve the goal to increase the use of AVFs and to reduce the use of TCs. We continue with femoral cannulation in pre-AVF period, increase JCs in patients preparing for transplantation, and reduce the use of SCs.

P7

HEMOGLOBIN VARIABILITY AND ALL-CAUSE MOTALITY IN HEMODIALYSIS PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: Hemoglobin (Hb) variability has been reported to be associated with mortality in dialysis patients in some but not all studies. We aimed to establish the prognostic significance of Hb variability with all- cause mortality in hemodialysis patients through this meta-analysis

Methods: Medline, Embase, Cochrane Library and Web of Science were searched for studies assessing the association between Hb variability and all-cause mortality adjusted for other covariates in hemodialysis patients.

Results: We included 3 studies of 5 cohort, with a total of 274094 patients. Forest plots displayed that the combined HR for all-cause mortality was 1.09 (95% CI, 1.01-1.08, P< 0.00001) per 1 g/dl increase of Hb variability.

Conclusion: In current evidence, our meta analysis found an association between Hb variability with all-cause mortality in patients receive hemodialysis therapy, but it should be further confirmed in clinical trails.

P8

OCCULT HEPATITIS C AND ASSAY SENSITIVITY IN PATIENTS WITH TREATMENT-INDUCED VIRAL CLEARANCE

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Background: Occult hepatitis C is defined by the presence of HCV RNA in the peripheral blood mononuclear cells (PBMCs) and liver cells, in the absence of serum HCV RNA.

Objective: To detect the persistence of occult hepatitis C in hemodialysis patients and patients without renal disease with treatment-induced clearance of hepatitis C virus (HCV) infection, using assays with a very low detection limit of viremia.

Methods: A group of 13 hemodialysis patients and a group of 43 patients without renal disease, with treatment-induced HCV infection clearance were investigated in the study. The hemodialysis patients were treated with pegylated interferon α-2a only, while the patients without renal disease were treated with a combination therapy of pegylated interferon α and ribavirin. Sustained viral response, defined as an absence of serum HCV RNA, 6 months after completion of the antiviral treatment, was confirmed by a reverse transcriptase-polymerase chain reaction (RT-PCR) assay with a detection limit of 20 IU/ml. Detection of a possible persistence of HCV RNA in the PBMCs and plasma samples was assessed by an ultrasensitive RT-PCR assay, with a very low detection limit of viremia (2 IU/ml).

Results: HCV RNA was not detected in the PBMCs and plasma samples of hemodialysis patients and of patients without renal disease, when assessed by the ultrasensitive RT-PCR assay.

Conclusions: When sensitive RT-PCR assays were applied, to determine if treatment induced clearance of HCV infection had been successful, occult hepatitis C could not be detected by an ultrasensitive assay, neither in hemodialysis nor in patients without renal disease.

P9

COMPARISON OF INTERNAL FILTRATION AMONG IN-HOUSE DIALYZERS BASED ON A TWO- DIMENSIONAL MOMENTUM TRANSPORT MODEL

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Objectives: The removal of middle molecules for the treatment of renal pathologies may be provided by designing dialyzers enhancing internal filtration. A two-dimensional axisymmetric mathematical model describing steady momentum transport in dialyzers allowing for the prediction of the extent of internal filtration at varying geometry and operating conditions was recently developed and validated. In this work, a comparison of in-house dialyzers, differing in total surface area, geometry and permeability, is reported based on the model-predicted internal filtration for each module at fixed operating conditions.

Methods: The mathematical model was used to calculate the rate of internal filtration for eight in-house dialyzers at blood and dialysate flow rates typically used in clinics and zero net ultrafiltration flow rate. The dialyzers differed in geometry (i.e. inner fiber diameter, module effective length, number of fibers, total surface area) and membrane properties (i.e. ultrafiltration coefficient). Dimensional analysis was used to identify how the dialyzer-related parameters determining momentum transport may be combined to enhance internal filtration.

Results: At given operating conditions, good correspondence was found between the value of the pressure modulus, combining geometrical and transport parameters, and the rate of internal filtration for each module. At given pressure modulus, higher internal filtration was calculated for the modules having higher packing density. No good correspondence was found between the value of all the dimensional parameters singularly considered (i.e. total surface area, membrane permeability) and the rate of internal filtration, as well as between the pressure drop in the blood compartment calculated for each module and the rate of internal filtration.

Discussion: Model predictions show that internal filtration depends on the interplay among geometrical and transport parameters and may be helpful to design dialyzers enhancing the removal of middle molecules

P10

INTRADIALYTIC BLOOD PRESSURE PATTERN RECOGNITION BASED ON DENSITY PEAK CLUSTERING

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End-stage renal disease (ESRD) is the final stage of chronic kidney disease (CKD) and requires hemodialysis (HD) for survival. Intradialytic blood pressure (IBP) measurements are necessary to ensure patient safety during HD treatments and have critical clinical and prognostic significance. Studies on IBP measurements, especially IBP patterns, are limited. All related studies have been based on a priori knowledge and artificially classified IBP patterns. Therefore, the results were influenced by subjective concepts. In this study, we proposed a new approach to identify IBP patterns to classify ESRD patients. We used the dynamic time warping (DTW) algorithm to measure the similarity between two series of IBP data. Five blood pressure (BP) patterns were identified by applying the density peak clustering algorithm (DPCA) to the IBP data. To illustrate the association between BP patterns and prognosis, we constructed three random survival forest (RSF) models with different covariates. Model accuracy was improved 3.7~6.3% by the inclusion of BP patterns. The results suggest that BP patterns have critical clinical and prognostic significance regarding the risk of cerebrovascular events. We can also apply this clustering approach to other time series data from electronic health records (EHRs). This work is generalizable to analyses of dense EHR data.

P11

PATIENT-SPECIFIC PULSE WAVE PROPAGATION MODEL IDENTIFIES CARDIOVASCULAR RISK CHARACTERISTICS IN HEMODIALYSIS PATIENTS

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Objectives: There are several non-invasive cardiovascular state biomarkers based on the pulse (pressure) wave propagation properties, but their major determinants are not fully understood. In our study we aimed to provide a computational framework to precisely dissect the information available in non-invasively recorded pulse wave in hemodialysis patients.

Methods: Radial pressure wave profiles were recorded before, during and after hemodialysis sessions in 35 hemodialysis patients and once in a group of 32 healthy volunteers. Each recording was used to estimate six subject-specific parameters of pulse wave propagation model. The model describes blood flow in the system of fifty-five arterial segments using one-dimensional equations for flow in compliant and tapering vessels. Pressure profiles were also analyzed using SphygmoCor software (AtCor Medical, Australia) to derive values of already established biomarkers, i.e. augmentation index (AI) and sub-endocardial viability ratio (SEVR).

Results: AI remained on average stable at 142 +/- 28% during dialysis and had similar values in both considered groups. SEVR, which pre-dialytic value was on average lower by 12% compared to healthy participants, was improved by hemodialysis, with post-dialytic values indistinguishable from those in healthy population (p-value > 0.2). The model, however, identified that the patients on hemodialysis had significantly increased stiffness of both large and small arteries compared to healthy counterparts (>60% before dialysis with p-value < 0.05 or borderline) and that it was only transiently decreased during hemodialysis session. Additionally, correlation-based clustering revealed that AI reflects the heart ejection profile and SEVR is associated with stiffness of larger arteries.

Discussion: Patient-specific pulse wave propagation modeling coupled with radial pressure recording, correctly identified increased arterial stiffness in hemodialysis patients, while regular pulse wave analysis based biomarkers failed to show significant differences.

P12

CHANGES OF HAEMATOCRIT, HAEMOGLOBIN AND TOTAL PLASMA PROTEIN DURING HAEMODIALYSIS

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Objectives: Relative blood volume (RBV) changes during haemodialysis (HD) are typically estimated based on measurements of haematocrit (HCT), haemoglobin (HGB) or total blood protein concentration (TBP). The aim of this study was to measure changes in the above parameters during HD in order to compare the RBV estimation methods.

Methods: 11 anuric patients (age 62.6 ± 12.4 years, 8 females) were studied during a 1-week maintenance HD treatment. The study included data from 28 HD sessions (1, 2 or 3 consecutive sessions for each patient) with dialyzer blood flow rate 270 ± 50 mL/min and ultrafiltration 2.6 ± 0.7 L. Blood samples were collected from the arterial port in the fistula at the beginning and at the end of each session. The haematologic analysis of blood was performed using the automatic analyzer Advia® 2120 (Siemens Healthcare) with HCT calculated as the product of the red blood cell count (RBC) and mean corpuscular volume (MCV) in the analyzed sample. The measurements of total plasma protein (TPP) were performed using the clinical chemistry analyzer Advia® 1800 (Siemens Healthcare).

Results: During the 28 analyzed HD sessions HCT increased by 9.7 ± 6.9% (mean ± SD), MCV decreased by 1.5 ± 0.2%, HGB increased by 11.1 ± 6.2%, TPP increased by 16.4 ± 9.3%, while TBP (calculated as the sum of TTP and HGB weighted by HCT) increased by 10.8 ± 5.8% (all changes statistically significant, p< 0.0001). The increase of HGB and TBP were almost equal with a very small (0.3%) and insignificant (p=0.16) difference.

Discussion: Tracking HGB or TBP during HD can be treated as equivalent. The relative difference between HCT and HGB increase during dialysis can be explained by the concomitant decrease in MCV. Due to reduced red cell volume, the HCT-based estimate of RBV can underestimate the actual blood volume changes.

POSTER SESSION PT02: VADS: NEW METHODS

P13

MICRO BEARING DEVELOPMENT FOR IMPLANTABLE VENTRICULAR ASSIST DEVICES

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Ventricular Assist Devicesare are implantable blood pumps developed to provide mechanically circulatory support to congestive heart failure patients. The centrifugal impeller on VAD is supported by micro bearings. The main design requirements for these micro bearings are: reliability, low friction, wear resistance, precision motion, bio compatibility and hemolyze proof.

The bio compatibility and friction are concurrent requirements due to limits imposed to the materials selection by the first one. The best pair of materials in terms of friction and wear resistance sometimes do not fulfil the biocompatibility requirements. To explore the design performance of micro bearing for DAV applications three type of bearing were developed, a single point contact, a conical friction and four configurations of micro rolling bearing.

The support bearings and shafts were manufactured in Alumina (Al2O3), Zirconia (ZrO2), Ultra High Molecular Weight Polyethylene (UHMWP), and stainless steel, according the friction desired. They were manufactured using conventional precision micro machining process and 3D printer. After manufacturing all bearings parts had its surfaces characterized for geometrical and roughness.

Experiments were performed under constant load of 1, 5 and 10N and rotational speed of 2.000, 3.000,

4.000 and 5.000 rpm. The experiments were done with and without lubrication. Wear, surface damage and deformation of the bearing parts were measured at pre-defined set of time. The results allowed the development of design

charts comparing the results for each type of micro bearing, depending on the load and speed. Te bearings were also assembled in a test pump and its performance in therm of vibrations, and pressure under the same functional paramenter were evaluated on a test bed.

P14

OPENHEART PROJECT – IMPROVING INTERNATIONAL COLLABORATION IN THE FIELD OF MECHANICAL CIRCULATORY SUPPORT THROUGH AN OPEN-SOURCE RESEARCH COMMUNITY

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Objectives: Currently an estimated 85% of all global research resources are wasted due to false and non- reproducible results or inefficient translation of knowledge into useful applications. Adoption of large-scale collaborative research with a strong replication culture has been shown to be successful in several biomedical fields. The OpenHeart Project is an open-source project, which aims to improve international collaboration and research practices within the field of Mechanical Circulatory Support (MCS). Key objectives are:

- Improved collaboration and standardization
- Improved and open educational tools
- Development of new and improved solutions for MCS

Methods: To facilitate collaborative research an open research platform was developed. A website was implemented to inform researchers about the background, aims and progress of OpenHeart. Embedded team collaboration tools provide the opportunity to propose collaborations and projects to other OpenHeart members as well as raising current research questions. An MCS wiki is being implemented to define common research terms within the field and provide standardized protocols developed within the community. Data repositories will allow PhD students and researchers to upload and share their work within the OpenHeart community. The uploaded data will be open-source (creative commons license CC BY 4.0), thus free to share, copy and redistribute.

Results: Team collaboration tools, MCS wiki and data repositories have been implemented using the software solutions Stride, Confluence and Bitbucket (Atlassian, Sydney, Australia). Atlassian offers free user licenses to open-source projects, thus participation in OpenHeart is free for everyone. The platform can be found online under www.openheartproject.org and we invite everyone to visit and join OpenHeart.

Discussion: Successful implementation of the OpenHeart Project will improve inter-laboratory collaboration and standardization within the field of MCS. Development of free education tools will improve training and education of emerging researchers and subsequently improve research outcomes.

P15

A NEW METHOD TO GENERATE A PULSED FLOW IN ROTARY BLOOD PUMPS

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Objectives: Objective of the research effort is to develop a new method to generate a pulsed flow for a rotary blood pumps (RBP) without changing the speed of the pump. There is general consensus, that a pulsed flow is desirable for blood pumps, clinically used as VAD achieved by a periodical change in rotational speed of the RBP that may can lead to an increase of blood damage, making this method unviable. In addition, the inertia of the rotor reduces the effectiveness of this method.

Methods: The new method is based on inclusion controllable valve at the the recirculation channel (RC) of RBP.The valve is operated periodically changing the hydraulic resistance of RC. As a result the pulsed flow is generated at the output of RBP-RC system, while the speed pump remains constant. The studies were carried out on a pediatric mock circulation. The dynamics of the system has been investigated for several clinical applications: VAD, Total Artificial Heart (TAH) and Heart Lung Machine (HLM).

Results: LVAD. The simulation of heart failure (Q =1l/min, Pao=80/60 mmHg): ΔPao - 13 mm Hg (a nopulsing mode) vs ΔPao -22 mmHg (a pulsing mode).

TAH. Pao -96/76 (80) mmHg, Pla -18/14(16) mmHg Q (LV) - 2.8/0.8 (1.8) l/min and Q (RV) -2/1.6 (1.7) l/min HLM. Pao - 79/43 (56) mmHg, Q - 3.2/0.8(1.9) l/min

Discussion: The research demonstrates the viability of the new method to generate a pulsed blood flow without changing the RBP speed. The method is universal and can be applied with different RBPs models to various clinical therapies.

P16

SYNCHRONIZED VENTRICULAR ASSIST DEVICES BASED ON ULTRASONIC MOTORS

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Background: Continuous-flow left ventricular assist devices (LVADs) have revolutionized advanced heart failure care. These compact, fully implantable heart pumps are capable of providing meaningful increases in survival, functional capacity, and quality of life. Implantation volumes continue to grow, but several challenges remain to be overcome before LVADs will be considered as the therapy of choice for all patients with advanced heart failure. They must incorporate design elements that reduce shear stress and avoid stasis to reduce the frequent adverse events of bleeding, stroke, and pump thrombosis. These adverse events are mainly caused by the pump patient interface due to the constant blood flow, which could not synchronize with the native diseased heart.

Methods: To develop a synchronized ventricular assist device, several actuating technologies are investigated in terms of response time, thrust force, weight, volume, and controllability. Then an ultrasonic motor is chosen as the actuator of ventricular assist devices. Finally a bionic pulsatile blood pump prototype with a diameter of 86mm and a thickness of 47mm is developed and investigated in a mocked circulatory system.

Results: A flow of 5L/min is achieved with an average afterload of 100mmHg. A shifting vortex flow is found in a bionic blood chamber that would be redirected to the aorta during ejection to form a persistent recirculating flow field, which is similar to the echocardiographic flow field in a native left ventricle. The prototype is synchronized to the mimicked cardiac cycle in a mocked circulatory system, and the hemodynamic measurements are recorded with varying time delay from 0% to 90% of the cardiac cycle in 10% steps. Experimental results suggest that a time delay of 40% would benefit the improved arterial perfusion.

P17

NECESSITY OF INTERNAL FLUID VOLUME MONITORING IN THE LEFT VENTRICULAR ASSIST DEVICE PATIENT

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Objective: Research suggests Ventricular Assist Device (VAD) therapy allows for ventricular off-loading to relieve heart failure symptoms. Internal fluid volume monitoring as part of Cardiac Resynchronization therapy assists in the decision for diuretic usage in volume decompensation. This study examined the significance and reliability of fluid monitoring and thoracic impedance levels in VAD patients, as little research exists currently.

Methods: Retrospective data was analyzed on patients implanted with a VAD from 9/2012 to 9/2017 (n=40, 75% male). Fluid monitoring levels (OptiVol [Medtronic, n=18] and Corvue [St. Jude, n=6]) were evaluated to look for relative relationships in VAD patients. Those without monitoring devices were excluded (n=16). Pearson correlation and Chi-Square analyses were used to test relationships.

Results: Medtronic data showed strong negative correlation between OptiVol levels and days on device [Mean days 207.19 +/-132.63); r=-0.754, n=18, p=0.000). Hospitalization within 3 days of obtaining fluid volume levels was not related to elevated OptiVol levels (X2 [1, n=12]=4.80, p=0.28). Thoracic Impedence was statistically related to being hospitalized within 3 days (X2 [1, n=4]=4.00, p=0.046). The Corvue cohort demonstrated no statistical relationship between fluid levels and hospitalization (X2 [1, n=4]=0.44, p=0.51); and no significant relationships were identified in either group on Brain Natriuretic Peptide (BNP) or proBNP levels (p>0.05).

Discussion: Medtronic devices have shown an inverse relationship to hospitalization, while no relationship exists for Corvue devices. Although the cohort sample was small, clinically it appears that despite higher fluid volume levels, VAD patients are being off-loaded adequately to prevent hospitalizations. A larger, multi-center study is suggested to support these findings and further establish the ongoing importance of internal fluid volume monitoring.

P18

INDUCTIVE ENERGY TRANSFER UNIT BASED ON CLASS-E AMPLIFIER WITH LOWERED MISALIGNMENT SENSITIVITY

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Objectives: This study is focused on the development of design method of inductive energy transfer (IET) unit for implantable biomedical devices. Developed method takes into account device specifics and ensures stable efficiency of energy transfer.

Methods: Developed method elaborates design of the IET unit based on class-E power amplifier. Geometrical parameters of the transmitting and receiving coils are initialized explicitly in this method and used for calculation of IET

unit parameters. Self-inductance of each coil and their mutual inductance were calculated as a function of displacements using a numerical solution of Neumann\'s equation. Class-E power amplifier reactive components values were calculated and adjusted to provide highest IET efficiency for a range of possible coils displacements.

Three pairs of coils were selected for validation of the method. The outer diameter of the coils (70 mm) is typical for IET units used with ventricular assist devices. Other geometrical parameters such as number of turns and inner coil diameter are different for each coil. Electrical parameters of the unit were simulated in LTSpice software. Experimental verification of the numerical calculations is provided.

Results: Design method of IET unit based on the class-E power amplifier was developed. The method ensures high efficiency and output power for different mutual orientations of transmitting and receiving coils. IET efficiency is above 80% for specified axial distance between the coils (15...20 mm). Close agreement of measured and calculated output power and energy transfer efficiency is demonstrated.

Discussion: Inevitable displacements of the transmitting and receiving coils in IET unit for implantable biomedical systems lead to detuning of class-E amplifier and deterioration of energy transfer parameters. Presented method ensures robustness of the IET unit. Limitations attributed to optimization of geometrical parameters of the unit with class-E power amplifier are evaluated.

P19A

COMPACT MOCK CIRCULATORY LOOP FOR LONG-TERM DURABILITY TESTING OF A PULSATILE TOTAL ARTIFICIAL HEART

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Objective: In vitro durability testing of a Mechanical Circulatory Support System is a useful method prior to chronic animal trials or clinical use. Furthermore initiating durability testing early in the design process can lead to a more reliable design and device. The objective of this study was to develop a suitable long- term durability tester for the ReinHeart pulsatile Total Artificial Heart (TAH).

Method: A specialized Mock Circulatory Loop (MCL) was designed including arterial and pulmonary compliances, adjustable systemic and pulmonary resistances and left and right inlet reservoirs (representing left and right atrium and the venous compliance) to evaluate the durability of the ReinHeart TAH under realistic conditions. In addition a self-sufficient monitoring and data acquisition system was developed to allow long-term independent running of the tester.

Results: The MCL is able to simulate several physiological conditions such as a flow of 5 L/min with a mean aortic pressure of 100 mmHg (80 / 120 mmHg), mean pulmonary pressure of 20 mmHg (15 / 35 mmHg) and a left and right atrium pressure of 10 mmHg. The MCL (including the TAH) is surrounded by a phosphate buffered saline solution (pH 7.4, osmolarity of 310 mosm/l) tempered at 37°C (+-1°C). The pump fluid is a blood analogue water and glycerol solution (viscosity of 3.6 mPas, osmolarity of 310 mosm/l). The monitoring system is constantly recording the four mentioned pressures, the fluid temperature and all important intrinsic TAH parameters. It generates warnings if any parameter exceeds their defined threshold and is able to stop the test if necessary.

Discussion: With the designed tester a long-term durability test of a TAH can be performed and properly monitored throughout a long period of time and keeping its maintenance effort as small as feasible.

P20

TWO PHASE BLOOD MODEL FOR UPSCALED MODELS USING ALGINATE BEADS

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Objectives: In a scaled model of different flow geometries frequently used water-glycerol mixtures do not suffice, because the fluid mechanics influence of red blood cells is not represented. The objective is the development of a blood model fluid, which has the bulk properties of blood and as well the properties of a second phase, the red blood cells.

Methods: Beads made of alginate are used as a model for red blood cells because their mechanical-elastic properties are similar to those of erythrocytes. A water-glycerol or water-polyethylene glycol mixture is used as a model for plasma. The plasma model must have a certain viscosity to achieve the Reynolds similarity. Furthermore, the spheroidal beads should have a slightly higher density than the surrounding medium and thus float in motion for several minutes. Depending on the scaling, several million beads are required. This implies that fabrication and quality control of the alginate beads poses a considerable challenge. A camera tracks the flow path of the beads through the specific geometry. Because of their transparency, it is possible to look at several layers in the fluid by choosing the

appropriate light sections. Subsequently, the flow analysis of the beads is performed by using the PIV technique.

Results: Alginate beads are suitable to represent red blood cells in a model fluid. Preliminary flow analysis has been performed in a model of the ventricular assist device Heartmate II. The results showed a good agreement between the predicted behavior and the actual experiments. Moreover, the results of the experiment lead to a possible optimization of the geometry of future rotor blades in blood pumps in order to reduce hemolysis.

Discussion: The proposed blood model shows promising results in an initial case, a flow in a narrow channel. Further channel geometries will be explored.

P21

EFFECTS OF IMBALANCED INFLOW AND OUTFLOW DISTRIBUTIONS ON DOUBLE-FLOW FONTAN PUMPS

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Introduction: Although Fontan circulation improves survival for univentricular patients, cardiovascular complications impair outcomes. Inclusion of a pump with a single impeller, two inflows, and two outflows at the cavopulmonary connection may reverse compromised hemodynamics. To maintain physiologic venous return mechanisms, pump inlet pressures should remain equal under typically imbalanced flow from the inferior and superior vena cava. Furthermore, imbalanced outflow conditions should not adversely impact pump functionality. The aim of this study was to identify the hydraulic behavior of four pump designs in-vitro under imbalanced flow distributions.

Methods: Two previously described pump designs—PD1 and PD2—and two new pump designs—ND1 and ND2—were 3D printed and tested in a modular platform simulating Fontan circulation. Pump hydraulic performance was measured at an operating speed corresponding to a pressure head of 8-10mmHg and flow of 4.5L/min. Imbalanced flow conditions were achieved by varying the two inflow ratios (1:1, 1:2, 1:0) with balanced outflows or vice versa. Imbalances were quantified as differences between either inlet or outlet pressures (ΔP).

Results: Each pump reached the aforementioned operating point at the following speeds: ND1 2800rpm, ND2 3100rpm, PD1 5300rpm, PD2 6000rpm. At 4.5L/min and 1:2 flow ratio between the inflows, inlet ΔPs were: ND1 5.3mmHg, ND2 4.1mmHg, PD1 3.5mmHg, and PD2 2.2mmHg. ND pumps depicted a quadratic relationship between the degree of inflow imbalance and inlet ΔPs; PD pumps depicted a non-monotonic behavior. At 4.5L/min and a 1:2 flow ratio between the outflows, the difference between outlet ΔPs ranged from 2.0-4.6mmHg.

Discussion: Four double-flow pump designs for Fontan were evaluated for their performance. Imbalanced outflow conditions did not adversely impact pump behavior. PD devices indicated instabilities during unbalanced inflow conditions. For the ND pumps, design features were identified that can be modified to balance inlet pressures, thereby maintaining physiologi venous return mechanisms.

POSTER SESSION PT03: VADS MISCELLANEOUS & OTHER

P22

DIAGNOSIS OF THE PERISTALTIC MOTION FOR THE DEVELOPMENT OF THE ARTIFICIAL ESOPHAGUS

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For the development of the artificial esophagus, shape memory alloy actuator had been used and evaluated in our University. However, the peristaltic motions are sometimes different in every patients, and some patients sometimes have the aspiration pneumonia. For the development of the artificial esophagus, precise evaluation of the peristaltic motion have to be diagnosed quantitatively.

For this purpose, newly developed peristaltic motion diagnosis machine had been invented, studied and evaluated in this study (Jpn.Pt Appl 2017-86322). This patent can be not only used for the analysis of the peristaltic motion, but also used for the diagnosis of the taste in the liquids and foods. Stereo video camera imaging had been used in the experiments using the healthy adult volunteers. Experiments of the drinking motion for the several kinds of liquid, and the experiments for eating some kinds of bread which is delicious, or not delicious, had been carried out after ethical committee allowance.

Time series data for the X axis, Y Axis, and Z axis motion had been evaluated and the spectral analysis of the 3D stereo video image had been performed. And the results showed the interesting properties of time series data depending on the taste and the spectral analysis showed interesting properties with the bread which was tasted as delicious, or as hard to eat. Peristaltic motion and drinking speed had been thought to be different depend of the kinds of liquid or foods.

The results of this study had suggested the importance of the automatic control for the artificial esophagus in future, because the peristaltic motion must be altered depending upon the kinds of liquid and the taste of the foods.

P23

CONSTRUCTION CONCEPT OF A PORTABLE DEVICE FOR ADAPTIVE INSULIN THERAPY BASED ON NONINVASIVE GLUCOSE CONTROL

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Objectives: The most common way to compensate Type I diabetes is pump insulin therapy. The closed-loop blood glucose (BG) control will allow significant improvement of quality and efficiency of insulin therapy. The use of noninvasive continuous glucose monitors could enable more frequent measurements without any discomfort to the patient improving the effectiveness of control. To ensure efficient closed-loop relationship between closed-loop elements prediction algorithms are used.

Methods: A closed-loop consists of a portable noninvasive glucose monitor (PNG) and an insulin pump (IP). The closed-loop control is based on the model predictive control ensuring cross correlation of data received from the PNG and the predictive control parameters. The decision of a required dose of insulin is made on the basis of the data computed by the developed closed-loop.

For closed-loop elements tests special test bench simulating the BG change in a model solution was used. To test the algorithm for short-term prediction we suggest using the DirecNet database that includes clinical daily BG tracks.

Results: PNG test shows the noninvasive BG measurements error of 25%, with average error in normoglycemia of 16.09%. Clarke error grid analysis shows that over 94% of the data fall within zones A and B, and 0% in zone E. The IP technical test has marked the maximum dose error at 3.1 %. Predictive algorithm tests at 15% noise shows relative prediction error of 6.6%.

Discussion: The closed-loop elements tests show characteristics defining high performance indicators of the Device as a whole. However, the system should be tested in animal trials because this is the only way to obtain an objective assessment of its operation *in vivo*.

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P24

CURRENT SITUATION ANALYSIS OF THE REIMBURSEMENT PRICE OF NEW MEDICAL DEVICES IN JAPANESE INSURANCE SYSTEM DURING 2015-2017

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Background: The factor of the price determination for the medical devices to be commercialized is different between the United States, Europe and Japan. The official price of medical devices in Japan is set by the Central Social Insurance Medical Council (known as Japanese the "*Chu-i-kyo*"; government advisory board) in consideration with comparable medical devices price, innovation, usefulness, improvement, manufacturing, selling, distribution cost etc. When determining the price of new medical devices, the calculation method differs depending on whether there are medical devices function category exist or not by the central council of social medical insurance.

Objective: The objective of this study is to obvious recent trends of reimbursement price of the medical devices in Japanese medical insurance system.

Methods: Documents of the "*Chu-i-kyo*" which include the council event date, products name, corporate desired reimbursement prices, actual redemption prices, foreign average prices, calculation methods, are published online. The documents data from Feb/2015 to June/2017 were selected to analyze (medical devices presented with corporate desired reimbursement prices, $n = 59$; medical devices presented with foreign average prices, $n = 45$).

Results and Discussion: As for cost accounting system, the actual reimbursement prices were about 0.74 times the corporate desired redemption prices, and the tended to linearly increase with rise ($n = 25$). On the other hand, regarding to similar function category, the actual reimbursement prices were well matched to the corporate desired reimbursement prices ($n = 34$). As for cost accounting system, the actual reimbursement prices were about 1.13 times the foreign average prices ($n = 20$). On the other hand, regarding to similar function category, the actual reimbursement prices were about 0.71 times the foreign average prices ($n = 25$).

Conclusion: It was suggested that the redemption price listed in Japanese insurance system was correlated with corporate desired redemption price and with foreign average price.

P25

AN ALTERNATIVE APPROACH TO INVESTIGATE BIOFILM IN MEDICAL DEVICES

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Objectives: Biofilms are assemblages of bacterial cells irreversibly associated with a surface where moisture is present. Controlling biofilm formation is a mandatory feature. The aim of this study is to propose a predictive method to screen biofilms on new materials during biomedical device manufacturing and testing.

Methods: We provide a protocol that investigates the bacterial biofilm development in medical devices. Crystal violet staining and advanced stereomicroscopy approaches were applied on samples previously incubated with 4 bacteria strains as recommended by IEC 60601-2-16. This alternative ex vivo platform is able to discriminate the "bio-adhesive properties" of the biofilm on the different materials thanks to the presence/absence of the staining. Qualitative and semi-quantitative read-outs are performed by the analysis of the stained area. This approach could be then translated in an *in vivo* assay investigations.

Results: Three-dimensional stereomicroscopy observations of biofilms showed the presence of a crystal violet layer of positive cells developing onto the material surface. Uncontaminated medical device, reported as a control, showed the specificity of the staining. The quantification of the total positive area was performed using a binary conversion (black/white) and reported as ratio between positive area/total areas with a percentage value. Coated surfaces were also investigated: treated samples showed a reduction in biofilm formation.

Discussion: This proposed alternative and rapid protocol represents a reliable and versatile method to detect, monitor, and measure biofilm colonization by an easy, more affordable, and reproducible method. Furthermore, the method may be used to reduce *in vivo* testing within a predictive platform that could be further enriched by the proposed molecular assays. In conclusions, this new platform could be advantageous for manufacturers and during the R&D phases, before selecting the most suitable material.

P26

EFFECT OF THE ELECTRIC FIELD ON EPITHELIAL CELLS IN THE INVESTIGATION OF TRANSCUTANEOUS ENERGY TRANSMISSION

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Background: Heart failure is a growing syndrome in the world. Ventricular assistive devices (VADs) are being used as target therapy. To avoid infection due to driveline trespassing patient's skin, transcutaneous energy transmission systems (TETs) have been developed to feed VADs. TETs usually act by magnetic coupling between coils. We are developed and testing new TETs configuration, using capacitive coupling through a dielectric composed by a polymer and patient's skin.

Objective: To verify thermal effects from electric field over biological tissue, using mouse skin and melanoma culture cells during energy transmission.

Methods: Two experiments were conducted using mouse skin samples to assemble coupler capacitors and one experiment was conducted using murine melanoma culture cells. Samples were placed between Petri dishes and their lids. Three other samples of these tissues were reserved as control group. The capacitors have been connected in parallel with each other and in series to a load resistor. This set was excited with an electric field at 200 MHz of frequency during 90 minutes and, after this time; the samples were submitted to cellular viability test (XTT).

Results: Total capacitance from three capacitors was measured, resulting in 934.5 nF. After 90 min, temperature from capacitors increased to 280.15 K and from load resistor reached 306.15 K. Temperature from capacitors showed an increase of 2 K at the end of the experiment. Results from XTT assays did not demonstrate significant difference between cellular populations and control samples.

Conclusion: Biological samples remained viable after the electric field application. Research may be carried out under other temperature conditions, as well as intensity and frequency of electric field, searching for a threshold of tissue damage. An equivalent circuit model simulating capacitive coupling for power transmission is been developed and values will be compared with results from this experimental bench.

P27

IN VITRO INVESTIGATION ON CEREBRAL HEMODYNAMICS IN A PATIENT-SPECIFIC CEREBRAL ARTERY MODEL USING PIV DURING ASPIRATION TROMBECTOMY

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Objectives: Mechanical removal of blood clots from cerebral arteries is either performed directly with aspiration methods or supported by endovascular aspiration through endovascular catheters. Since stroke intervention is a life-sustaining action, detailed in vivo measurements cannot be performed in the meantime. In order to improve the

patients' outcome during stroke intervention, the applied methods have to be studied in terms of efficiency. Numerical simulations for thrombectomy scenarios exist, but so far no in vivo data during thrombectomy is available for validation.

Methods: In this work a test facility was developed which allows studying hemodynamic effects on a patient-specific cerebral artery model. Detailed insight into fluid mechanics for aspiration methods is gained by applying particle image velocimetry for visualizing velocity fields inside a hollow and flexible silicone model. First, the test facility was tuned to a physiological scenario according to in vivo data and the consistency of the optical measurement technique was verified. Then different scenarios were investigated and analyzed.

Results: The presented test facility showed to be suitable to investigate thrombectomy scenarios in vitro on hemodynamic effects and subsequently on their efficiency. Collected data showed the inefficacy of aspiration catheters when using them distal from the clot. Besides, acquired data showed good agreement to numerical simulations adressing aspiration thrombectomy and cerebral flows, giving new insight to cerebral blood flow.

Discussion: The developed test facilty gave new insight to cerebral flows especially during thrombectomy. Allthough autoregulation mechanisms are not simulated, measurements could be carried out supporting clinical understanding and numerical simulations in the field of cerebral flow related to neuroradiologic interventions.

P28

ARTIFICIAL ORGAN AND ITS ROLE AGAINST MEGA-DISASTER

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Several mega-disaster, including serious nuclear disasters were caused frequently recently. Progress and problems of artificial organs and their roles are reviewed. Materials and Methods: The study was done based on our actual clinical experience against mega-disaster among which the Fukushima Daiichi Nuclear Plant explosions 2011, followed the Higashinihon earthquake/tsunami with more than 20,000 death or missing, the Tokyo Subway Sarin Attack 1995, the Indian Ocean Tsunami 2004, September 11 in New York 2001 the Chernobyl incident 1986, flu pandemic 2009, etc. Results: It is evident that many casualties increased, partly by the insufficient artificial organ and its managing system, while many were apparently saved with appropriate emergency use of artificial organs. Discussion and Conclusions: The role of artificial organs are classified into three: First, appropriate role for saving lives of casualties are expected and proved among which blood purification systems for acute and/or chronic diseases, ECMO for serious hypoxic lung diseases, etc. Second it is expected and partly worked but not sufficiently useful because of insufficiently prepared in an limited bad condition/situation, because lifelines are not prepared enough, especially in the disaster struck area. And as the last or third, artificial organs(devises) have works as dangerous/harmful tools, especially during acute phase such as during earthquakes and tsunami. As conclusions, the role and risk of artificial organs should be well understand and should be educated, considering the risk of mega-disasters.

P29

ANALYSIS OF EXTENDED BOLUSES IN PATIENTS WITH TYPE 1 DIABETES USING THE VOICEDIAB SYSTEM

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Objectives: Patients with diabetes type 1 being treated with continuous subcutaneous insulin infusion with an insulin pump have to set insulin boluses to compensate food intake. Insulin boluses were usually estimated based on the content of carbohydrates in the meal, but it was lately proved that the proteins and fats also need to be taken into account by extended bolus (EB) delivery. As the EB calculation extends the time of estimations some patients may avoid its delivery.

The aim of the study was a comparison of EB number and daily EB insulin dosages in 4-day period between patients who estimated the EBs by themselves or with the support of the VoiceDiab system which makes it based on the voice description of meal.

Methods: Forty four patients were randomly assigned to supported by the VoiceDiab system (N=23) and unsupported (N=21) groups. The groups were similar in terms of body mass index, glycated hemoglobin, age, gender and duration of diabetes.

Results: Mean daily EB dosages were 14.6±7.7 IU (±SD) and 18.3±10.1 in the supported and in the unsupported group, respectively, and they were not significantly different ($p=0.17$). Mean numbers of EBs were 8.1±3.5 and 8.3±3.4 in the supported and in the unsupported group, respectively, and the difference between them was insignificant ($p=0.84$).

Discussion: The results of the current analysis revealed that patients attending this study were capable of estimation

of EBs and the VoiceDiab system didn't improve the number of EBs and didn't change the EB dosages. The VoiceDiab supported group had larger time with the glycemia in range 70-180 mg/dL than the unsupported group (58.6% vs 46.6%, respectively) and this difference could not result from EB number or EB insulin dose.

P30

MINIMALLY INVASIVE TREATMENT OF HEARTMATE III–LVAD DRIVELINE INFECTION BY INFECTION SITE TARGETED VACUUM ASSISTED CLOSURE

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Objectives: Drive-line infection is one of the most frequent complications following LVAD treatment and there is no consensus about the management of this important clinical problem. The standard approach to treat the foreign-body infection is complete device ablation which is not always feasible and preferred method. Here we describe a minimal invasive method for the treatment of HeartMate III-LVAD driveline infection by infection site targeted Vacuum Assisted Closure Closure.

Methods: A-56 year old male patient presented to our outpatient clinic with fever, elevated C-reactive protein and abundant purulent discharge through the drive-line exit. He had HeartMate III-LVAD implantation 5 months ago as bridge to transplantation after being diagnosed with idiopathic-dilated terminal cardiomyopathy. The thoracoabdominal CT showed an abscess along the LVAD driveline (Figure 1-A). Culture results were positive for Methicillin Sensitive Staphylococcus Aureus. The patient underwent a surgical intervention through a trap-door incision next to the drive-line of the LVAD in order to drain the abscess and for the debridement of the infected tissues. At the end of the procedure, VAC was applied. After 13 days of VAC therapy, we eventually obtained negative culture results and therefore could surgically close the wound. He had 4 weeks of antibiotherapy (Vancomycin and Imipenem).

Results: The patient was discharged 18 days after surgery in good condition (Figure 1-B) and underwent successful heart transplantation 3 months later. During the transplant surgery, no sign of residual infection along the HeartMate III drive-line was observed.

Discussion: Drive-line infection following LVAD implantation is an important complication and management is challenging. Device ablation and reimplantation of a new device is the most radical treatment. This case report presents a successful and less radical approach for the treatment of LVAD driveline infections.

POSTER SESSION PT04: BLOOD TRAUMA

P31

NUMERICAL AND EXPERIMENTAL ANALYSIS OF HEMOLYSIS IN A SELF-DESIGNED BLOOD PUMP

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Hemolysis is caused by a high speed rotation of the blood pump impeller, which is a vital problem in a mechanical circulation assist system and has not yet been resolved in the blood pump design. In the present research, computational fluid dynamics (CFD) was applied to analyze the blood flow in a self-designed blood pump. Erythrocyte damage index was calculated based on the distribution of wall-shear-stress and stress-exposure-time to predict the location of hemolysis. Simulation results revealed that inside the blood pump there are no evident flow separation, stagnation and re-circulation. WSS accounted for 4% in 0-10Pa, for 80% in 11-150Pa, and for 16% in 151-200 Pa. The area where shear stress was greater than 200 Pa was less than 0.0015 %. Furthermore, those high WSS areas were at the trailing edge, where the flow velocity was fast and the exposure time was short, so should not cause serious hemolysis. According to the CFD analysis, hemolysis in this blood pump will not seriously occur. Meanwhile, the blood pumps were manufactured using titanium alloy and underwent 6 hours *in* vitro standard hemolysis tests. The blood sample was collected each hour to measure the concentration of free hemoglobin (FHB) in the plasm. Based on the obtained FHB, the modified index of hemolysis (MIH) and the normalized index of hemolysis (NIH) were calculated consequently. Experiment results showed that the NIH was 0.0043904 g/100L and the MIH was 0.0004249, similar to the results of hemolysis prediction of numerical simulation. The consistence of erythrocyte damage index prediction and NIH, MIH test results implied that CFD analysis is able to predict hemolysis of blood pump and thus very helpful in the design of low hemolysis blood pump.

P32

A NOVEL LABORATORY DEVICE FOR THE SIMULTANEOUS INVESTIGATION OF MULTIPLE FACTORS REGADING BLOOD TRAUMATIZATION

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Objectives: Mechanical circulatory support devices are generally associated with blood damage and coagulation, mainly caused by interactions of blood with foreign surfaces, non-physiological flow conditions, and high temperatures. Computational Fluid Dynamics has been established as a method for predicting blood damage within these devices. However, no numerical model has been found to be applicable to all devices. To expand the knowledge regarding blood traumatization, a new laboratory device has been designed.

Methods: The laboratory device is based on a Couette rheometer with a rotating outer cup and a stationary bob, ensuring laminar flow conditions over the whole range of shear forces. Both outer cup and bob are exchangeable to allow the installation of different surfaces and materials. The laboratory device is designed as a static filling device, enabling the independent adjustment of shear force and exposure time. Two high precision spindle bearings ensure a radial run-out accuracy of 0.004 mm, which facilitates the use of very small shear gaps leading to high shear forces. The temperature management is realized by a water circuit inside of the bob.

Results: The device enables the traumatization of blood in defined conditions, particularly foreign surfaces, temperatures and shear forces. The unique feature is the ability to expose blood to all three traumatization influences simultaneously, while every influence can be adjusted independently. Furthermore, the liquid's torque, which is proportional to the acting shear force, is measured in between the two cylinders by means of a highly sensible torque sensor. This facilitates a precise and continuous control of the acting shear force on the blood.

Discussion: Preliminary viscosity tests with water and glycerine are in good agreement with reference values. The next step is going to be an extensive study regarding blood viscosity and traumatization.

P33

BLOOD OBTAINED FROM HAEMOCHROMATOSIS PATIENTS IS MORE SUSCEPTIBLE TO MECHANICAL SUBLETHAL DAMAGE THAN HEALTHY DONORS

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Background: Although individuals with haemochromatosis (HH) – a disease characterised by an accumulation of iron above bodily needs – are able to donate blood in numerous countries, whether the obtained blood is viable for use in transfusion remains unresolved. Given red blood cells (RBC) from HH patients are rheologically different from those of healthy individuals, and that blood product destinations (e.g., mechanical circulatory support) expose blood to high shear environments, assessing the tolerance of HH blood to mechanical stimuli is necessary.

Objectives: The aim of the present study was to assess the susceptibility of HH blood to sublethal levels of mechanical stress, compared with healthy age-matched controls.

Methods: Blood samples collected from 'uncomplicated' HH patients (n = 13, 56 ± 8 yr) and healthy controls (n = 12, 54 ± 9 yr) were suspended in polyvinylpyrrolidone at a low haematocrit. Deformability of RBC suspensions was assessed via ektacytometry at baseline (i.e., unsheared), and following exposure to 25 shearing conditions of varied durations (1-64 s) and shear stress magnitudes (1-64 Pa). Data was subsequently placed into an x (duration), y (shear stress), z (deformability) matrix, prior to being interpolated into a 64 64 matrix using thin-plate splines. A 3-dimentional surface mesh plot was subsequently created using this interpolated matrix, which provided changes in cell responsiveness following various shearing conditions.

Results: The salient findings of the present study indicate that RBC obtained from individuals with HH exhibit more pronounced impairments in deformability, above and beyond that of healthy controls, following subhaemolytic levels of shear exposure.

Conclusion: The findings demonstrate that HH blood is more susceptible to mechanical stress when exposed to high-shear environments typical of many circulatory support devices.

P34

SUBLETHAL DAMAGE TO ERYTHROCYTES ALTERS LOW-SHEAR BLOOD FLOW

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Objectives: The ability of red blood cells (RBC) to aggregate is a primary determinant of low-shear blood viscosity, and thus also blood fluidity. Previously we have identified that exposure to supraphysiological and subhaemolytic shear stress changed the RBC membrane biochemistry and decreased cell electronegativity, which was associated with increased RBC aggregation. The aim of the present study was to extend these findings and explore the effects of sublethal trauma to RBC on the dynamics of cells in low- shear flow.

Methods: Healthy RBC were washed and isolated before being resuspended in a plasma-like substitute. RBC

suspensions were exposed to 100 Pa of shear in a Couette shearing system for 60 s. RBC were then transferred to a custom-built slit-flow microfluidic chamber (0.254×10 mm) that allowed for visualisation and concurrent laser-diffractometry. Flow rates of RBC suspensions were progressively increased to yield a shear range of 0.01-5 Pa. Using an inverted microscope the physical characteristics of the cells could be observed (i.e., cell orientation, altered morphology, presence/size of aggregates). Laser-diffractometry was used examine cell deformability; diffraction patterns are round for cells at stasis, and progressively ellipsoidal as RBC deform.

Results: Sublethal damage to RBC increased the formation of aggregates that tumbled in low-shear flow, resulting in atypical trends of captured diffraction patterns. Increased shear was subsequently required to disaggregate rouleaux prior to cell orientation and deformation. Curiously, laser-diffractometry with concurrent visualisation revealed that laser-diffraction distortions were also observed with deforming subpopulations of rouleaux that had failed to disaggregate.

Discussion: Exposure of RBC to subhaemolytic shear stress (100 Pa) alters cell behaviour in subsequent low-shear flows. It is plausible that blood exposed to similar shears in mechanical circulatory support may demonstrate similar responses *in vivo*, and thus may disrupt low-shear blood behaviour in addition to the well-described changes in cell deformability. These data indicate that cell aggregates in low-shear flow may provide a novel index of sublethal blood trauma.

P35

ESTIMATION OF HEMOLYSIS LEVEL AND THROMBUS RISK FORMATION OF THE PEDIATRIC PULSATILE CIRCULATORY SUPPORT SYSTEMS BASED ON CFD MODELING

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Objective: The objective of this study is to determine the hemolysis level and the thrombus risk formation using an approach based on the mathematical modeling of the pulsatile circulatory support system.

Methods: For the quantitative estimation of blood damage caused by the working blood pump, the value of the normalized index of Hemolysis and the thrombus susceptibility potential (TSP) index developed by

R. Medvitz were used. In this paper, the estimation of the hemolysis index was carried out on the basis of the Eulerian approach. The Giersiepen and Heuser power law models were used for blood trauma estimation. The simulation of pulsatile blood flow inside the blood pump chamber was based on a 3D realistic model of the blood chamber. The stroke volume of the system was 30 cc. The pump rate was 75 bpm. The simulation was performed with mechanical tilting disk heart valves «MIKS» with a hole area of 1,54 cm2. The time intervals of diastole and systole phases were both equal.

Results: Calculating the hemolysis index using the Eulerian approach for flow rate of 5 liter per minute and the considered power low models of blood damage allowed to obtain the following results: 6,41·10-5 (g/100L) and 1,50·10-5 (g/100L), respectively. The using of Giersiepen power low model gave larger values of the hemolysis than the Heuser power low model, which is consistent with the literature data. The maximum value of Hemolysis and TSP was observed in the valve areas.

Conclusions: The obtained maximum values of the normalized index of hemolysis using the Eulerian approach correspond to the requirements for these systems for prolonged implantation conditions and the absence of the possibility of thrombus formation in the first two weeks of circulatory support systems application.

P36

HEMOLYSIS OF MAHIDOL UNIVERSITY CENTRIFUGAL BLOOD PUMP DURING PULSATILE MODE AND NON-PULSATILE MODE

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A centrifugal blood pump are widely used as a ventricular assist device (VAD). In Thailand, an extracorporeal circulatory support device are normally implanted more than an internal VAD. Therefore, a Mahidol University Centrifugal Blood Pump (MUBP) are developed for support Thai-patient. In this study, the hemolysis of MUBP during pulsatile and non-pulsatile modes was investigated.

Method: This study uses mock circulation loop to simulate the body circulatory system. The anticoagulated equine blood that used in this experiment was provided by Faculty of Veterinary Science, Mahidol University (approved by the Animal Ethics Committee). A 500 milliliter of blood was used into the mock circulatory circuited. This experiment was run at 25ºC. The hemolysis level was defined by Modified index of Hemolysis (MIH). The plasma-free hemoglobin of each speed conditions were compared. The speed of MUBP was set as 1500±250rpm and 1500±500rpm at pulsatile mode (60 cycle per min) and 1500 rpm at non-pulsatile mode. The pump flow was set around 3.5 liter per min. The system was operated for 6 hours (blood sample was obtained every hour).

Results: Plasma-free hemoglobin levels in all speed condition increased with the duration of experiment. The MIH

level of pulsatile mode was higher than non-pulsatile mode. Additionally, the MIH level of 1500±500rpm pulsatile mode was higher than the 1500±250rpm pulsatile mode as 24.92 and 22.89, respectively.

Conclusion: The pulsatile mode of MUBP was increase the hemolysis level than non-pulsatile mode. The higher amplitude of pulsatile mode made the MIH increasing. The investigation of long term hemolysis and difference speed in MUBP during pulsatile mode should be study in future work.

P37

IN-VITRO INVESTIGATION OF SHEAR-INDUCED PLATELET ACTIVATION USING FLOW CYTOMETRY

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Objectives: Objective of our study is using flow cytometry to establish new design criteria for blood pumps by investigating the impact of shear stresses on platelet activation. The applied shear stresses are similar to the ones occurring in rotary blood pumps. The results show, which shear stress levels (including repetitions) have a high potential to activate platelets and should be avoided as activated platelets can lead to thrombus formation.

Methods: The blood is exposed to sine half-wave shaped shear stresses in a range of 40-200Pa. The exposure time is 25-65ms and up to 50 repetitions are applied. For activation quantification flow cytometry is chosen: The antibody CD41a is used for platelet identification; to quantify platelet activation the marker antibody CD62P (platelet surface P-selectin) is used.

Results: 50 samples of citrate human whole blood from 4 healthy donors are used. Measuring shear-dependent platelet activation was successfully established and performed.

Discussion: The shear device enables investigations of shear stresses occurring in rotary blood pumps on blood under controlled conditions. Together with the flow cytometry approach, this has the potential for use during in vitro medical device testing. In the future, the influence of short time stresses on other blood parameters can be investigated with this method to deduce design criteria for rotary blood pumps.

POSTER SESSION PT05: BIOMECHANICAL & LUNG

P38

ASSISTIVE TECHNOLOGY ORIENTED TO THE DEVELOPMENT OF PROSTHESIS FOR PEOPLE WITH UPPER LIMB AGENESIS

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Objectives: Verify the user\'s eligibility requirements, in the period of pre-prosthetization, reduces significantly the indicators of prosthesis abandonment, impacting positively in the satisfaction of the final user and in the cost of the process. Besides that, it is relevant to search for the development of low cost prosthesis, which attend people\'s needs according to their specificities. The objective of this study is to explain about the development of upper limb prosthesis for people with agenesis, using the additive manufacture and basing on guidelines that consider the user\'s individual demands as a way to develop a suitable product to their needs.

Methods: It has been realized a systematic review about upper limb prosthesis, product development and occupational therapy. Then, guidelines have been elaborated to investigate the user\'s eligibility for prosthesis usage, including the user\'s analysis and his functional needs and the analysis of technical requirements for the elaboration of the prosthesis. A study case has been realized with two people for the application of the guidelines and posterior confection of the prosthesis.

Results: Two people, a child and an adult, with upper limb agenesis were eligible for the study. The analysis of the requirements was realized individualy, considering the specificities of age, gender, occupation and the user\'s expectations and prosthesis were developed for these two people.

Discussion: The analysis of demands of the user and the product are important for the success of prosthesis development. While verifying what is important for each person, it is perceived how their needs can vary, even with similar characteristics, according to their specificities and life context. The additive manufactute is a fast alternative, of low cost, which can auxilary in the development of individualized and custom-made prosthesis, improving quality of life, self-esteem and people\'s independence.

P39

CUSTOM PARAMETERIZATION OF PROSTHETIC SUPPORT DEVICE PROTOTYPE FOR IRREGULAR UPPER LIMB AGENESIS

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Objectives: The prosthetic support device of the upper limb can be elaborated from photographic images of the upper limb and upper limb with hand agenesis to compare and configure the parameterization. However, for the upper limb with agenesis and presenting irregular deformation, it is necessary to have customized procedures to

parameterize and make the prosthetic device. The objective of this research is a case study to elaborate a prototype of the prosthetic device for the user who has agenesis of hand and forearm with malformation, which resides far from the research site (800 Km). The function of the support device is to contribute to the future definitive protection of the user.

Methods: It began with the bibliographic basis in the main themes of hand agenesis, 3D laser scanner system, muscle and musculoskeletal system of the upper limb, prosthetic devices. Then, the health professional sent the plaster modeling of the upper limb with hand agenesis. Silicone was used to obtain positive modeling. The measurements were captured by the 3D laser scanner and transferred to parameterization software in the CAD environment. The prototype of the support device was fabricated with Fused Deposition Modeling (FDM) and additive printing and passed into the assembly process. The parametrization validation test was using the positive silicone modeling in the device prototype.

Results: Positive silicone modeling of the limb with hand agenesis and forearm malformation fit precisely into the prototype.

Discussion: The prototype of the prosthetic support device presented precision and speed in the parameterization process, the use of laser-scanner 3D and additive manufacture contributed to the low cost of the prototype, the health professional will be responsible for minor adjustments to the user,and the user will have follow-up of the rehabilitation program for use of the prosthetic support device.

P40

THE LAYERS OF COMPOSITE NANOMATERIALS AS ELECTRODES IN AN ARTIFICIAL MUSCLE

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Artificial muscles (AM) based on electroactive polymers contain metal electrodes based on noble metals (Au, Pt, Pd, etc.). However, the disadvantages of such electrodes are the complexity of depositing layers, the inaccessibility and high cost of precious metals. We investigated the layers of a composite nanomaterial with the prospect of using them as electrodes in an AM. Composite nanomaterial (BSA/SWCNT) consisted of bovine serum albumin (BSA, matrix) and single-walled carbon nanotubes (SWCNT, filler). The aqueous dispersion of the composite nanomaterial contained: 20 wt.% BSA and 1 wt.% SWCNT. Dispersion was applied to flexible substrates (polyimide, polyethylene terephthalane) by silk screening. In the liquid state, the layers were irradiated with a laser until they dried completely. The following mode of laser radiation (LR) was used: generation wavelength – 970 nm, specific power – ≤ 1 kW/m2. Note that LR during the formation of layers does not overheat the substrates and this process is much simpler than depositing metal layers on polymer substrates. The layers had thicknesses of 0.5-10 μm. Electrical measurements showed: a maximum specific conductivity of ~ 200 S/m, a minimum surface resistance of 0.1 mOhm×m2. In the range bending angle of 0-300 °, cyclic bends increased the resistance of the layers by 15%, but for numerous more than 100 times bends, the resistance change was practically stopped. The investigated BSA/SWCNT layers are promising for performing the function of electrodes in an artificial muscle based on an ionic electroactive polymer.

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P41

NANOCOMPOSITE LAYERS AS PROTOTYPE OF A TENSORESISTOR SENSOR

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Strain gages are in demand for controlling the deformation of artificial muscles or the work of artificial organs. Traditional tensoresistive sensors based on metal and semiconductor materials have a very low relative strain (e≤0.2 %) and not a high sensitivity to deformation (S~100÷200). Sensors of both types are difficult to bend and, therefore, limit the movement of the biological object. We studied mechanical properties of the layers of different nanocomposites containing single-walled carbon nanotubes (SWCNTs) in terms of their possible use as prototype of a tensoresistor sensor. The nanocomposites were prepared using different matrices (acrylic paint (AP) or bovine serum albumin (BSA)). The matrix and filler were diluted in distilled water to obtain water dispersions of groups AP/SWCNT and BSA/SWCNT with an SWCNT concentration of 3 mass.%. The dispersions were used to deposit the layers by silk screening onto polyester substrates. The resistive strain sensor prototypes were layers with: (15÷20) mm'(8÷10) mm'(0.5÷5) μm. The dependences of resistance R on the bending angle q were similar for all layers: at q=±30°, the $R(q)$ curves represented approximately

linear dependences (with an error of ≤10%); beyond this range, the dependences became nonlinear. Using the minimum bending radius (~2 mm) and $d \leq 1$ μm, we obtained the estimate $S \sim 150 \div 300$, which is of the same order of magnitude as the available data or exceeds them. Thus, the investigated nanocomposite layers prototypes as tensoresistors of groups AP/SWCNT and BSA/SWCNT are promising for use as strain sensors.

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P42

ADAPTIVE, VARIABLE LUNG VENTILATION – SIMULATION STUDIES

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Objective: In order to conduct ventilation with a maximal comfort for a patient, in adaptive ventilation (AV) the ventilation frequency is automatically set to minimize the work of breathing (WOB). In variable ventilation (VV), breath-to-breath tidal volume (TV) is automatically changed to improve lung mechanics and gas exchange by a better alveoli recruitment. AV based on a lung mechanics model has such drawback that an adjusted frequency of ventilation depends on fidelity of on-line calculation of airway resistance (Raw), lung compliance (CL) and dead space ventilation (DSV). This is practically impossible to achieve. So, our objective was to develop a control system for adaptive, variable ventilation that would not have the mentioned above drawback.

Method: Our original (patent pending) concept of AV frequency adjustment is based on automatic seeking of the minimum of WOB by so called an extreme controller. Measurements of pressure and flow of inspiratory gases enable to calculate WOB. WOB values obtained for two successive cycles are compared and a sign of their difference decides if the controller increases or decreases ventilation frequency. Thus, there is no need to know values of Raw, CL and DSV.

The developed AV system was connected with a lungs mechanics model and simulation of their interactions was conducted for different type of lung pathology.

Results: The obtained results show that the whole system reacts properly to dynamic changes of Raw and CL treated as disturbances and finds automatically WOB minimum after several cycles. The adaptive ventilatory system generates small TV oscillations, close to a minimum of WOB. Such oscillations have positive effect as during spontaneous breathing.

Discussion: The proposed adaptive, "noisy" ventilation with variable TV can potentially improve respiratory function of a patient, arterial oxygenation and reduce histological damage in comparison to standard, conventional ventilation with constant TV.

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EXPERIMENTAL INVESTIGATIONS OF THE BONE CEMENT INJECTION AND ITS DISTRIBUTION INSIDE A VERTEBRAE MODEL

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Objectives: The paramount objective of the following research was to experimentally inject the PMMA-based bone cement into the patient-specific vertebrae models and analyze its distribution among the vertebrae microstructure.

Methods: Several patient-specific vertebrae digital models were reconstructed basing on the DICOM image set obtained during micro-CT examination. Afterwards, the data were converted into the stereolitography (STL) format and imported into the 3D slicing software Ultimaker Cura. Finally, physical models with preserved inner microstructure were 3D printed. The next phase focused on performing the cement injection into the prepared models on the designed experimental rig. The last part of the study comprised examination of the bone cement distribution inside each filled model with the use of micro-CT technique.

Results: Authors designed and modified the experimental setup allowing one to inject the PMMA-based bone cement into the 3D printed physical model of the patient-specific human vertebrae. Despite the same flow conditions and similar location/depth of the syringe-model connector, several discrepancies between investigated cases could have been observed, i.e. cement flow time, pressure characteristics and cement distribution among the microstructure.

Discussion: After the analysis of the cement flow characteristics and their differences among each experiment, it can be stated that one of the most significant factors influencing the PMMA-based cement flow is its initial aeration. This parameter cannot be neglected during a vertebroplasty procedure or during an estimation of a mathematical cement model.

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P44

DEVELOPMENT OF MULTI-FUNCTIONAL DETOXIFYING FILTER TO SUPPORT IMPAIRED FUNCTIONS OF KIDNEY AND LUNG

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A multi-functional detoxifying filter (MDF) is a filter apparatus that offers multiple blood purification functions, including high-volume hemofiltration, blood oxygenation, and CO2 removal. Thus, it replaces impaired renal and lung functions. The MDF includes a hemofiltration filter portion and an oxygenation filter portion, which are coaxially placed in the core portion. The hemofiltration filter and the oxygenation filter have a common structure in which a cylinder-shaped container is charged with semi-permeable membranes and port- processed at both ends using a synthetic resin. Hence, the internal space of the hemofiltration filter and oxygenation filter can be divided into two flow regions.

In-vitro blood experiments were conducted to investigate hemodialytic performance and gas exchange rates of the MDF. Two to four liters of fresh bovine blood was used as a blood substitute. Uremic marker molecules were also added to the blood reservoir. No technical problems concerning the MDF were encountered. Partial CO2 pressures were substantially decreased, and reduction ratios of the uremic molecules solutes were satisfactory, achieving over 90% in 6 hours.

The devised multi-functional detoxifying filter (MDF) delivering multiple blood purification functions offers a simple but efficient way to support impaired functions of kidney and lung.

P45

O2 AND CO2 MASS TRANSFER IN BLOOD OXYGENATORS AND ARTIFICIAL LUNG DEVICES

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Objectives: Mass transfer resistance for O2 and CO2 have to be reduced for efficient operation of membrane oxygenators and artificial lung devices. In this study we investigate the influence of blood side concentration polarization effects for O2 and CO2 applying different high performance membranes. The findings are relevant both for the development of new membrane materials and the design of suitable contactor geometries.

Methods: A model was developed to account for the individual membrane permeances of O2 and CO2 used in blood oxygenators and artificial lung devices. Membrane fluxes were coupled to concentration polarization effects via a resistances-in-series approach. Sherwood correlations for different blood channel geometries were applied to consider the membrane contactor design. The model was calibrated by experimental gas permeation data for two membranes of interest – commercial polymethylpentene membranes and bi-soft segment integrally skinned poly(ester urethane urea) membranes (IST Patent US9181384).

Results: Blood velocities, specific membrane area, empirical Sherwood correlations based on selected channel geometries, and blood gas saturation were varied through a factorial design study. Results show, that blood side mass transfer resistance is dominant for laminar flow regimes usually applied in such devices. Gas side mass transfer resistance for the transfer of O2 and CO2 are low in all cases.

Discussion: A simplified 1D mass transfer modelling approach can be used to quickly estimate the contactor device performance. However, a more sophisticated CFD study is required to include the influence of more complex device geometries and to estimate shear stress effects on blood hemolysis.

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P46

CFD SIMULATION OF BLOOD GAS TRANSPORT IN A HOLLOW FIBER MEMBRANE PACKING FOR DESIGN OPTIMIZATION OF AN INTRACORPOREAL MEMBRANE OXYGENATOR

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Objectives: Although extracorporeal membrane oxygenators have developed to a reliable respiratory technique, the development of intracorporeal devices remains a challenge due to anatomical limitations. To meet these constraints while delivering significant blood gas exchange, highly efficient devices need to be developed.

Methods: Experimental methods are limited to provide only pointwise information. Computational fluid dynamics (CFD)

can supplement this information and enables a three dimensional and time dependent description of the blood gas exchange in the membrane contactor. This allows to evaluate local membrane performances and makes CFD a suitable choice for effective membrane oxygenator optimization. In the scope of this research an in-house solver *membraneFoam*, based on the open source CFD code *OpenFOAM®*, was utilized. It resolves the diffusive transport of blood gasses through the membrane while simulating the flow on both, shell- and lumen-side of the hollowfiber.

Results: Parallel flow of blood on the shell side of a membrane fiber packing as well as sweep flow in the inner of the fiber lumen was simulated for co- and counter-current set-up. Both flows were connected by blood gas perfusion through the membrane using *membraneFoam*. The CFD simulations are in good agreement with Sherwood correlations. As demonstrated in literature, the diffusive boundary layer is accountable for the main transport resistance in blood gas exchange. Simulation results show a fast development of this boundary layer within the first 0.5 mm of fiber length. The layer then stays stable in laminar flow regime.

Discussion: CFD simulations allow to optimize the fiber packing and systematically design static mixers to improve gas exchange. Additionally, phenomena as bypassing and total pressure loss can be investigated. By resolving the diffusion through the membrane, the foundation for evaluation of different membrane types is laid.

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POSTER SESSION PT06: VADS & OTHER NUMERICAL SIMULATIONS

P47

SINGLE VENTRICLE SYNCARDIA SUPPORT IN FAILING FONTAN - A HEMODYNAMIC INVESTIGATION

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Objective: The Fontan procedure has been a very successful palliative treatment for univentricular heart disease. But over time many patients seem to experience progressive failure of the Fontan circulation. Implantation of a systemic ventricular assist devices may not address the underlying circulatory impairments. The objective of this experimental study was to determine if a single ventricle of a total artificial heart is an adequate replacement of a failing ventricle in the Fontan circulation.

Method: An experimental study was performed using a mock Fontan circulation loop in combination with SynCardia temporary total artificial hearts (50cc, 70cc) and corresponding drivers (Freedom Driver, Companion Driver C2). Important limiting parameters, namely pulmonary resistance, venous reservoir and driver's beat rate were alternated.

Results: An increase of the transpulmonary pressure gradient decreased the blood flow for all four investigated combinations in the mock Fontan circulation. The 70cc ventricle supported, as expected, a higher cardiac output than the 50cc with both drivers. A higher left atrial pressure supported an increased filling of the ventricle, resulted in a higher cardiac output. Independent of driver choice and pulmonary vascular resistance a preload sensitivity of the single ventricle was observed. The pump rate influenced the cardiac output only to a small extent due to an inversely proportional behavior of filling volume to pump rate.

Conclusion: The 70cc ventricle driven by the Companion Driver provided a blood flow above 5 l/min over a wide range of transpulmonary pressure gradients, which is typically elevated in Fontan patients. The results of this experimental study show that a single artificial ventricle is capable of supporting a sufficient blood flow. These results may promote the treatment with a single artificial ventricle as a bridge to transplantation of failing Fontan patients.

P48

NUMERICAL ANALYSIS OF CANNULA TIP DESIGN INFLUENCE ON STAGNATION AND RECIRCULATION ZONES IN LEFT VENTRICULAR

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Objectives: Cardiovascular diseases are globally the most common cause of death today. Patients with end-stage heart failure have a very poor prognosis with standard medical therapy, with survival rates as low as 25% at 1 year and 8% at 2 years. In view of a limited number of donors available, the development of mechanical circulatory support devices is still challenging task for the treatment of patients with advanced heart failure. Continuous-flow left ventricular assist devices (LVAD) are increasingly used to support such patients.

The main cause for device malfunction is LVAD thrombosis, when patients are exposes to the risk of sudden death. Thrombus formation arises from the combined effect of

elevated shear stress levels and recirculating flow patterns in specific regions within a device. The inflow cannula is the connection between the left ventricle and the pump being one of the critical regions of LVAD.

Method: To investigate the correlation between LVAD cannula tip design and potential for stagnations and recirculation zones formation in left ventricular, the intraventricular flow field was digitally modeled by computation fluid dynamics analysis (OpenFOAM-extend 3.2). Seven different cannula tip designs were simulated, including blunt (5 mm, 15 mm), trumpet, beveled, caged, crown (Incor), blunt 25 mm (AVK-N).

Results: The results showed that the cannula tip design affected the stagnation and recirculation zones size. Whereas caged, crown and trumpet cannulas owned the minimal zones of thrombosis formation, our result indicated that the caged tip form is the most suitable for LVAD.

Discussion: Our findings suggest that cannula tip design has influence on hemodynamic in left ventricular. We demonstrated that inappropriate cannula tip design generates massive recirculation and stagnation zones, which can cause thrombus formation.

P49

ASSESSMENT OF CENTRIFUGAL BLOOD PUMP AS VENTRICULAR ASSIST DEVICE IN THE HYBRID CARDIOVASCULAR SIMULATOR

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Objectives: Evaluate centrifugal blood pump (CBP) assistance in a Hybrid (numeric and physical) Cardiovascular Simulator (HCS) and its speed control.

Background: HCS model is a tool composed by two sections: 1) a physical section composed by: a reservoir, mimicking a passive left atrium; a pumping chamber with two bilealeft valves, as left ventricle; an air tight compliance chamber; a proportional valve as systemic vascular resistance and a set of tygon tubes. The electromagnetic actuator of pumping chamber, the air volume inside the compliance chamber and the proportional valve are controlled by a real time platform through the numeric section. 2) The numeric section is composed by: vena cava; right heart; pulmonary artery; lungs and pulmonary vein. All compartments of numeric section have been programmed in LabVIEW® RT. Interaction between both sections is made through pressure and flow signals which are acquired at physical section by sensors. CBP has been used as ventricular assist device by researchers around the world due to its blood pump efficiency. However, during controller development, a special attention has to be applied to CBP speed control adjustment.

Results: HCS allows us to observe the impact of CBP assistance under pump speed changes for several heart conditions. From results was possible to observe that when the pump runs at high speed, aortic valve remains closed. On the other hand, at lower pump speeds, the blood returns from aorta to left ventricle impairing cardiac assistance. Also, through Pressure x Volume loop was possible to analyze specific characteristics of CBP assistance.

Conclusion: Evaluation of CBP assistance at HCS tool was performed, indicating that a precise speed control of CBP is mandatory in order to keep adequate heart assistance. Further, HCS could be used as tool during CBP speed adaptive controller development.

P50

ANATOMICAL FITTING DESIGN OF AN INTRAVENTRICULAR BALLOON PUMP

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SUBTOPIC: VAD AND OTHER HEMODYNAMIC AND CARDIOVASCULAR SUPPORT DEVICES

Objectives: Current ventricular assist devices (VADs) are limited in application by their high cost. Development of a population specific low-cost pump could provide mechanical circulatory support to a broader range of severe heart failure patients. Dimensions, placements, functions and anatomical constraints are critical components to include in the design of implantable devices. This study aimed to design an intraventricular balloon (IVB) based on left ventricles (LVs) with dilated cardiomyopathy.

Methods: Ten computed tomography scans of patients with dilated LVs were segmented using Mimics, to create 3-dimensional models. Analytical tools in 3-Matic (e.g. surface fitting, extrema analysis), a 3D modelling software, were used for identifying the LV functional landmarks (e.g. papillary muscles, valves) and for reducing the LV models to parametric shapes. The IVB landing zone was defined as the region where the IVB can be actuated without interfering with LV functional landmarks. The IVB shape was designed in Solidworks, to fit the landing zone of the target population.

Results: The IVB landing zone was defined by the superimposition of the normalised simplified LV shapes and functional landmarks. The anatomic fitting resulted in a

balloon parametric model defined by its dimensions and position with respect to the LV apex and main axes. A single scalable IVB geometry was established to fit the target population.

Discussion: Within the sampled population, anatomical fitting data revealed a single-sized IVB may be suitable to provide mechanical circulatory support for heart failure patients with dilated cardiomyopathy. A larger dataset will be required for validating the proposed IVB design and identifying potential limitations.

P51

CFD MODEL DEVELOPMENT FOR THE FDA CENTRIFUGAL ROTARY BLOOD PUMP

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Objectives: Computational fluid dynamics (CFD) is widely used to predict the performance and flow dynamics of rotary blood pumps (RBPs). However, researchers have been unable to agree on a consistent numerical modelling approach, resulting in large variations in performance predictions as exemplified by the Food and Drug Administration (FDA) RBP benchmarking study. The purpose of the present study was to develop a suitable CFD modelling approach.

Methods: The FDA RBP was simulated using ANSYS Fluent 17.1 (turbulent, transient solution) to predict the HQ curves (pressure head vs flow rate) and velocity fields. The most appropriate modelling options (mesh sensitivity, sliding mesh etc.) were identified through preliminary simulations and from literature. Various turbulence models (k-ω SST, Reynolds Stress Model (RSM) and Stress-Blended Eddy Simulation (SBES)) were trialled. The predictions were compared to experimental data including HQ curves and velocities obtained from particle imaging velocimetry provided by the FDA.

Results: The most widely used models for RBPs, the k-ω SST and RSM, under-predicted the pressure head developed. The predicted HQ results for the SBES model showed very good agreement to the experimental data, with all simulated points falling within the experimental error bounds. The velocity profile calculated (SBES) between the impeller blades fell within the experimental results but some deviation was shown for the profile across the diffuser.

Discussion: The FDA pump geometry included radial blades and a relatively large diffuser angle. This generates a transitional, separating and recirculating flow. The SBES model provides the best prediction of this challenging flow because it explicitly calculates the larger turbulent structures, and models the effect of the smaller turbulence scales. For a more typical RBP design (curved blades and smaller diffuser angle) the error resulting from the less computationally expensive k-ω SST model may be acceptable.

P52

ARTIFICIAL INTELLIGENCE FOR DATA PROCESSING FROM A VENTRICULAR ASSIST DEVICES TEST BENCH FOR PREDICTING FAULTS

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One of the major contemporary challenges is to make sense of the rapidly growing amount of data in health; in order to improve the interface for decision making, impacting the longevity of patients with VAD. This work proposes an in vitro test platform for DAVs to obtain dynamic behavior variation, over time, since these devices are time-varying systems. For this, it is important to classify and store fault data that occur during the lifetime of the DAV, which affect its reliability. Therefore, intelligent behavior, assigned to the test platform with the self-tuning of the variable setup, ensures the control of the performance of the DAVs, within operating ranges inherent to the needs of a patient with heart failure, allowing the increase of their longevity. The research is descriptive of the prospection of a DAV test platform, which consists of: (i) a comparative analysis between standard curves of a validated VAD, with the curves of a VAD under test, considering the deviations of the variables: pressure, flow, vibration, pH, temperature, viscosity, rotation and current; (ii) an intelligent behavior identifies deviations in the reference curves resulting from the occurrence of failures, and reacts by performing an auto-tuning to cause a new set-up of the cited variables and that are adequate to the needs of a patient; and (iii) development of a acquisition and data processing, from the test jig, to describe the time variant behavior of a VAD and prediction of behavior for self-tuning decision making. This work highlights the main points for the classification and qualification of the results of the tests improving the interface for decision making of the adjustment of the setup of variables that allow a longevity of the DAV.

Key words: Modeling of tests, Ventricular Assist Device, Reliability, Test bench, Artificial Intelligence.

P53

FLUID-STRUCTURE INTERACTION SIMULATIONS OF FLEXIBLE MEMBRANE-BASED LVAD

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Objectives: Computer simulations play a crucial role in the mechanical design of Ventricular Assist Devices (VADs), providing quantitative information in view of the optimization of the pump efficiency and the minimization of blood trauma. Our goal is to perform a computational study of the Fluid-Structure Interaction (FSI) problem, arising in blood pumps developed at CorWave SA, where the oscillations induced by an elastic membrane generate physiological blood flow.

Methods: FSI simulations have been initially conducted in a 2D axisymmetric geometry by means of commercial software for computational fluid dynamics, in particular: Comsol, Adina and ANSYS Fluent. In addition, more advanced techniques, like the Extended Finite Elements Method (X-FEM), already implemented in the academic Finite Element library LIFEV, have been considered to describe the FSI dynamics in a 3D scenario avoiding remeshing techniques by keeping the fluid mesh fixed on the background and moving the structure one on the foreground. In particular, X-FEM maintains high accuracy in the interface proximity, thanks to a local enrichment of the space domain.

Results: Preliminary studies performed with the off-the-shelf software highlighted the effect of oscillation frequency on membrane deformation and flow patterns due to local turbulence or to the membrane impact against the pump walls. However, the three-dimensional nature of the observed vibration modes on the membrane suggests adopting customized techniques that support 3D framework and high parallel computing. As a result, X-FEM approach has been initially studied on simplified configurations showing interesting results.

Discussion: Despite their appreciable accuracy in the description of FSI dynamics, commercial software proved to have low predictive power in case of geometrical modifications and limited computational efficiency. On the other side, our results indicate that X-FEM is a promising numerical strategy that will be soon applied in the real pump domain.

P54

REPLACEMENT OF THE VAD - NATIVE VENTRICLE PUMPING SYSTEM WITH AN EQUIVALENT VENTRICLE: A COMPUTATIONAL MODEL STUDY

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Objectives: easing hemodynamic data analysis during VAD assistance, describing comprehensively the pumping system (PS) composed of the left native ventricle (NV) and the HeartMateII (HMII) VAD.

Methods: the PS is replaced by an equivalent ventricle (EV) with the same filling characteristics and heart rate (HR) of the NV. A two-step procedure is implemented on a lumped parameters cardiovascular model, including the HMII model (based on second order polynomials). Inputs to the first step are NV HR, mean arterial pressure, arterial elastance (Ea), total cardiac output and end diastolic volume (Ved). The corresponding outputs are equivalent stroke volume (SVeq), end systolic volume (Veseq) and Emax (Emaxeq). After outputs calculation, they are refined on the second step by feeding the simulator with the parameters calculated in the first step.

Three sets of experiments were performed to test the procedure: 1-2: with constant circulatory parameters, two different Emax of the NV (0.44 and 0.9 mmHg·cm-3) were set in the model: VAD speed ranged from 8000 to 12000 RPM, step 500 RPM. 3: with constant VAD speed (9000 RPM) and Emax (0.9 mmHg·cm-3) peripheral resistance ranged from 600 to 2400g·cm-4·s-1, step 200g·cm-4·s-1

Results: the EV showed an increasing Emaxeq and a decreasing Veseq with pump speed, for both Emax values, compared to the NV. Ved is governed by the filling characteristics of the NV. The intersection between Ea and Emaxeq lines can be used to identify the conditions for EV maximum power transfer to the load.

Conclusions: the EV merges the NV with the VAD, giving useful information on the ventriculo-arterial coupling of the PS. Its optimization can support pump speed setting and pharmacological therapies. The results depend on the pump type and the study will be extended to pulsatile VADs.

P55

INTRA-AORTIC BALLOON PUMP INVESTIGATION ON A HYBRID (HYDRO-NUMERICAL) CARDIOVASCULAR MODEL

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Objectives: The main goal of this study is to demonstrate advantages of a hybrid modeling compared to purely mechanical or purely numerical models, as far as investigations of intra-aortic balloon pump (IABP) are concerned. A hybrid (hydro-numerical) cardiovascular system model (HCM), utilized in this study, has been made in the Nalecz Institute of Biocybernetics and Biomedical Engineering of

PAN in Warsaw in the close cooperation with the Institute of Clinical Physiology of CNR in Pisa.

Methods: A hybrid application, presented in the study, has been especially developed for IABP investigations. HCM is composed of two main sections. The numerical section containing systemic and pulmonary circulation in the form of lumped parameter Windkessel models and left and right ventricles described by the time-varying elastance models. The cardiovascular model includes also the coronary circulation. The aortic valve is represented by its numerical model reproducing finite valve opening and closing times as well as a time variable valvular resistance. The physical section is made in the form of an elastic tube which elasticity can be modified by the numerical capacitance (NC), connected in parallel. Connection of numerical and mechanical HCM parts is realized by physical-numerical interfaces – impedance transformers. Three impedance transformer modules are needed, two for connecting both ends of the physical section of the aorta and one for connecting NC.

Results: Number of simulations have been performed for different IABP timing conditions, various balloon driving pressures and different NC values. The results were presented in the form of the left ventricular pressure- volume loops and time traces like aortic pressure before and after the balloon, describing a performance of IABP assistance.

Discussion: HCM tests have shown its main advantages: high reproducibility of experimental conditions and high accuracy of model parameter settings, as well as remarkable functional flexibility.

POSTER SESSION PT07: VADS EXP MODELLING

P56

COMPARISON OF TUG FORCE, LEAKAGE AND RESHEATHING BEHAVIOUR OF TWO LAA OCCLUSION SYSTEMS: AN IN-VITRO STUDY

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Objectives: The study aimed to develop *in-vitro* bench tests for LAA occlusion (LAAo) devices regarding tug force and leakage.

Methods: Two LAAo devices, namely the WATCHMAN™ and the Occlutech® occluder, in the sizes 27, 30 and 33 mm were tested regarding tug force and leakage. The testing was performed at out-of-the-box conditions and after repeated resheathing in the novel *in-vitro* test setups.

Results: The tug force of the WATCHMAN™ devices was significantly higher when compared to the Occlutech® occluders at baseline and across the entire sizing range of all device sizes (maximum tug force: 2.6 ± 0.1 N for WATCHMAN™ vs. 1.8 ± 0.1 N for the Occlutech®; $p < 0.01$). Repeated resheathing of the WATCHMAN™ devices resulted in a maximum reduction of diameter of 7.9 %, while resheating of the Occlutech® implants did not influence device diameter. No significant impact of resheathing on tug force was measured for either device. Leakage was tested in silicone models and at baseline both occluder systems showed perfect sealing. However, resheathing lead to leakage around the WATCHMAN™ devices. This Leakage increased with additional resheathing up to 91.1 ± 7.9 % after resheathing four times.

Discussion: The WATCHMAN™ LAA occluder series showed progressive deformation and increased peridevice leakage after resheathing, presumably as a result of diameter reduction. However, stability of the WATCHMAN™ was not impaired by resheathing and was significantly higher than that of the Occlutech® devices. This is most likely due to the anchoring mechanism of the WATCHMAN™ system, which hooks into the tissue rather than relying mainly on radial force.

P57

FLOW-INDUCED VESSEL-WALL VIBRATION AT LAMINAR FLOW RATES – AN EXPERIMENTAL INVESTIGATION

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Objectives: Perivascular tissue vibration (PV) is already known to be a sign of arterial stenosis or of a well-working arteriovenous vascular access. But why does PV already occur at laminar flow rates?

Methods: Steady-flow in vitro studies were performed within a simple model that represents the transition from a rigid to an elastic vessel. Therefore a silicone tube was connected with a latex balloon to simulate a sudden change of the diameter and a strongly complaint vessel. The perfusion was performed with distilled water using a centrifugal pump (BioMedicus, Inc. USA). A piezoelectric miniature acceleration sensor (KS95B.100, Metra, Radebeul, Germany) was fixed onto the balloon for vibration measurement and subsequent frequency analysis. The diameter of the connector and the flow rate were varied.

Results: Independent of the diameter of the connector, PV was always measured at turbulent flow rates on the balloon surface. The frequency analysis of the vibrations revealed the dependence on the Reynolds number. Nevertheless, the occurrence of the vibrations at laminar flow rates and small diameter of the connector was the most important result of our investigation. The flow through a 2.4-mm connector generated wall vibrations at Reynolds number of 1500.

Conclusions: The jump in diameter between the connector and the balloon causes a turbulent free jet leading to local pressure fluctuations at laminar flow rates, which are responsible for PV. A connector with narrow lumina can be defined as a nozzle, which creates a jet flow mixing with the nearly-at-rest surrounding fluid. The result is a turbulent free jet at lower Reynolds numbers (less than 2300).

P58

DEVELOPMENT AND PRECLINICAL VALIDATION STUDY OF ACCURATE QUANTIFICATION METHOD OF AORTIC INSUFFICIENCY DURING LEFT VENTRICULAR ASSIST DEVICE SUPPORT BY THERMODILUTION ANALYSIS

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Purpose: Aortic insufficiency (AI) is an intractable complication during long term left ventricular assist device (LVAD) support. However, accuracy of the evaluation of LVAD-AI in these days is not satisfactory. To solve this problem, we are developing new evaluation method applying thermodilution technique used for evaluation of shunt of congenital heart disease because LVAD-AI is also shunt formative disease. The purpose of this study is to evaluate the validity of our evaluation technique both in vitro and in vivo.

Methods: Both in vitro and in vivo experiment models, the magnitude of LVAD-AI was represented by recirculation rate (RR), defined by regurgitant flow(RF) divided by pump flow(PF). Both models had the property of AI, and heart failure with full bypass LVAD drive, which meant heart did not eject forward flow across aortic valve. The magnitude of AI was controllable in both models. We placed two thermistors and one port for saline(i.e. heat) injection at outflow conduit. After injecting liquid, value of RR is calculated by analyzing time-temperature curve of the thermistors and compared to control value of RR calculated from flowmeter. The injection and analysis was repeated with changing magnitude of AI and relation of both RR values were evaluated.

Results: Good correlation was observed between two values of RR, both in vitro and in vivo evaluation (correlation coefficient = 0.984 in vitro, and 0.959 in vivo) And two values were almost the same.

Conclusion: This technique was proved to be able to calculate RR, an index of LVAD-AI, precisely and accurately. This method can be clinically applied by left-sided cardiac catheterization if a dedicated catheter with two thermistors and an injection hole is developed.

P59

INFLUENCE OF PARAVALVULAR LEAKAGE AFTER TAVR ON LEFT VENTRICULAR WORK AND CORONARY FLOW: AN IN-VITRO STUDY

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Objectives: The aim of this study was to assess the influence of paravalvular leakage (PVL) on stroke work and coronary flow (CF) after transcatheter aortic valve replacement in a pulse duplicator.

Methods: A Medtronic CoreValve 29mm aortic valve prosthesis was used for the measurements in a pulse duplicator. The aortic root model used features three sinuses of valsalvae, two coronary arteries and a mechanism to induce progressive PVL at each of the sinuses. Pressure, flow and PV-loops were measured at normotensive conditions (no PVL, 5L/min cardiac output (CO), 100mmHg mean aortic pressure (MAP)) and at various degrees of PVL up to leakage rates considered severe in clinical routine. The PV loops allowed for the calculation of left ventricular work.

Results: CO decreased steadily with increasing PVL up to a minimum of 3.4L/min at severe PVL at 40%. MAP decreased as well with increasing PVL (MAP 60mmHg at 40% PVL, $p<0.01$). The stroke work required to maintain normotensive conditions with PVL increased significantly with more severe leakage up to a maximum of 2.2J at 40% PVL (baseline 1.27J, $p<0.01$).

Coronary flow decreased with increasing rates of PVL by up to 33% and 43% for the left and right coronary artery, respectively, at 40% PVL. The location of the PVL with regards to the coronary ostia did not show any impact on

CF. Readjusting the stroke of the pulse duplicator to normotensive conditions resulted in an increase of CF back to baseline values.

Discussion: The increased stroke work necessary to regain sufficient CO, CF and MAP when PVL is present puts additional strain on the left ventricle potentially promoting hypertrophy and subsequently heart failure. Effects of PVL location on CF such as the Venturi effect that have been described in literature were not seen.

P60

OVERCOMING FLOW VARIATIONS OF SYRINGE INFUSION PUMPS WITH REAL-TIME FLOW MEASUREMENT FOR CARDIOVASCULAR SUPPORT

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Objectives: The use of syringe infusion pumps for the continuous intravenous administration of drugs is a standard technique used in anaesthesia and critical care medicine. Today's pressure-controlled syringe infusion pumps are well known for start-up and occlusion alarm delays and their susceptibility to hydrostatic pressure changes. These issues are mainly related to the plastic syringe itself and the mechanical compliance of the syringe infusions pump assemblies.

The aim of this study was to (1) investigate the simulated pharmacokinetic course of continuous epinephrine administration during start-up, vertical displacement and infusion line occlusion and to (2) compare it with a new syringe infusion pump system designed to overcome the compliance issues.

Methods: We measured the flow of a syringe infusion pump, which is in clinical use, using an in-vitro setup mimicking relevant clinical scenarios. The measured data was used as an input to the numerical simulation, which models the pharmacokinetic response to an exogenous epinephrine infusion. Experiments were repeated with a newly developed syringe infusion pump system, which uses real-time flow measurement for feedback control.

Results: The simulation study of epinephrine showed that the effects of flow rate variations lead to a reduction of its blood plasma concentration of up to 40% in case of a vertical displacement of the pump relative to the patient. The new approach of a syringe infusion pump system was able to achieve a start-up to steady state flow in less than 10 seconds instead of minutes. Its performance was unaffected by pressure changes and the system could detect occlusions within seconds.

Discussion: During clinical scenarios, the effects of flow variations of syringe infusion pumps can lead to substantial deviations in the blood epinephrine concentration. With the novel feedback controlled syringe infusion pump system, these adverse effects can be overcome.

P61

PEGYLATED CARBOXYHEMOGLOBIN BOVINE AMELIORATES MYOCARDIAL INFARCTION IN A RAT MODEL

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Artificial oxygen (O2) carriers were reported to be protective in ischemia/reperfusion (I/R) in various organs including the heart, which maintains circulation despite developing its own ischemia, further aggravating O2 supply/demand balance and leading to infarction (MI). In the current study, 20 rats underwent ligation of the left anterior descending artery, treated with 10 mL/kg of PEGylated carboxyhemoglobin bovine (SANGUINATE®, S+, n=10) or saline (S-, n=10) initially and daily thereafter for three days (a total of four doses), and were followed by weekly echocardiography for four weeks. They underwent repeated left ventricular pressure volume relationship analyses (PVR) followed by necropsy. Echocardiography showed milder increase in end-systolic dimension, preserved fractional shortening (36 vs 26%, $p< 0.01$), and milder mitral regurgitation (MR) in S+ compared with S- rats, respectively. PVR revealed a milder increase in end- systolic volume, larger stroke volume (101 vs 74 L, $p< 0.005$), cardiac output (33.4 vs 23.8 mL, $p=0.004$), and preserved stroke work (9.0 vs 5.1, $p< 0.002$) in S+ rats in actual determination and under a wide range of standardized loading conditions four weeks after MI. Excised heart showed significantly limited area of MI (8.9 vs 13.3%, $P=0.028$). The results suggest that SANGUINATE® in long-term repeated doses may preserve myocardium, mitral competence, and cardiac function after MI. The mechanism of action and optimal treatment for MI remain to be studied.

P62

4D FEM STUDY OF DISTURBANCES ON THE CONDUCTANCE CATHETER METHOD

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Objectives: VADs (Ventricular Assist Devices) are used to support the weakened heart muscle in supplying organs with oxygenated blood. The placement of the pumps in the left ventricle and aorta can be used to derive relevant vital parameters, such as the volume of the left ventricle by e.g. impedance volumetry. It was shown by Baan et al. that impedance volumetry can be done by the so called conductance method. In practice, this method has some shortcomings e.g. calibration, correction factor, catheter placement, etc.. Therefore, this study presents a 4D FEM simulation, in which various influences on the measurement with the conductance method are analyzed.

Methods: Since the sources contributing to an impedance cardiography signal are still discussed, the FEM simulation is used to evaluate those influences separately. The simulation contains a simplified anatomical model of the thorax, in which the volume of the heart is varied. Volume changes of the left and right ventricle as well as of the aorta are implemented. Additionally, conductivity changes of flowing blood are considered as erythrocytes change their electrical properties depending on their velocity and orientation.

A pathological change of the myocardial tissue was implemented by variations of electrical conductivity and the dielectric properties of the heart muscle. Additionally, the variation of electrode position for the best possible measurement of the left ventricular volume was performed.

Results and Discussion: First results show that the estimated volume is very sensitive to changes of electrode positions. A closer placement of electrodes to the muscle tissue results in an increase in measurement error. Interestingly, a volume variation in the right ventricle influences the volume measurement of the left ventricle.

The observations from this study can be used to optimize volume estimation in the left ventricle and to investigate the cardiac status using this technique.

P63

OFFLINE DOPPLER SIGNALS ANALYSIS AS THE INITIAL STUDY OF NON-INVASIVE BLOOD PRESSURE MEASUREMENT FOR PATIENTS WITH CONTINUOUS FLOW HEART SUPPORT

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Objectives: The accurate, non-invasive blood pressure measurement (NIBP) as well as recognition and management of hypertension in patients supported by continuous flow VADs (CF-VAD) is an essential component of optimal clinical care. Limited understanding of the distinct hemodynamics of these pumps makes measurement and medical management of NIBP quite challenging. One of possible solution may be utilization of Doppler detector in NIBP measurement.

Methods: The Doppler blood flow signal vs pressure in cuff curves in N=16 CF-VAD supported patients (HVAD, HeartMate2, HeartMate3) were registered and analyzed off-line. Patients were diversified regarding age, supporting time, physical activity etc. The MD4 pocket-size Doppler together with UD48V ultrasound Doppler designed for bilateral diagnostics of peripheral vessels (SONOMED, Warsaw, Poland) were used for radial artery Doppler signal detection. Signals were registered during the manual blood pressure measurement at arm or forearm (above Doppler probe).

Results: Performed study have shown a significant variability of blood flow morphology regarding CF-VAD type and patient's status. The simple Doppler detector gave a satisfying signals for analyses of artery blood flow vs artery compression pressure dependence. The periodic pump flow changes were clearly observed in signals. The systolic pressure was determined in every one case. However, diastolic pressure determination seems to be complex, due ambiguity of flow signal changes in this area.

Discussion: Blood flow in peripheral arteries in CF-VAD supported patient is complex and quasi-physiological. A prototype ultrasonic Doppler-based semi-automatic NIBP measurement system for patients supported by CF-VADs was developed. It confirmed good quality of blood flow signal detection for whole range of flow, related with artery obstruction caused by precisely controlled cuff pressure. Advanced offline Doppler signals analysis will be performed, including simultaneous catheter-based pressure monitoring, to validate specific blood pressure values determination algorithm.

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P64

CONTINUOUS FLOW HEART SUPPORT REMOTE MONITORING

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Objective: Nowadays, about 50% of continuous flow VADs (CF-VAD) are applied as destination therapy (refer

to INTERMACS'2015 report). Early after implantation, multi-organ failure, right heart failure and strokes (ischemic or hemorrhagic) pose the greatest risk. Extension of durable devices to a greater participation of patients with ambulatory heart failure requires more effective prevention of serious adverse events. In order to continuous remote monitoring of CF-VAD patients and system components the IT platform has been developed.

Methods: Central Patient Monitoring System (CPMS) for heart assist devices monitoring was developed. CPMS system collects remotely medical parameters (INR, anticoagulants dosage, weight, blood pressure, pulse, temperature, saturation, wound status) as well as CF-VAD parameters (blood flow, power consumption, pulsation index, pump speed). Adverse events in CF-VADs patients under 24/7 emergency hotline with medical and technical support were compared to patients under remote monitoring with CPMS utilization.

Results: From 2015 to 2017 n=27 HVAD implantations were performed in Silesian Heart Diseases Centre. Routine medical and technical support was used for devices monitoring. The longest support is over 1000 days (n=4) and 11 patients are between 400 – 600 days on support. 394 technical control visits were analyzed, 161 of them were for emergency in hospital or patient's home. 49 technical call consultations and patients log-files were performed. 63 malfunction of HVAD system elements were observed: 41% controller and 27% battery failures. 49 complaints of HVAD elements were carried out and 19 repair was performed (e.g. driveline jacket break, battery socket loosen). Patient's accessories break-down added up to 15% and 10% of malfunction affected blood pump.

Conclusions: CPMS for heart assist devices monitoring is during first clinical studies. Comparing analysis will be performed for CF-VADs patients controlled with and without CPMS system.

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POSTER SESSION PF01: SOFT TISSUE & SENSORY ORGANS ENGINEERING

P65

THE COMPARATIVE ANALYSIS OF ELECTROSPUN AND CASTING SILK FIBROIN SCAFFOLD PROPERTIES

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Objectives: There are large field of problems that regenerative medicine is have to solve, which needs more new techniques to fabricate scaffolds for tissue engineering. One of these new methods is electrospinning which allows defining scaffold structure and properties. Also it is crucial to select a biocompatible material with the complex of appropriate physical and chemical characteristics. Bombyx mori silk fibroin suits all of these parameters. The main goal of this investigation was to fabricate silk fibroin scaffolds by casting method and electrospinning method and comparative analysis of scaffold properties in vitro and in vivo.

Methods: Silk fibroin scaffolds were obtained by two methods: casting method and electrospinning method. Scaffold structure was researched by scanning electron microscopy and scanning probe nanotomography. To evaluate cytotoxicity of scaffolds MTT method was performed. Cell adhesion and proliferation were investigated in mice fibroblasts 3T3 model. The produced scaffolds were used as wound coatings for Wistar rat full-thickness skin wound regeneration.

Results: It was shown that electrospun mats have fibrous porous structure with an average fiber thickness 300 nm. Casting films have a rough micro- and nanorelief with no porosity. The obtained scaffolds do not have cytotoxic effect and facilitate cell adhesion and proliferation, wherein cell adhesion at the electrospun mats was an increase of 15 per cent over casting films. Both scaffold types have promoted skin wound regeneration and have restored native skin structure. Histological analysis did not evolve inflammatory process.

Discussion: Structure is the most essential parameter, which affects scaffold regenerative potential. The fabricated scaffolds has a different structure, which leads to cell adhesion level diversity and regeneration process distinctions. Electrospun mats have high elasticity and swelling properties, thus, electrospinning is promising to application in regenerative medicine. Thereby both types of scaffolds can be utilize in different tissue engineering fields and are perspective for regenerative medicine.

P66

DERMO-EPIDERMAL ORGANOTYPIC CULTURES FOR FOR THE ASSESSMENT OF IRRITATION AND CORROSION

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Introduction: The assessment of potential human health risks posed by chemical substances is required by many regulatory bodies such as the OECD (Organization for Economic Co-operation and Development) before commercialization.

Today, studies for chemical hazard identification are mainly based on animal experiments. Nevertheless, ethical

issues raised by animal research have led to the development of *in vitro* systems to evaluate skin toxicological responses. Most of them consist of human keratinocytes deposited on a support and cultured in such a way as to form a stratified epidermis. However, they are only composed of keratinocytes, neglecting the effect of other skin constituents. Cultures containing the dermal end epidermal component can provide an attractive *in vitro* system to investigate, in a more real model, toxic skin responses, which represents a distinct advantage over keratinocytes-based models, which do not mimic very well the environment found *in vivo*.

Objective: This study aimed to produce dermo-epidermal organotypic cultures (OCs) as platforms to perform irritation and corrosion tests.

Methods: Cells were obtained from skin samples after informed consent and skin models were constructed by seeding keratinocytes on fibroblast-containing fibrin gels. After 21 days of culture, the OCs were analyzed morphologically (hematoxylin–eosin staining), and functionally (immunohistochemical characterization of epidermal proteins). The irritant and corrosion potential was determined by means of viability measurements (MTT assay), after exposure to test substances, according to 431 and 439 OECD tests guidelines.

Results: Skin models showing similar morphological and functional characteristics to those of native skin were obtained, However, it was not always possible to obtain a complete epidermal stratification. The models were able to correctly classify different chemical substances.

Discussion: The OCs showed a high chemical classification capacity. Further studies should be done to produce correctly differentiated models in order to increase prediction capacity.

P67

CHICKEN CHORIOALLANTOIC MEMBRANE AS A MODEL FOR IN VIVO EVALUATION OF THE ANTIMICROBIAL ACTIVITY OF MODIFIED SKIN SUBSTITUTES AGAINST INFECTION BY STAPHYLOCOCCUS AUREUS AND PSEUDOMONAS AERUGINOSA

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Introduction: Wound repair is fundamental to restore the integrity and regular function of the skin. An inefficient recovery of autologous tissue may increase the susceptibility of patients to infections caused by multiresistant microorganisms. Tissue engineering currently offers strategies for the treatment of these lesions, through the use of autologous cutaneous substitutes based on biopolymers such as fibrin, in which different cell populations can be incorporated in order to favor the production of important innate immune system proteins, including antimicrobial peptides.

Objective: This project aimed to develop a protocol for the use of the chorioallantoic membrane (CAM) *ex ovo* model for the evaluation of antimicrobial activity of cutaneous substitutes composed of keratinocytes and fibroblasts, which overexpress the LL 37 antimicrobial peptide.

Methods: Commercial fertilized eggs of domestic chickens were incubated at 39 ° C for 4 days.The eggs were then opened from the apical side and placed on a Petri dish. Once the embryo was exposed, skin grafts from surgeries leftovers were transplanted on the CAM vasculature of 8-day-old chicken embryos. After the implant, the embryos were reincubated for two days and a wound of 5mm approximately was generated. This wound was grafted along with cutaneous substitutes that contained genetically modified cells, and were cultured at 37 °C, 5% CO2 and 90% humidity. Two days after incorporating the substitute, a suspension of 1000 Colony Forming Units (CFU) of *Staphylococcus aureus* and *Pseudomonas aeruginosa* strains was added. Subsequently, the tissue was processed and seeded in culture to evaluate the strains growth and the CFU/graft.

Results: The quantification of CFU in the skin grafts treated with the genetically modified skin substitutes showed significant differences compared to the controls (grafts infected with the microorganisms, but treated with unmodified substitutes).

Discussion: The protocol used is promising as an alternative to prevent infections in skin wounds associated with microorganisms of clinical relevance, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa.*

P68

GENERATION OF TUNABLE CROSSLINKED FIBRIN-AGAROSE TISSUE-LIKE MODELS FOR TISSUE ENGENEERING APLICATIONS

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Objectives:

The aim of this study was to generate custom tissue-like bioartificial tissues using fibrin-agarose hydrogels (FAH) biomaterials subjected to chemical crosslinking in order to improve their biomechanical properties.

Methods: FAH and nanostructured FAH (NFAH) were elaborated using human plasma and type VII agarose.

Hydrogels were crosslinked by using 0.25% to 0.5% of glutaraldehyde or genipin in order to regulate the hydrogel porosity and fibrillar arrangement. Hydrogels were recellularized with human primary fibroblasts. Cell viability and scanning electron microscopy (SEM) analyses were carried out.

Results: Cell viability analysis showed that highest biocompatibility corresponded to hydrogels treated with the lowest concentrations of the crosslinking agents, and that genipin-treated biomaterials were more biocompatible and supported cells functions. SEM characterization revealed that the highest concentrations of the crosslinking agents result in a significant increase of fibers density and a reduction of porosity. The structural pattern with the highest porosity and the lowest fibrillar density corresponded to FAH, whilst the lowest porosity and the highest fibrillar density were obtained in NFAH models crosslinked with 0.5% glutaraldehyde.

Discussion: FAH-based scaffolds treated with chemical crosslinking agents demonstrated to be biocompatible ex vivo. SEM characterization suggests that the structural properties of the biomaterial can be controlled and tuned by modifying the type and concentration of chemical crosslinking agent. Therefore, distinct patterns of porosity and fibrillar arrangement could be designed to generate more biomimetic substitutes for specific tissue engineering applications.

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QUALITY CONTROL OF MAGNETIC TISSUE-LIKE SUBSTITUTES ELABORATED BY TISSUE ENGINEERING. AN IN VIVO STUDY IN WISTAR RATS

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Objectives: Magnetic nanoparticles (MNPs) may be used in tissue engineering to support the regeneration of damaged native human tissues. In this study, we performed a quality control analysis of magnetic tissue-like constructs based on fibrin/agarose hydrogels (FAH) by evaluating in vivo biodistribution and biocompatibility of these materials.

Methods: Magnetic tissue-like constructs based on FAH containing MNPs were fabricated and subcutaneously implanted in 5 adult Wistar rats. As controls, FAH without MNPs was implanted in other 5 animals. After 1 and 12 weeks, animals were subjected to magnetic resonance imaging (MIR) and histological analyses. The implant area, liver, kidneys, spleen and lymph nodes were histologically analyzed using H&E and Perl's histochemical method (for iron).

Results: MIR showed hyper-intense areas in the region of implantation after 1 and 12 weeks, but no signs of the presence of MNPs nor structural alterations were observed in peripheral organs. Perl's histochemical analysis revealed some positive staining areas in the implant regions and in some distal organs. Only a local macrophage and lymphoplasmocytic-rich inflammatory reaction was observed at 1 week around the implants in FAH and FAH-MNPs groups, but this inflammatory reaction decreased at 12 week. Indeed, all organs were histologically normal during 12 weeks.

Conclusions: MRI and histological analyses demonstrate that MNPs are retained in the implant area after 12 week of implantation, and no alterations were detected in distal organs. For these reasons, we believe that magnetic tissue-like FAH-MNPs constructs could be useful as local treatments in future tissue engineering applications.

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POSTER SESSION PF02: ANTI-INFECTIVE BIOMATERIALS & DRUG DELIVERY SYSTEMS

P70

INFLUENCE OF SURFACTANT CONCENTRATION IN GELLING LIQUID ON SIZE AND SHAPE OF POLYETHERSULFONE MICROCAPSULES PRODUCED FROM POLYMER SOLUTIONS OF DIFFERENT VISCOSITIES

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One-step electrostatic microencapsulation using 3-nozzle head of our construction allows manufacturing of synthetic polymer polyethersulfone microcapsules (with or without alginate cores) suited for biomolecule or cell immobilization and application as therapeutic delivery systems or bioartificial organ components. Microcapsules are manufactured by gelation of 2-/3-layer droplets, formed by 2 or 3 liquids co-extrusion (polymer solution/glycerin/optionally alginate solution) into gelling bath.

Objectives: In our previous experiments 0.5% of Tween-80 has been used to lower gelling liquid surface tension and ensure complete droplets immersion. However, Tween-80 destabilizing effect on cellular membranes could be problematic during cell microencapsulation. Study objective was to investigate how microcapsule geometry is affected when surfactant is removed from gelling liquid or its concentration is significantly reduced.

Methods: Microcapsules were produced from polyethersulfone solutions of 3 different viscosities (63, 251, 686 mPas). Medium and high viscosity solutions were gelled in water baths containing 0, 0.004, 0.016, 0.25% of Tween-80. Low viscosity solution was gelled at 0, 0.0005, 0.001, 0.002% of Tween-80. To simplify experimental setup microcapsules did not contain alginate cores. Microcapsules size and shape were analyzed microscopically.

Results: The presence of surfactant in gelling bath was not essential for proper gelling of high viscosity solution. In fact, microcapsules obtained without surfactant were most spherical, uniform in size and shape, statistically larger than microcapsules produced using Tween-80. Medium and low viscosity solutions gelled properly only in the presence of surfactant at minimum concentrations of 0.016% and 0.002%, respectively. At lower concentrations droplets immersed partially forming tail- or collar-like deformations.

Conclusions: Surfactant concentration has unexpectedly high influence on microcapsule final geometry, which seems to be established during gelling. Surfactant elimination from microencapsulation process is beneficial in case of high viscosity polymer solutions. Gelling of less viscous solutions requires surfactant use, but can be performed at significantly lower concentrations than previously used.

P71

ANTIBIOTIC-LOADED BONE ALLOGRAFTS FOR PROPHYLAXIS AND TREATMENT OF BONE INFECTIONS

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Background: Every surgical procedure is accompanied by an immanent risk of bacterial infections. This matter needs to be especially considered in transplantations of bone allografts for regeneration of lost tissue in dental and orthopedic applications, as the debridement is likely to result in worsening of the initial situation. One particular challenge is the population of bioimplant surfaces with biofilm forming bacteria such as *staphylococcus epidermidis*which are less prone to antibiotic treatment. The loading of bone allografts with antibiotic agents demonstrates a promising approach to prevent bacterial infections. In the present study the pharmacokinetic properties of several antibiotics incorporated into allografts were analyzed *in vitro* and *in vivo*.

Design and Methods: Freeze-dried bone allograft (FDBA) blocks were rehydrated in antibiotic solutions of either Clindamycin, Gentamycin, Rifampicin, Vancomycin and a mixture of Vancomycin and Rifampicin for biofilm treatment for 10 minutes prior to *in vitro analyses* or *in vivo* implantations. The *in vitro* concentration of remaining antibiotics was assessed every 24 hours with a total follow-up of 10 days. For analysis of the *in vivo* release the femur implantation model in rabbits was used in 30 rabbits with explantations at day 1 and 3. The remaining amounts of the antibiotics and the biocompatibility of the antibiotic-loaded allografts were analyzed.

Results: Antibiotics are easily incorporated into FDBA blocks and steadily released for a period of over ten days. Especially within the first 3 days high concentrations were released. Furthermore, an excellent biocompatibility of all FDBA blocks combined with the different antibiotics was shown.

Conclusion: The use of FDBA as carriers of antibiotic agents bares great potential in clinical application by eliminating systemic antibiotic-related side effects, minimizing risks of antibiotic resistance formation, and consequently minimizing the risk of surgical site infections and postoperative complications.

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DIFFERENTIATION AND HETEROGENEITY OF BIOMATERIAL-INDUCED MULTINUCLEATED GIANT CELLS: CONNECTION BETWEEN INFLAMMATION AND TISSUE REGENERATION

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Introduction: Biomaterial-associated multinucleated giant cells (BMGCs) have been found within the implantation beds of many biomaterials. Their exact differentiation and their involvement in the inflammatory and healing events remain mostly unclear. Various findings suggest that these cells belong to the cell line of the foreign body

giant cells (FBGCs) providing a phenotypic heterogeneity equivalent to that of macrophages, whose pro-inflammatory activation profile has been proposed to promote the process of tissue regeneration. To substantiate our hypothesis of the differentiation and of the phenotypic and functional relationship between macrophages and BMGCs, antibodies for the detection of giant cell-specific antibodies as well as for detection of different pro- and anti-inflammatory macrophage subpopulations were applied.

Materials and Methods: In a first study tissue samples from a clinical study were used to analyze the origin of BMGCs in the implant beds of a synthetic and a xenogeneic bone substitute using two antibodies against integrin molecules specific for osteoclasts (β-3 integrin) or FBGCs (β-2 integrin). In a second study silk fibroin (SF) was subcutaneously implanted in 24 rats. (Immuno-) histochemical staining methods and histomorphometrical techniques were applied to analyze the heterogeneity of BMGCs.

Results and Discussion: The data show that the BMGCs induced by both kinds of bone substitutes are FBGCs, as they express only β-2 integrin in contrast to the osteoclasts. These cells express both pro- and anti-inflammatory molecules to the same extent within the implantation beds of silk fibroin scaffolds, which substantiates the heterogeneity of FBGCs comparable to that of macrophages, whose M2-phenotype appears to be related to a successful tissue remodeling outcome.

Conclusions: These data give new insight into the tissue reaction to biomaterials. Based on this new knowledge further research concerning the proteomic profile of the FBGCs is necessary.

P119

BACTERIAL ADHESION IN VITRO ON SURFACE OF TANTALUM AND TITANIUM TREATED WITH LASER SHOCK PROCESSING (LSP)

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Introduction: Adherence of bacteria to surgically used metallic orthopedic and dental implant materials is one of the most important virulence factors for local foreign body infection and a prerequisite for the development of biofilms. Bacteria of major concern in that regard are especially of the genus of *Staphylococcus* and Streptococcus, which represent by far the most common pathogen found in infected orthopedic and dental surgical implants, respectively. Rabenseifner et al, in an animal study, has shown that tantalum implants allow fracture healing despite inoculation with *S. aureus*, whereas stainless steel implants do not. This leads to the assumption that tantalum or tantalum-coated implants may perform well in infected and possibly infected environments, and may become an alternative or adjunct to currently used implant materials in trauma applications.

The purpose of our study was to evaluate bacterial adhesion to pure tantalum and tantalum treated with LSP versus currently applied metallic implants in orthopaedic surgery.

Experimental methods: Disks of Ti6Al4V and pure tantalum (Ta) were treated with LSP with spot diameter of 1,5 mm and three different pulse densities: 2500 (LSP1), 1600 (LSP2) and 625 (LSP3) pulses•cm2 to achieve changes in surface hydrophobicity, the topography, and compressive residual stresses, critical parameters for the corrosion and fatigue performance of a biomedical implant. Bacterial adhesion experiments with the strains: Staphylococcus aureus ATCC29213, Streptococcus sanguinis ATCC10556 and Escherichia coli ATCC25922 was carried out.

Results and Discussion: The adhesion of the three bacterial strains regardless of the test surfaces follows the same trend in terms of density of adhered bacteria: *S. aureus* > *S. sanguinis* > E. coli. Untreated Ta samples show a smaller adhesion rate than the untreated TiAlV ones. Also, the adhesion of the three strains studied is always smaller on surfaces treated with LSP1.

P73

BACTERIAL ADHESION IN VITRO ON SURFACE PLA/MG COMPOSITES TREATED WITH LSP

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Introduction: Biodegradable polymeric materials based on polylactic acid (PLA) are currently available for repair applications of bone fractures with low load bearing, gaining popularity due to the avoidance of a removal operation, low immunogenicity, and toxicity. However, their use in clinical practice has been limited to their lack of bioactivity and low mechanical properties. A new strategy to improve the mechanical properties of PLA is the introduction of magnesium (Mg) particles where the polymeric matrix will benefit from the Mg higher strength and modulus, and Mg will benefit from the surrounding protective matrix. Despite these advantages, the composite degrades too fast, and the strength drops sharply just from the initial stages. Gaseous hydrogen and the pH increase associated with the corrosion process might further irritate the injured tissue. A straightforward strategy to tackle hydrogen accumulation is to

reduce the corrosion rate by using a promising surface treatment such as Laser Shock Processing (LSP).

A significant problem associated with the use of permanent but biodegradable implants is the appearance of infections. The purpose of this research is the achievement of information of the characteristics of the early attachment of bacterial strain of *Staphylococcus epidermidis* to polymer-Mg composites treated with LSP.

Experimental Methods: PLA was loaded with spherical Mg particles <50 μm in size processed by extrusion and molding by the CENIM-CSIC. PLA/Mg composite material was subjected to LSP treatment by the UPM Laser Center with different parameters. Bacterial adhesion experiments with the gram-positive strain *Staphylococcus epidermidis* ATCC35983 were carried out.

Results and Discussion: The surface of PLA/Mg composite material without LSP treatment generates bactericidal effect on *S. epidermidis* at short contact times. However, when the samples of composite material were treated by LSP, the bactericidal effect appeared later.

P74

THIN ELECTROSPUN PVDF-TRFE FIBER MEMBRANE WITH PIEZOELECTRIC EFFECT TO CONTROL DIFFUSION

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Objectives: This study aims to investigate the influence of piezoelectric polyvinylidene fluoride-co-trifluoroethylene (PVDF-TrFE) fiber membranes on the diffusion rate of inorganic ions for medical applications such as controlled drug release devices. The experiment is based on the direct piezoelectric effect, wherein PVDF- TrFE membranes induce voltage due to mechanical deformation.

Methods: Solutions of PVDF-TrFE and non-piezoelectric poly(ε-caprolactone) (PCL) were electrospun on commercially available cellulose membranes (cut-off 12-14 kDa; CelluSep®) to generate modified thin fiber membranes (wall thickness = 60-80 μm; analyzed via scanning electron microscopy (SEM)). Membranes were tested in a custom-made two-chamber filter system. Chamber A, containing an aqueous solution of

0.3 M NaCl, was separated from chamber B (deionized water) by the modified membrane. Change in conductivity of deionized water (1.4 μS/cm) was measured for 150 min in static and cyclic loading (5 N; 10 Hz) conditions.

Results: Static tests with unmodified cellulose membranes revealed a conductivity of 235 μS/cm. Experiments with modified PCL membranes showed a conductivity of 182 μS/cm, while conductivity for PVDF-TrFE membranes was 4 μS/cm. Cyclic loading led to an increase in conductivity for unmodified membranes (5530 μS/cm; 24x), as well as for PVDF-TrFE membranes (1915 μS/cm; 479x). SEM images showed more salt accumulation on PCL fibers than on PVDF-TrFE fibers after static tests.

Discussion: This study demonstrates that the piezoelectric effect is a promising tool to control the diffusion of inorganic ions. The modified PVDF-TrFE membrane efficiently inhibited diffusion under static conditions when compared to the control. Application of cyclic loading and induction of the piezoelectric effect of the polymer strongly increased diffusion compared to the static condition by 47800 % as well as to the control by 2300 %. Based on these results, modified PVDF-TrFE membranes can be conceived suitable in medical applications such as controlled drug release devices.

P75

CHARACTERIZATION OF ELECTROSPUN MEMBRANES OF P(LA-CO-GA) AND P(CL-CO-GA)

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Objectives: The main objective of this work was to achieve electrospun membranes of poly(lactic-co-glycolic) P(LA-co- GA) and poly(caprolactone-co-glycolic) P(CL-co-GA) and their characterization for making a suitable material for controlled drug delivery.

Methods: The polymeric solutions were prepared by solving P(LA-co-GA), with acid and ester terminations in equal proportions, and P(CL-co-GA) in different solvents (1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and chloroform/methanol) at different concentrations. Polymer solutions were loaded in a syringe attached to a pump to be electrospun in a homemade equipment.

The samples were analysed by Scanning Electron Microscope (SEM) to study their morphology and to optimize the main electrospinning parameters to obtain electrospun membranes without defects.

Results: Fibres were obtained for P(LA-co-GA) dissolved at a concentration of 10%wt/v in HFIP. By increasing the concentration to 25%wt/v fibre diameters above-micron size were obtained. On the other hand, the increase in the voltage give rise to the reduction of the beads in the samples.

P(CL-co-GA) solutions in HFIP showed a lower viscosity, which hindered obtaining electrospun membranes. For that reason, P(CL-co-GA) was dissolved in chloroform/methanol because chloroform allows reducing the concentration of the polymers while keeping an adequate viscosity for electrospinning.

Discussion: We conclude that HFIP is a proper solvent for P(LA-co-GA), but P(CL-co-GA) requires chloroform/methanol as solvent because a higher concentration of the copolymer is necessary to obtain fibres.

By modifying the main electrospinning parameters, it was possible to manufacture electrospun membranes with above-micron diameter of fibres.

P76

USE OF CATIONIC LIPOSOMES EMBEDDED INTO POLYELECTROLYTE MULTILAYER SYSTEM FOR CONTROLLED RELEASE

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Objectives: Cationic liposomes of (N-{6-amino-1-[N-(9Z)-octadec-9-enylamino]-1-oxohexan- (2S)-2-yl}-N′-

{2-[N, N-bis(2-aminoethyl)amino]ethyl}-2-[(9Z)-octadec-9-enyl]propandiamide) (OO4) and dioleoylphosphatidylethanolamine (DOPE) contain a higher amount of amino groups than classical lipids. Here, a polyelectrolyte multilayer system (PEM) made of chondroitin sulphate (CS) and collagen type I (Col) was prepared by Layer-by-Layer technique (LbL) with the liposomes embedded in terminal layers. Due to their intrinsic charge, they might be used as a polycation in LbL for the controlled release of components to promote osteogenic differentiation.

Methods: Characterization of the PEM was performed using ellipsometry at dry conditions. This technique was used to investigate the thickness on silicon substrate coated with PEM consisting of CS, liposomes, COL as terminal layers. The layer growth behavior of PEM was studied using Surface Plasmon Resonance (SPR). Cell adhesion and liposome uptake studies by C2C12 cells were carried out with immunofluorescence staining and flow cytometry analysis.

Results: SPR results shows a linear growth with an increase in the angle shift corresponding to the adsorbed mass of PEM. An increase in thickness was found for layers adsorbed with 150mM NaCl as solvent. Especially the increase after liposome adsorption was significant. The cell studies indicated that cells seeded on terminal liposome layer showed a higher amount of cells on the surface. Population of cells that took up liposomes are higher in the absence of serum than in medium with FBS.

Discussion: A novel liposome involving amino-functionalized lipid was embedded into PEM system of col and CS. The quantification of liposome uptake indicated that the population of cells that took up liposomes were higher in the absence of serum and there was a reduction of liposomes uptake after the addition of Col as terminal layer. These results showed that CS system is convenient for final adsorption of liposomes, due to the positive surface charge.

P77

DEVELOPMENT OF ANTI-INFLAMMATORY SURFACES USING MICROTOPOGRAPHIES

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Objectives: Longevity, functionality and compatibility of medical implants are crucial for the quality of life of patients. Thus, testing biomaterials is required for clinical application. The biomaterial implantation launches a series of interactions jointly called the foreign body response (FBR), which is also affected by the topography of implant materials that modulates the attraction and activation of macrophages. Therefore, the adhesion of macrophages was investigated here towards polymeric substrates with different micro- geometrics. Microchannels of 1:1 ratio of ridge and groove, variable lines and hexagonal pillars with 1:1 ratio were fabricated onto 0.5 mm thick poly (methyl methacrylate) (PMMA) polymer foils as model implant material.

Method: Nanoimprint lithography (NIL) was selected for its fast and large production of micro- and nanostructures. Thus, master stamps were fabricated on 2,5" Si wafers, were dry-etched for different times resulting in stamps with structure depths of 1.0 and 2.0 μm, respectively and were spin-coated with an anti- adhesive material (methylnonafluoroisobutyl ether and methylperfluoroisobutyl ether). The imprint parameters were varied in terms of heating temperature, pressure and cooling temperature. The structures were visualized *ex situ* with scanning electron microscopy (SEM).

Results: The structures were imprinted at a heating temperature of 140°C, 40 bar pressure and a cooling temperature of 85°C. The SEM illustrates successful formation of the different geometries without any ruptured or shifted edges together with the ability of getting 1 μm depth on PMMA foils. Subsequently, Giemsa stained macrophages were visualized to study adhesion and morphological changes on micro- structured in parallel to plain PMMA

surfaces. Results depict the different cellular responses in terms of cell number, spreading and orientation.

Conclusion: NIL is a suitable method for the fast fabrication of microstructures on different polymeric substrata. Moreover, the observed effects on macrophages may pave the way to minimize FBR after implantation of biomedical devices by structuring the material surface.

P78

GELATIN MODIFIED POLYVINYLIDENE FLUORIDE MEMBRANES AS A DUAL SYSTEM FOR ELECTROSTIMULATION OF CELLS AND CONTROLLED DRUG DELIVERY

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Objectives: In recent years, the use of poly(vinylidene fluoride) (PVDF) in tissue engineering has increased, mainly due to its piezoelectricity, which enables the electromechanical stimulation of pluripotent cells to drive their differentiation. The hydrophobic nature of this material hinders its wettability and diffusion of nutrients in cell culture. The aim of this study is the development of new PVDF porous membranes containing a gelatin hydrogel in the pore structure to increase the diffusion of water soluble substances, enhance the adhesion of cells and enable the delivery of growth factors.

Methods: Microporous membranes of PVDF with a structure based on the agglomeration of spherulites were obtained by freeze-extraction from a polymer solution. The pores were filled with an *in situ* enzymatically crosslinked gelatin. The material was characterized structurally and physicomechanically to verify the presence of the hydrogel inside the membrane. After culturing with mesenchymal stem cells, focal adhesions and proliferation ratio were analysed by immunohistochemistry and total DNA quantification, respectively.

Results: The membranes with gelatin exhibit a slightly higher elastic modulus, higher percentage of mass loss in thermogravimetric testing and the presence of characteristic absorption peaks of pure gelatin in the FTIR spectra. The surface presents domains of gelatin combined with groups of PVDF spherulites in the CryoSEM images. In addition, mesenchymal stem cells seeded at low density present spread morphology and higher proliferation in the membrane with gelatin.

Discussion: The results demonstrate the presence of the gelatin in the membrane in the first layers of the material, with a positive effect on cell culture in terms of adhesion and proliferation. The system is very promising for the future electromechanical stimulation of cells and delivery of growth factors.

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P79

ION-IMPLANTED TROJAN HORSE SURFACES WITH ANTIMICROBIAL ACTIVITY AND ANTI-INFLAMMATORY POTENTIAL

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Background and Objectives: Hospital acquired infections are the most frequently occurring adverse event in healthcare globally, with implantable devices particularly susceptible due to microbial biofilm formation. Furthermore, implant introduction often results in inflammation and production of foreign body giant cells (FBGCs), ultimately resulting in aseptic loosening. Gallium (Ga) has shown great efficacy as an antimicrobial with anti-inflammatory properties. Defensin (De, hBD-1), a component of innate immunity has also shown promise as an antimicrobial agent. Hence, our aim is to synergistically combine the strengths of each strategy to impart antimicrobial activity and biocompatibility to implantable polymer- based devices.

Materials and Methods: PLA films were fabricated and modified using plasma treatment or Ga-implantation. Following this, De was immobilized on the surfaces. Physicochemical characteristics were probed using Atomic Force Microscopy, Nano Thermal Analysis and Lorenz Contact Resonance. The antimicrobial effects of De were tested using the Disc Diffusion Assay. The surfaces were then subjected to a 14-day Biofilm Formation Assay, followed by immunofluorescence staining and confocal microscopy. The surfaces were also tested for their inflammatory potential via the FBGC formation assay and through ELISA of pro-inflammatory cytokine IL-1β, normalized using the QBlue Cell Viability Assay.

Results and Discussion: Ga-implantation resulted in increased surface stiffness. Linker-free immobilization of

defensin was confirmed on the plasma treated and Ga-treated surfaces. Ga-implantation and De-immobilization both independently and synergistically proved to impart antimicrobial activity to the surfaces and the antimicrobial effects of hBD-1 appeared to be potentiated by surface immobilization. IL- 1β expression reduced initially with increasing Ga concentration, but increased over all with introduction of chemoattractant De. FBGC formation was significantly decreased in all Ga- and Ga-De-treated groups in comparison with untreated PLA.

Conclusion: These innovative surfaces have the potential to prevent biofilm infection without introducing any cytotoxicity, but eliciting initial macrophage activation, which is highly desired for implantable devices, thereby preventing infections and improving the healing process.

POSTER SESSION PF03: SCAFFOLDS & BIOMATERIALS

P80

EVELOPMENT OF STRUCTURAL AND CHEMICAL ENFORCEMENT OF NEOINTIMAL GROWTH AS THE BLOOD CONTACTING SURFACE FOR THE VASCULAR PROSTHESIS

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Objectives: Thromboembolism event around the cannula is one of the critical problems after implanting a ventricular assist device(VAD). We have developed the surface modification based on the titanium(Ti) micro-porous structure for promoting early neointimal growth. The purpose of this study is the evaluation of our Ti micro- porous structure with the surface modification, as the scaffold materials of the vascular prosthesis.

Methods: Ti powders, sifted among 125 to 150 micrometer, were mixed with the 10 wt% of thermoplastic wax. The mixture was warmed up in 50 degC and injected into a mold. Green specimens were sintered in 1,100 degC at argon gas condition for 1.5 hour, to make the porous structure by the combination of each Ti powders. These specimens were studied for the mechanical properties and the cell adhesion evaluation. Part of specimens were hydrolyzed, and then treated with the collagen solution for the urethane-like modification. Modified specimens were implanted around connective tissues and muscular in rats for evaluating the specimens' interaction.

Results: The theoretically predicted micro-porous specimens showed the similar strength compared to bovine femoral bone. And the cells invasions and collagen rich structure were observed inside the micro-porous structure. Organ adhesion tests showed the higher strength compared to the bulk Ti specimens. Discussions: Our micro-porous scaffold is based on the Ti that is known as the biocompatible materials. By modifying as the cell scaffold for the structural and biochemical point of views, the possibility of critical events after VAD implantations might be decrease by the early neointima on Ti materials. The results of this study indicated the advantages of modified microporous surface structure as the blood contacting surfaces of the vascular prosthesis.

P81

INFLUENCE OF LASER RADIATION ON CONDUCTIVITY OF A NANOCOMPOSITE BASED ON CARBON NANOTUBES AS A MATERIAL FOR CARDIAC PATCHES

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In this work an influence of laser radiation on conductivity of nanocomposite was studied. The nanocomposite was made by mixing of albumin, collagen and chitosan with aqueous dispersion of carbon nanotubes. The component concentrations were the following: albumin – 20%, collagen - 2 %, chitosan – 2% and nanotubes – 5%. Then the obtained dispersion was deposited onto silicon substrates coated with silicon dioxide coating using three methods. The first method consisted of forming a thin layer of nanocomposite by a thermal evaporation of dispersed water component at room temperature. The second and the third methods comprised forming the layer by continuous wave laser radiation of 970 nm wavelength and 0.1 MW/m2 power density, and by pulsed laser radiation of 1064 nm wavelength, 110 ns pulse duration and 50 kHz frequency, respectively. Thickness of the formed layers was about 10 μm. The conductivity of the thin layers of the nanocomposite was measure with probe station MPS 150 (Cascade Microtech, USA) by the Van der Pauw method. The conductivity of the samples formed by laser radiation is about 4 times higher than of the samples obtained by thermal method for continuous wave laser method and more than 2 times higher for pulse laser method. This increase is related to formation of nanotube scaffold under laser radiation. As a result, new electrical contacts are obtained in carbon nanotube places of connection and it leads to a reduction in resistivity of the nanocomposite and an increase in conductivity. Conductivity of the laser formed nanocomposite corresponds well to conductivity of the native heart tissue. This work is sponsored by the Ministry of Education and

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P82

FORMATION TISSUE-ENGINEERED CONSTRUCTIONS USING OF NANOSECOND LASER PULSES

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Influence of laser pulses with nanosecond duration allowed to create tissue-engineered constructions for the restoration of damaged heart tissues and blood vessels. The composition of the initial dispersion medium was includes 25 wt. % of bovine serum albumin, 0.001 wt. %. single walled carbon nanotube (SWCNT) and water. Otherwise, to increase the biocompatibility properties, bovine collagen can be used within 2 wt. %. Influence of laser radiation leads to the transformation of the disperse media into tissue- engineered constructions with predetermined shape. In this way, it is possible to create such materials, that have bioresorbability and biostability for restoration of heart tissues and blood vessels. Laser radiation influence of above the threshold value of intensity was fundamentally different, because it causes nonlinear effects in the dispersed media. That`s why, it is necessary to know the optical characteristics of the material. For this purpose, investigation by Z-scan with open aperture and the method of fixed material location was conducted. Nonlinear optical characteristics for albumin and collagen dispersions with SWCNT were obtained: linear absorption coefficients 2.7 1/cm and 2.91 1/cm, nonlinear absorption coefficients 350 cm/GW and 70 cm/GW, threshold fluence 0.051 J/cm2 and 0.026 J/cm2. The exposure time of nanosecond laser pulses with frequency of 10 Hz was less than 10 seconds. Minimal spraying occurs when using beams with a fluence less than 75 J/cm2. Tissue-engineered constructions were obtained from the disperse media for the restoration of damaged heart tissues and blood vessels. Formation of such materials can be produced by action of laser radiation above threshold fluence and less than 75 J/cm2 with small exposure time and sufficiently high accuracy.

P83

INFLUENCE OF FIBRE DIAMETER AND CHEMICAL COMPOSITION ON THE BIOLOGICAL BEHAVIOUR OF ELECTROSPUN POLYESTERS (PLA, PCL AND THEIR BLEND) INTENDED AS CELL SUPPORTS

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Objectives: The goal of this work was the analysis of the role of the chemical composition and the morphology of the electrospun fibres of membranes of polylactic acid (PLA), polycaprolactone (PCL) and their blend (PLAPCL) in the biocompatibility of the membranes seeded with human mesenchymal stem cells.

Methods: To obtain the electrospinning membranes, polymeric solutions were prepared by solving the polymers in different solvents: pure polymers (PLA and PCL) were solved in chloroform-methanol, and the blend in dichloromethane-dimethylformamide. By varying the main electrospinning parameters (polymer concentration, ratio of solvents, flow rate, voltage and distance needle-collector) the diameter of fibres could be tailored.

Cell viability was determined by MTT and the morphology of the cells adhered on the membranes was evaluated using scanning electron microscopy (SEM). Cell adhesion and spreading on the membranes were also analysed.

Results: It was possible to obtain electrospinning membranes with two fixed fibre diameters with dissolutions of the pure polymers and their blend. The diameters of the fibres were 0.8 μm for the under-micron membranes and 1.8 μm for the above-micron membranes.

PLA and PCL with 0.8 μm diameter of fibres showed a difficult management in comparison with the membranes of thicker fibres. Cell behaviour was highly different between membranes. Spreading and cell proliferation was higher in PCL and PLAPCL with 1.8 μm diameter of the fibres. Similar results were also observed in MTT and SEM assays.

Discussion: The scaffolds interact with cells resulting in a different degree of adhesion and spreading which are essential processes involved in regulation of cell functions. Our results showed that during the experimental period of viability, PLA and PCL scaffolds did not induce any cytotoxic effects on the behavior of cells. However, the bioactive properties were better developed in PCL and PLAPCL membranes of 1.8 μm fibers.

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STUDY OF CHARACTERISTICS OF CELLULAR AND TISSUE ENGINEERING CONSTRUCTIONS FOR TISSUE REPAIR IN CARDIOVASCULAR SYSTEM

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Objectives: The purpose of this work is creating and analysis of characteristics for samples of three-dimensional cellular and tissue engineering constructions for layer-by-layer reconstruction of heart and blood vessels. Samples of constructions are made by moving a laser beam in a path on surface of liquid that consists of albumin, collagen, chitosan and carbon nanoscaffold, so that it becomes solid and the structure promoting attachment of cells is forming. Parameters of interaction of the components in obtained structures are determined by modeling. Studies of biocompatibility in vitro with endothelial cells have also been conducted.

Methods: Modeling of interaction between samples components and their layers with each other and with components of cell membranes was carried out using molecular dynamics method. Biocompatibility of the samples was evaluated after their incubation with endothelial cells. The samples with cells were stained after for 48 hours of incubation and observed in a fluorescent microscope to analyze their effect on cellular morphology.

Results: Interaction energies for organic molecules with carbon nanoscaffold and for combinations of structure layers were determined during the modeling. Adhesion energy was the most in contact between the layers of the nanoscaffold and albumin. The interaction energy between the layers of samples and cell membrane protein reached a stable value already in 2 ns. In vitro studies of the samples proved their biocompatibility and the absence of negative influence on cell morphology.

Discussion: Samples obtained by the described technique can be made with any shape for reconstructing a defect according to its features. The values of the interaction energies obtained by modeling indicate the stability of both the structure and its connections with cell membrane. The obtained samples have the prospects of their use as a material for reconstruction of defects in tissues of a cardiovascular system.

P85

DEVELOPMENT OF A THREE-DIMENSIONAL POLY (GLYCEROL SEBACATE) SCAFFOLD FOR AN IN VITRO MODEL OF LYMPH NODE

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Objectives: The main purposes of this work are (a) the study of different temperatures and environmental conditions during the synthesis of poly(glycerol sebacate) (PGS) to assess its physicochemical performance and (b) the development of a PGS-based multilayer three-dimensional (3D) porous scaffold with stratified porosity for the simulation of the tissue architecture of the lymph node *in vitro*.

Methods: Sebacic acid and glycerol were reacted 1:1 ratio at 130°C for 24 h under different atmospheres (Ar, N2, O2, humid air and compressed air) to obtain the prepolymer (pPGS). Afterwards, the resulting mixture was poured out in: a glass mould to achieve 1 mm thickness 2D films, and into a squared Teflon mould with NaCl particles (212 – 250 μm for the inner zone, ≈ 17 μm for the external layers) for the 3D stratified porous scaffold. Their physicochemical and morphological properties were studied by means of different techniques such as: rotational rheometry, Fourier-transform infrared spectroscopy (FTIR), thermomechanical analysis (TMA) and scanning electron microscopy (SEM). Regarding their biological characterization, enzymatic degradation and cell cultures techniques were carried out with mice L929 fibroblast cultures.

Results: The rheological behaviour of pPGS shows that the higher the synthesis temperature, the lower the maximum viscosity achieved, and the lower the time of curing required. Similar effects were assessed by changing the atmosphere. FTIR spectra showed differences in the characteristic peaks of OH, C=O and C- O groups. TMA shows slight variations in the apparent elastic modulus, which can be attributed to a different crosslink bonding. Differences in cell migration through the different sized 3D scaffold layers have been observed.

Discussion: The data showed an influence of the environmental conditions (curing temperature and atmospheres) on cross-linking efficiency. Furthermore, cells were able to migrate within the inner zone but could not trespass throughout the outer layers of the 3D-biomaterial.

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BIOMECHANICAL EVALUATION OF ACELLULAR MATRICES DERIVED FROM PORCINE ESOPHAGEAL MUCOSA, PORCINE SMALL INTESTINE, AND BOVINE PERICARDIUM

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Objective: To compare the viscoelastic behaviour of three extracellular-matrix-derived meshes used as medical devices or as scaffolds in regenerative medicine.

Methods: Three biological meshes of different origins were assessed: porcine esophageal mucosa, PEM, porcine small intestine submucosa, PSIM, and bovine pericardium, BP, all of them designed to be used as medical devices or as biological scaffolds. All the essays were performed in a constant-temperature water bath at 37°C.

Scanning electron microscopy (SEM) images were obtained to characterize the structure of the matrices with regard to the orientation of fibers and the surface of the matrices. Characterization of viscoelastic properties of the matrices was performed by *creep* tests, applying stress in the direction of the fibers and perpendicular to them (a load of 500 MN was applied for 60 minutes); and by means of dynamic-mechanical tests at frequencies from 0.1 to 35 Hz on *shearing*, applied between parallel plates. All trials were performed in triplicate.

Results: membrane stiffness in longitudinal sense decreases in the series PEM – PSIM – BP while in transversal sense the order was BP-PSIM-PEM. Results of the dynamic-mechanical analysis were similar to those obtained in tension in transversal sense. These results agree with SEM findings related to the orientation of the collagen fibers that form the matrices.

Discussion: differences in mechanical properties are ascribed to the orientation and integrity of the proteins of which they are composed, in this case, lateral adhesion between oriented collagen fibers play an important role in the properties of the membrane. In addition, these biomechanical properties are of biomedical significance because they inform about the in vivo behaviour of the matrices.

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MATERIAL SELECTION FOR THE NEW POLYURETHANE VALVES DESIGNED FOR POLISH HEART PROSTHESES

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Objectives: The new polyurethane valves (PUV) were designed for Polish pulsatile ventricle assist devices (PVADs) named ReligaHeart®. The single-leaflet inflow valve and two-leaflets outflow valve consist of flexible leaflets and valve house, metal cores equipped. The flexible valve design has to guarantee athrombogenicity, by reduction of turbulence and sufficient valve wall washing. The study aim was matching an appropriate executive material for valve cores, as compromise of leaflets stiffness and elasticity.

Methods: The study was performed using finite element method (FEM) for opening and closing conditions of single- leaflet inflow valve and two-leaflets outflow valve. The analyses concerned pressure and fixation conditions during valve opening and valve closing motion. In both cases pressure was adjusted to the maximum values occurring in PVAD blood chamber during heart assist. Therefore the maximum pressure value for inflow valve was 75mmHg in the opening position, and 300mmHg in closing position. However, for the outflow valve the pressure value during opening was set to 300mmHg, while for closing to 75mmHg. Simulations were performed within the stainless steel 316L and titanium GRADE-II as potential materials for leaflets core.

Results: According to analyses for both valve types, leaflets with core made of titanium GRADE II were characterised by lower stress, maintaining similar stiffness. In case of outflow valve stress on leaflets core in closed position was 350MPa for titanium alloy, and 470MPa for 316L. However, in open position the deformation was equal 9,87mm for titanium alloy, and 8,26mm for 316L. The results revealed the impact of material data on leaflets stiffness, crucial for utilisation in PVADs.

Discussion: Conducted simulations show that new valve constructions allow control of valve functional parameters according to executive materials. This property were used for valve construction adaptation to target application.

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CAN THE DIFFERENCE IN STRUCTURE OF FIBRIN GELS IMPROVE CELL ENCAPSULATION?

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Objective: Our study aimed to reveal structural differences of fibrinogen modifications with polyethylene glycol (PEG) to understand their influence on cells for their implementation in tissue engineering.

Methods: PEG was bonded to fibrinogen using O,O'-bis[2-(N-succinimidyl-succinylamino)ethyl]polyethylene glycol (NHS-PEG) in molar ratios of 10:1 and 5:1. The fibrinogen structure and gel mechanical properties were characterized using FT-IR spectroscopy, differential scanning calorimetry, scanning electron microscopy, small angle X-ray scattering, and atomic force microscopy (AFM). Within gels, we encapsulated 3T3 cell line and analyzed cell viability, proliferation rate, and synthesis of extracellular matrix proteins.

Results and Discussion: The fibrinogen chemical modification was proven via FT-IR analysis. The destruction process of all fibrinogen types occurred without remarkable stages. We characterized the quaternary structure and oligomeric composition of pure and PEGylated fibrinogen in solution as well as 3D organization of corresponding gel structures. The scattering data were analyzed using ATSAS software, which permitted us to estimate the radius of gyration, particle maximum size and excluded volume and to construct 3D macromolecule models in solution and gel form with the resolution of 20-30 Å. In particular, ab initio modeling provided us with low resolution shapes of fibrinogen molecules in solution, and from the excluded volume of the particle envelopes it is possible to determine the oligomeric composition of the particles. The use of high resolution crystallographic structures of fibrinogen allowed us to perform rigid body modelling in the case of oligomer formation and restore the mutual orientation of the oligomeric species. In addition, our samples were characterized via AFM that permitted us to achieve a clear picture of their structure. Therefore, all data collected, incl. cell experiments, allowed us to reveal optimal composition that provided the needed particle sizes and homogeneity level for successful cell encapsulation. This work was supported by the Russian Science Foundation (18-15-00407).

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CELL-FREE MEDIATED CONTRACTION OF PLASMA-DERIVED FIBRIN AND COLLAGEN TYPE I HYDROGELS

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Keywords: contraction, plasma-derived fibrin, collagen type I, natural hydrogels, skin engineering

Objectives: Skin burns are a massively worldwide problem; a treatment is needed for 500,000 burns in the US alone. Fibrin and collagen type I hydrogels are usually used as optimal scaffolds for skin replacement therapy. These hydrogels tend to shrink before implantation in patients, making the study of fibrin and collagen type I matrix of extreme relevance. The stimuli response to simulated physiological environment has been the subject of study on collagen hydrogels, no previous work has been done on fibrin hydrogels. Here, we report a complete study on the behaviour of fibrin and collagen type I hydrogels. We discuss whether if the weight, área and mechanical changes in the hydrogels are due to the changes in the protein concentration inside the hydrogel or due to changes in the structure of the matrix.

Methods: Plasma-derived fibrin and collagen type I hydrogels were prepared following the protocols described previously. Gelation time was checked through flip-flop method, swelling studies consisted on the measurement of weight and area differences among hydrogels at different time-points. Protein release was studied through the classical Bradford Assay and Western Blot. Furthermore, rheology characterization of gels was performed at all conditions.

Results: Commercial fibrinogen hydrogels achieved gelation under 4 minutes. Human plasma and collagen type I hydrogels were formed in around 13 and 40 minutes respectively. We show that human plasma and collagen type I hydrogels tend to shrink over time when they are soaked on solutions at different conditions.

Discussion: We found that the comercial fibrinogen hydrogels also shows a deswelling behavior over time. Our results demonstrate under different temperatures and pH conditions can induce drastic conformational changes on the fibrin and collagen type I hydrogels, exhibiting a swelling-deswelling behavior due to changes in the structure of the matrix and to the release of the proteins present in the plasma.

P90

PREPARATION OF HIGHLY POROUS MAGNESIUM-DOPED HYDROXYAPATITE FROM CUTTLEBONE AS BIOACTIVE MATERIAL

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One of the main objectives in bone tissue engineering is synthesis of biomaterials that resemble natural bone in structure and composition. Bone mineral has a similar chemical composition to synthetic hydroxyapatite (HAp, Ca10(PO4)6(OH)2) but contains several ionic substitutions.

Magnesium, Mg, is one of the predominant substitutes for calcium in biological apatite and plays an important role in bone growth.

Objectives: The objective of this work was to investigate the influence of Mg2+ concentration on chemical composition, morphology, porosity, crystallographic structure and biocompatibility of porous HAp scaffold derived from cuttlebone.

Methods: Hydroxyapatite and Mg substituted hydroxyapatites (Mg-HAp) were hydrothermally synthesised. Mg-HAp samples were prepared by addition of Mg2+ (MgCl2×6H2O or Mg(ClO4)2) with respect to (Ca+Mg)/P=10/6 molar ratio. The compositional and morphological properties of the scaffolds were studied by means of X- ray diffraction with Rietveld refinement, FTIR spectroscopy, thermogravimetric analysis and scanning electron microscopy with elemental mapping analysis. Cytotoxicity was determined using MTT assay on human embryonic kidney cell line, while osteogenic potential was evaluated by human mesenchymal stem cell culture.

Results: The highly porous interconnected structure is completely preserved after the hydrothermal conversion of cuttlebone. HAp structure is substituted with HPO42- and B-type carbonate. With the increase of magnesium concentration, more whitlockite phase (Ca10-xMgx(HPO4)(PO4)6) was formed. The homogeneous distribution of ions and non-cytotoxicity was confirmed. Histological and immunohistochemical analyses, and evaluation of osteogenic genes expression indicated better osteogenic properties of Mg doped scaffolds with respect to the pure HAp.

Discussion: The incorporation of Mg in the HAp lattice structure is limited unless other ions are incorporated simultaneously. Whitlockite can easily incorporate magnesium into structure ensuring better bioresorption under physiological conditions then HAp. Controlling the Mg substitution, the bioactivity and biocompatibility of 3D porous scaffolds based on substituted hydroxyapatite can be improved.

POSTER SESSION PF04: BONE & CARTILAGE TISSUE ENGINEERING

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IN VITRO UND IN VIVO BIOCOMPATIBILITY ANALYSIS OF A NOVEL BONE BLOCK CONSISTING OF PORCINE COLLAGEN AND A SYNTHETIC BIPHASIC BONE SUBSTITUTE AS AN ALTERNATIVE CONCEPT TO ALLOGENEIC MATERIALS

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Introduction: In the present study the cell- and tissue reactions to a new bone substitute material block made of synthetic biphasic hydroxyapatite/β-tricalcium phosphate (HA/β-TCP) granules (BCP) embedded in a naturally crosslinked porcine collagen matrix (maxresorb® flexbone) were analyzed *in vitro* and *in vivo*. A collagen containing cancellous allogeneic bone block (maxgraft®) and a synthetic biphasic bone block (maxresorb®) were used as controls. It was hypothesized that maxresorb® flexbone should exhibit regenerative properties comparable to allograft material.

Methods: An osteoblast cell line was used to evaluate the adherence and proliferation of the cells on the various biomaterials. Cells were added and at specific time points after addition were examined morphologically and stained to determine distribution and expansion on the materials. Proliferation and cytotoxicity assays were used to evaluate and compare the growth rate of cells and cell compatibility of the various materials. For the *in vivo* study the three materials were subcutaneously implanted in 45 rats for up to 60 days. Specialized established histological, (immuno-) histochemical and histomorphometrical methods were applied for analysis of the tissue response.

Results: The *in vitro* results showed that the novel bone block led to a comparable adherence, cell morphology and proliferation of osteoblasts in contact with the allogeneic material and only slight differences were observed in the proliferation of cells on the various materials. The *in vivo* results showed that the inflammatory tissue reactions, i.e., the numbers of MNGCs in case of the allografts and the novel bone block were comparable and significantly decreased compared to the numbers on the BCP group. Moreover, the implant bed vascularization was superior to the BCP material alone and comparable to the allogeneic bone.

Conclusion: The results show that the novel bone block composed of BCP granules and native porcine collagen (maxresorb® flexbone) appears to be a favorable alternative to allogeneic bone grafts.

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ALGINATE-AGAROSE HYDROGELS IMPROVE CHONDROGENIC PROPERTIES OF 3D POROUS POLYCAPROLACTONE SCAFFOLDS IN VITRO

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Objectives: 3D-PCL scaffolds have probed effectiveness to support cartilage regeneration in vitro. Recently we reported that alginate-agarose mixed hydrogels support not only chondrocyte proliferation but differentiation in vitro an in vivo. In this study we have generate a mixed scaffold consisting in a 3D-PCL porous structure combined with an agarose-alginate hydrogel containing primary isolated chondrocytes in order to evaluate the utility of these hydrogels to improve the chondrogenic properties of 3D porous PCL scaffolds.

Methods: PCL scaffolds were prepared by a mixed particle leaching/freeze extraction process. Acrylic microspheres (200 μm diameter) were used as a porogen. 3D-PCL scaffolds were associated with alginate (3%)-agarose (1%) hydrogels containing 2x106 chondrocytes/ml and cultured for up to 6 weeks in chondrocyte differentiation medium containing DMEM, 1% ITS, 1% FBS and 10 ng/ml TGF beta. 3D-PCL scaffolds non associated to hydrogel were used as control group. Chondrocyte differentiation was evaluated by collagen (type I and II) and aggrecan expression observed by immunofluorescence. Cell morphology was evaluated by fluorescence actin fibers staining using phycoerythrin-labeled phaloidine. In all cases, nuclei were stained with DAPI for cell content calculation.

Result: Chondrocytes cultured in PCL scaffolds associated with alginate-agarose hydrogels exhibited an increased in the cell content compared to control group. They grew grouped together forming spheroids of 15-20 cells, bigger than the ones present in controls, and expressed non-polymerized actin as well as high levels of type II collagen and aggrecan whose expression in the control group was lower.

Discussion: Results presented here demonstrate that alginate-agarose hydrogels improved the chondrogenic properties of PCL hydrogels in vitro.

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MORPHOMETRIC CHANGES IN ARTICULAR CARTILAGE REGENERATION WITH MICROSPHERIC SCAFFOLDS IMPLANTATION IN RABBITS

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Objectives: Articular cartilage injuries are commonly observed in young people after traumatisms, but actual treatments frequently evolve towards osteoarthritis. To improve cartilage regeneration we have implanted biodegradable microsphere scaffolds, and articular cartilage morphology was analyzed.

Methods: New Zealand rabbits underwent surgery, as an osteochondral injury was created in their knee trochlea. In group (A) a cell-free poly-lactic acid microsphere scaffold was implanted; group (B) received a mixture of chitosan and poly-lactic acid microspheres (50/50); group (C) underwent the same procedure but with no scaffold implantation. Finally, group (D) was the contralateral native knees, to establish reference values. Animals were sacrificed 12 weeks after implants; samples were decalcified, histologically processed and stained with hematoxylin-eosin, Masson's trichrome and toluidine blue. Image-Pro Plus was used to measure cartilage and subchondral bone thickness, cell density and surface regularity.

Results: Neocartilage thickness at the site of the lesion resulted in an increase of 47% (group A), 49% (B) and 40%

(C) with respect to control group D. Subchondral bone thickness increased in groups A and B (21 and 11%) but decreased for group C (13%). In the neocartilage, cell density decreased in group A (22%), but increased in groups B and C (23 and 35%). Surface regularity (interdigitation index) was 1.14 times higher than control D in group A, 1.28 in group B and 1.73 in group C.

Discussion: Cartilage thickness may increase as a result of immature cartilage during the regeneration process, whereas subchondral bone thickness decrease could be a sign of lower capability of the osteochondral complex in load bearing. A higher cellular density may be both a sign of immature cartilage or a fibrous one, whereas a better regularity was observed when scaffolds were used.

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MAGNETIC FIELD EXPOSURE OF PELLET-CULTURED HUMAN DENTAL PULP STEM CELLS

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Objective: Extracellular magnetic particles moving under the effect of an external magnetic field can reproduce the mechanical forces by acting on cartilage cells, which could improve articular cartilage regeneration. Our device generates a controlled magnetic field, which interacts with superparamagnetic particles of 20 μm diameter present in the extracellular matrix. Herein we present preliminary results obtained by applying a magnetic field on pellet-cultured human dental pulp stem cells that can differentiate to chondrocytes.

Methods: Human dental pulp stem cells (hDPSC) were centrifuged to form a cellular pellet and cultured in proliferation cell culture media into 0.5-mL microtubes. A magnetic field (30 T/m, pulse direction changing every 3 s) was applied in treated cells (group A) on a daily schedule of 2 treatment sequences ([20 min irradiation/40 min resting each]x2 and resting 90 min in between) for 3 days. For the whole treatment duration, control non-irradiated samples were kept outside the cell incubator at room temperature (group B in similar conditions that group A samples, whereas second control non-irradiated samples were maintained inside the cell incubator (group C). After the 3-days treatment period, viability assay (MTS) was carried out, and cell morphology was studied after hematoxylin-eosin staining.

Results: Irradiated samples showed a 44 and 46 % increase on viable cell number when compared to B- and C- control groups, respectively, whereas no differences were found between both control groups. No morphological differences were found between irradiated and control groups.

Discussion: Our designed magnetic irradiation treatment increase cell number and viability without affecting cell morphology when compared to control samples.

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GENERATION AND CHARACTERIZATION OF HUMAN HYALINE CARTILAGE MICROSPHEROIDAL AGGREGATES FOR TISSUE ENGINEERING APPLICATIONS

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Objectives: The aim of this study was to generate and characterize the structural and biological properties of human hyaline cartilage-derived chondrocytes microspheroidal aggregates (CCMSA) as potential alternative for cartilage tissue engineering.

Methods: In this study human hyaline cartilage-derived chondrocytes were isolated from small hyaline cartilage biopsies from healthy donors. Tissue samples were mechanically fragmented digested in collagenase solution and cells were obtained by centrifugation. CMSA were generated by seeding 2.5 x 105 cells in agarose microchips containing approximately 1250 micro-wells with an average diameter of 400 μm. The CMSA formation was controlled during 4, 7, 14, 21, 28 days of ex vivo development (EVD) by phase contrast microscopy analysis. In addition, cell viability and damage was determined by Live/dead and DNA release methods. Finally, the structure and extracellular matrix production was determined by histochemistry and immunohistochemistry.

Results: Microscopy revealed that Chondrocytes were able to self-assemble in agarose microchips and form stable CMSA from day 4 onward. The viability revealed that CMSA remained viable during the whole culture period (until 18 EVD) with a slight release of DNA. The morphometric analyses showed a progressive CMSA's compaction with an increased circularity. Histology demonstrated a uniform cell distribution pattern in CMSA with an increase of the ECM production, especially the acid proteoglycans and collagen type II over the time.

Discussion: This study demonstrated that human hyaline cartilage-derived chondrocytes are a suitable cell source for the generation of stable and function CMSA. These CMSA could be a promising alternative to generate functional and biomimetic bioartificial substitute for cartilage tissue engineering applications.

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PRECONDITIONING WITH MELATONIN WILL ENHANCE THE PROLIFERATION AND DIFFERENTIATION ABILITIES OF SENESCENT MESENCHYMAL STEM CELLS

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Objectives: Mesenchymal stem cells (MSCs) are vulnerable to oxidative stress-induced senescence, thus limit their application in vitro and in vivo. In this study, we hypothesized that melatonin would enhance the proliferation and differentiation abilities of senescent placenta derived mesenchymal stem cells (PDMSCs) via scavenging oxygen free radicals and balancing the homeostasis of cellular metabolism.

Methods: Different concentrations of hydrogen peroxide (H2O2) were added into the culture medium of PDMSCs after they were confluent. We used cell growth curve and flow cytometry to compare the cell growth rate and cell proliferation rate of PDMSCs in response to H2O2. Then we added different concentrations of melatonin in the medium before treatment with the specified concentration of H2O2. We detected the the expression levels of senescence β-Galactosidase, caspase 3 and membrane potential of each goup, and we also compared the proliferation rate, apoptosis rate and reactive oxygen species levels of each goup. Last of all, we compared the multilineage differentiation potency of three groups including control group, H2O2 group and melatonin+ H2O2 group.

Results: The concentration of 300 μm H2O2 was sublethal to PDMSCs that they underwent growth arrest and cellular senescence under this condition. Treatment with melatonin before H2O2 exposure would significantly prevent premature senescence in a dose-dependent manner. We improved the cell proliferation rate and the mitocondrial membrane potential of senescent PDMSCs after preconditioning with melatonin. We also demonstrated that melatonin would decrease β-galactosidase activity, caspase 3 and apoptosis rate of senescent PDMSCs. Preconditioning with melatonin also partly restored adipogenic, osteogenic, hepatogenic differentiation potential of PDMSCs that was inhibited by H2O2 induced senescence.

Discussion: Our findings disclosure that melatonin will rescue H2O2 induced senescence in PDMSCs and it is an effective antioxidant for application in enhancing proliferation and differentiation abilities of MSCs via balancing mitochondrial metabolism.

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CYTOSKELETAL STRUCTURES AND ELASTICITY MEASURES IN HUMAN MSC CULTURED IN ADHERENCE TO PLASTIC SURFACES OR IN SPHEROID BODIES

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Stress fibers are the most prominent cytoskeletal structures that appear in MSCs when they are cultivated ex vivo either in adherence to plastic surfaces or bound to extracellular matrix components. Stress fiber formation can influence mechanical properties of MSCs such as shape and membrane elasticity.

Stress fiber formation, intracellular filament- and mitochondrial organization as well as focal adhesion formation were investigated in MSCs by immunofluorescence microscopy and by laser scanning microscope, cultivated in adherence to plastic surfaces or in hanging droplet cultures forming spheric MSC aggregates. In addition, surface morphology and sub-membrane structure scans were performed by atomic force microscopy in deflection and height mode and elasticity measures were analyzed using the Young's modulus.

The occurrence of stress fibers increased during passaging of MSCs from P1 to P3, where stress fibers running in parallel according to the orientation of the MSCs were substituted during cultivation by robust, thick, criss-crossed pattern of actin cytoskeleton extending most of the length of the cell. MSCs grown in spheric cultures, in contrast, formed very discrete and thin f-actin filaments. The majority of stress fibers observed in adherent and spheric MSC cultures were ventral stress fibers anchored at each end by focal adhesions. Dense mitochondrial networks of P1 MSCs distributed throughout the cytoplasm were replaced by mitochondrial fragmentation in small and larger spheroids located around the nucleus during cultivation. Scanning by AFM showed intense submembrane f-actin filaments in P1 and P3 MSCs which could not be found in this intensity in aggregate cultures, that decreased elasticity.

In conclusion we can say that the occurrence of stress fibers in cultivated MSCs and the influence on elasticity of MSCs has to be taken into consideration when MSCs are expanded for a potential therapeutic use.

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ACTIN FILAMENTS AND MITOCHONDRIAL DYNAMICS IN RESPONSE TO PLATELET LYSATE CULTIVATION OF MESENCHYMAL STEM CELLS

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When MSCs are expanded for a potential cell therapeutic approach in humans the use of animal serum products is

prohibited. Human platelet lysate can replace fetal bovine serum for clinical-scale expansion of functional MSCs. Here we investigate the occurrence of actin filaments in MSCs that show mechano- sensitive properties, mitochondrial fusion and fission as well as membrane indentation profiles under the influence of cultivation with human platelet lysate.

Stress fiber formation, intracellular filament- and mitochondrial organization as well as focal adhesion formation were investigated in MSCs by immunofluorescence microscopy and by laser scanning microscope. In addition, surface morphology and sub-membrane structure scans were performed by atomic force microscopy in deflection and height mode and elasticity measures were analyzed using the Young's modulus.

The occurrence of stress fibers, running in parallel according to the orientation of the MSCs, was found sensitive to bioactive molecules within the human platelet lysate. Interestingly, the majority of stress fibers observed in adherent MSC cultures under the influence of human platelet lysates were ventral stress fibers anchored at each end by focal adhesions, while dorsal stress fibers or arches were rarely seen. Mitochondrial network dynamics due to a balance in mitochondrial fusion and fission was also found responsive to human platelet lysate. Finally, topographic scanning by AFM showed detectable sub- membrane f-actin filaments in MSCs cultivated in human platelet lysate that could directly influence membrane elasticity measured by the Young's modulus.

In conclusion we can say that the bioactive molecules within human platelet lysates can influence the mechano-biological behavior of MSCs cultivated in adherence to plastic surfaces.

P99

MICROSTRUCTURED ELECTROACTIVE PLATFORMS FOR BONE AND MULSCLE TISSUE ENGINEERING

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Tissue engineering (TE) and regenerative medicine are growing fields of interest due to promising results in regenerating tissue functions. Adhesion, proliferation and differentiation of specific cells can be promoted and/or improved by the use of active materials. In particular, piezoelectric materials allow incorporating electrical and mechanical stimuli to the cells. Further, many body tissues are subjected to varying mechanical loads, such as muscle and bone, and the charge surface can stimulate cell response. In particular, poly(vinylidene fluoride) (PVDF) shows a strong potential for applications in TE. PVDF is a biocompatible semi-crystalline polymer with the strongest piezoelectric properties among polymers and have the possibility to be processed in different morphologies. Furthermore, the proper design of piezoelectric polymer with the necessary biochemical cues can open the way to novel and more reliable TE strategies for cells. It is known that the scaffold topography have influence on the biological response, influencing the cell adhesion, morphology, proliferation and differentiation. In this way, different microstructured porous and non-porous scaffolds with surface topographies were developed based on this electroactive polymer for the multifunctional stimuli of bone and muscles cells. It has been proven that the combination of suitable topographies and the electroactive stimuli are required for proper cell line stimulation.

P100

PIEZO- AND MAGNETOELECTRIC BIOMATERIALS FOR TISSUE ENGINEERING APPLICATIONS

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Active materials with controlled cell-materials interaction represent a recent paradigm in tissue engineering (TE) applications. Among the most important stimulus influencing cell behavior are the electrical and mechanical. In this way, the use of electroactive polymers that deliver an electrical signal to the cells upon mechanical solicitation can, in fact, mimic signals and effects that occur in living tissues, allowing the development of suitable microenvironments for tissue regeneration. Thus, a novel overall strategy for bone and muscle tissue engineering was developed based on the fact that these cells type are subjected to mechano-electrical stimuli in their *in vivo* microenvironment and that piezo- and magnetoelectric polymers, used as scaffolds, are suitable for delivering those cues. For that, different kind of morphologies was achieved (such as microspheres to electrospun mats and 3D scaffolds) with piezoelectric polymers such as poly(vinilidene fluoride) - PVDF (biocompatible and non-degradable) and poly-L-lactic - PLLA and poly(3- hydroxybutyrate-*co*-3-hydroxyvalerate) - PHBV (both biocompatible and biodegradable). Finally, their performance in bone and muscle

tissue engineering and their suitability for the development of injectable electroactive gels was investigated.

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POSTER SESSION PF05: VASCULAR TISSUE & SOLID ORGAN ENGINEERING

P101

USAGE OF TISSUE ENGINEERING FOR THE TREATMENT OF LIVER FAILURE

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Objectives: Treatment of liver failure(LF) is an actual problem of medicine. Aim-creating technology for treatment of LF.

Methods: LF was modeled on Wistar rats by means of CCl4. Liver cells(LC) and mesenchymal stromal cells of bone marrow(MSC) were obtained by standard procedure. Suspension of LC(2,5-4,0x106cells/cm3) and MSC(0,5-0,8x106cells/cm3) was co-cultivated for 3 days and then applied on the composition of heterogenic implantable hydrogel(gr.2) or on recombinant spidroin based microgel(gr.3). Formed cell engineering constructions(CECs) were implanted into damaged rat liver. The animals were divided into 3 groups: control gr.1(n=25) without treatment-injected saline, and with treatment by CECs-gr.2(n=25), gr.3(n=25). Dynamics reduction of LF indices; liver and CECs morphology were investigated within 90 days after CECs implantation.

Results: In gr.1 the formation of liver cirrhosis took place without recovery of biochemical indices. In gr.2-3 all biochemical indices returned to normal levels within 30-60 days, but the recovery rate was higher in gr.2. The degree of liver damage to this term in gr.2 and 3 was significantly reduced in comparison with gr.1. Restoration of a hepatic lobe structure and liver architectonics also was better in the gr.2, 3. CECs were fully integrated into liver structures. In CECs viable hepatocytes, and newly formed bile ducts were detected. In liver parenchyma a hepatocyte proliferation, neogenic plethoric vessels and neogenic bile ducts were detected.

Conclusion: Implanted CECs become as the new centres of restoration of damaged liver. Use CECs based on the composition of heterogenic hydrogel(gr.2) was more preferable.The proposed technology can be used for treatment of LF.

P102

APPLICATION OF TISSUE ENGINEERED DECELLULARIZED CONNECTIVE TISSUE MEMBRANE FOR ALLOGENEIC ARTERIAL PATCH IMPLANTATION

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Objectives: Previously, we have reported that *in vivo* tissue engineered vascular tissues easily constructed in the subcutaneous tissues of the recipients functioned as superior grafts in the animal experiments. We also clinically applied them for the pulmonary arterial reconstruction of the child. However, since the formation of the vascular grafts depend on the conditions of recipients including high risk or immature patients, immaturity in the fabricated tissues might be problematic for the severely diseased patients because of their suppressed regenerative activity. Therefore, possibility of the allogeneic implantation of the grafts from the healthy donor to the diseased patient should be evaluated. The objective of this study is to fabricate cardiovascular grafts using allogeneic animals.

Methods: Silicone rod molds (diameter: 5 mm, length: 10 cm) were placed into subcutaneous pouches of beagle dogs, and after 4 weeks the implants with their surrounded connective tissues were harvested. Tubular connective tissues were obtained after pulling out the impregnated molds. Those were perfused with sodium lauryl ether sulfate (SLES) and Triton-X. Decellularized tubular connective tissues were stored in phosphate-buffered saline (PBS) at -20 degrees for 1 week. Decellularized tubular connective tissues were cut open and trimmed to elliptical sheets. Those were transplanted to the carotid arteries of another beagle dogs as vascular patches (n = 6). Vascular patch grafts were resected 1, 2 and 4 weeks after implantation (each group n = 2) and histologically evaluated.

Results: Echocardiography revealed no aneurysmal changes of the grafts. Histological evaluation revealed that patch grafts formed neointima on the luminal surface and graft walls had cell infiltration over time.

Discussion: Decellularized connective tissue membranes can be prepared and stored beforehand and can be used as allogeneic grafts. They could be one of the ideal allogeneic cardiovascular grafts.

P103

GENETICALLY MODIFIED HUMAN SKIN FIBROBLASTS AS A FEEDER LAYER FOR BIOARTIFICIAL LIVER DEVICES AND CYTOTOXICITY TESTS

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Objectives: Diseases leading to terminal hepatic failure are among the most common causes of death. The main limitations in the liver treatment are: shortage of liver donors, low number of available human hepatocytes and their rapid dedifferentiation *in vitro*. To overcome these obstacles the experiments have been directed to: optimization of hepatocytes culture conditions, use of various growth surface coatings and co-cultures. A novel approach to the hepatic cells cultivation consisting in use of genetically modified fibroblasts serving as a feeder layer. The aim of our research was to investigate the practicability of genetic modifications of human skin fibroblasts (HSF) to maintain and improve specific phenotype features of human hepatic cells for their application in bioartificial liver (BAL).

Methods: The genetic modifications were carried out with the use of self-produced lentiviral vectors bearing human *HGF* gene coding hepatocyte growth factor. The dead/live cells discrimination, apical vacuoles evaluation, quantitative measurements of albumin and HGF, flow cytometry analysis and metabolic activity tests were performed.

Results: This strategy enable to generate a new cell line HSF_HGF that stably produce by about 20% more of the growth factor than their unmodified fibroblasts. Our results showed that the C3A cells, commonly used as a model of the human hepatocytes, in co-culture with the HSF_HGF, produced more albumin, are characterized by increased metabolic activity and more efficient synthesis of apical vacuoles when compared to the cells cultured on polystyrene, collagen and co-cultured with unmodified fibroblasts.

Discussion: These findings strongly support our hypothesis that feeder layer comprised of genetically modified fibroblasts can constitute a base for a method for the long-term cultivation of primary hepatocytes. The new genetically modified cell line has potential for improvement of the co-cultured human liver cells phenotype features (albumin production, metabolic activity and vacuoles formation) and could be applied in cytotoxicity tests and construction of effective BAL.

P104

BIOFABRICATION OF KIDNEY TUBULES USING TUBULAR ELECTROSPUN POLYCAPROLACTONE SCAFFOLDS

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Background: The increasing prevalence of renal failure and shortage of donor organs call for alternative renal replacement therapies, as dialysis can only replace 20% of renal function. A major drawback is the insufficient clearance of large and protein-bound waste products, which depends on active tubular secretion. Therefore, renal tissue constructs can make a valuable contribution to renal replacement therapies, but suitable scaffolds have to be developed first.

Aim: Our aim was to fabricate tubular polycaprolactone (PCL) scaffolds that enable luminal epithelialization to mimic kidney tubes for the clearance of waste products.

Methods: Tubular scaffolds were fabricated by electrospinning 20% w/v PCL around 0.7 mm needle templates with 10-15 kV and a flow of 0.5-0.8 ml/hr for 20-30 min. Scaffolds were sterilized and coated with 25 µg/ml collagen IV injections with or without prior L-DOPA coating. 10*106 cells/ml were injected and cultured for a week before experimental readout.

Results: The fabricated PCL scaffolds were highly porous and consisted of micro- and nanofibers that tended towards an axial orientation pattern. We observed cell monolayer formation inside the scaffolds, using mouse- or human-derived renal tubule epithelial cells. This appeared to be dependent on porosity and charge.

Discussion: We were able to electrospin porous tubular PCL scaffolds for luminal epithelialization with renal cells. Thereby, a cellular barrier separates the inner and outer compartment that can be used for renal clearance studies, while biocompatibility leaves the door open for implantation purposes in the future.

P105

OPTIMIZATION OF ELECTROSPINNING PROCEDURE FOR GENERATING THE SCAFFOLD FOR PRODUCTION OF ARTIFICIAL BLOOD VESSEL

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Objectives: Every human tissue requires constant supply of oxygen and other essential nutrients. A network of blood vessels is crucial for the functioning of any part of the human organism. Dysfunction and/or lack of blood vessels is the cause of many serious dysfunctions and diseases. Therefore, we have tried to optimize the already known electrospinning methodology for creating a scaffold that we will use to form a new blood vessel. The scaffolds we used were made up of nanofibers of mixtures of polycaprolactone (PCL) and polyethylene glycol (PEG).

Methods: Electrospinning. A well-known method of electrospinning is used for creation of scaffold. The parameters of a wide range of PCL:PEG solutions, voltage, solution flow and collector geometries are optimized. Cell manipulation. The obtained scaffolds were used for seeding of different types of cell lines. A possible cytotoxicity of every produced scaffold was examined.

Results: Using a variety of PCL and PEG ratio combinations in chloroform/DMF solutions, we obtained a series of scaffolds that were further examined. By changing different parameters, such as the applied voltage, the solution flow and collector geometries, we received many synthesized scaffolds. Various healthy and diseased cell lines were then seeded on the obtained scaffolds prior to investigate the possible cytotoxicity. Such prepared scaffolds and scaffolds harvested with cells were microscopically analyzed.

Discussion: Optimization of many experimental parameters for creating a scaffold that can be used in tissue engineering is a demanding process. Scaffolds made with desired properties will be used for seeding of endothelial and smooth muscle cells to investigate their suitability for the creation of a blood vessel in vitro.

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POSTER SESSION PF06: BIOMATERIALS: TISSUE INTERFACE & SURFACE MODIFICATION

P106

EPIC LABEL FREE APPROACH FOR TOXICOLOGY SCREENING

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Objectives: Epic Label Free (ELF) is a new generation of technology applied for drug discovery and cell biology investigation, but it's poor explored for the evaluation of clinical safety of medical devices (DM). A new challenge for biocompatibility assessment for DM is represented to the definition of a new generation of ex vivo assays more predictive for the in vivo behavior of DM.

Methods: We propose the ELF technology for the evaluation of cytotoxicity of a DM-derived compound by analyzing the variation on Dynamic Mass Redistribution (DMR) of cells after administration. Seven time points were considered: 1 min, 20 min, 1h, 2h, 4h, 8h and 24h. We tested a DM-derived compound, named A, at 3 different concentrations: 250 μg/cm2, 550 μg/cm2 and 700 μg/cm2. As 'compound A' is largely used in cranioplasty, we introduced human cells (osteoblasts, HUVEC and iPS-derived neurons) allowing more customized cell-based assays that would mimic the specific 'biological environment' relevant to the intended use of a DM.

Results: For all three cell types (osteoblasts, HUVEC and iPS-derived neurons), the assay was able to discriminate the biological response DMSO-like (negative) from SDS-like (positive). For all cell types and for all time points, 'compound A'-treated samples showed a range of responses comparable with DMSO (DMSO-like profile). These findings were confirmed by microscopy observation after 24h, which underlined a cell morphology indicating the lack of toxic effect.

Discussion: Our data by ELF proved that 'compound A' at the tested concentrations is not toxic for primary and iPS-derived human cells confirming hits in vivo biocompatibility as material for cranioplasty implantation. This study provides an original method to evaluate biocompatibility according to the intended use for medical device development.

P107

TO ASSESS THE HOST RESPONSE TO A POROUS POLYMER CELL ENCAPSULATION DEVICE FOLLOWING SUBCUTANEOUS IMPLANTATION IN RATS

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Objectives: Type1 diabetes mellitus is a chronic disease that is characterised by elevated blood glucose due to a reduction in insulin production or insulin resistance. Treatment requires frequent exogenous insulin administration. Islet cell transplantation, is a promising treatment

whereby donor pancreatic islets are implanted into diabetic recipients. It requires chronic immunosuppression, has poor islet cell retention and long-term viability. Encapsulation systems developed to improve this process are still plagued by poor islet cell viability. We have designed a novel contoured porous polymer islet cell macroencapsulation device (β- shell). In this study, our objective was to characterise the host response to the β-shell without islets following implantation in the subcutaneous tissue of a rat.

Methods: β-shells were implanted in the subcutaneous dorsal space of female Wistar rats (n=4) for 28 days. β-shells were removed and H&E, Masson's Trichrome, and Picrosirus red staining were performed to assess the surrounding fibrotic capsule. Polarized light microscopy was used to analyse collagen fibre orientation within the capsule. CD31 and CD68 staining were used to evaluate angiogenesis and macrophage infiltration, respectively. SEM was performed on cross-sections of samples to assess the tissue/device interface.

Results: Masson's Trichrome stain enabled visualisation of a fibrous capsule of variable thickness surrounding the β-shell. Polarized light microscopy demonstrated the uniform orientation of the collagen fibres. CD31 and CD68 staining revealed the presence of blood vessels within this capsule. CD68 positive macrophages were evident at the tissue/device interface. SEM images of the tissue/device interface demonstrated β- Shell integration with surrounding tissue.

Discussion: Preliminary *in vivo* results demonstrate that the β-shell is well tolerated in dorsal subcutaneous space, and produces a favourable host response. Further work is needed to evaluate the effectiveness of the β-shell as a cell delivery vehicle.

P108

ASSESSMENT OF EARLY AND STATIONARY SERUM PROTEIN ADSORPTION ON PHEMA:PCL AMPHIPATHIC SUBSTRATES

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Objectives: The main goal of this work consist on the development of electrospunable polymer blends based on poly(hydroxyethyl methacrylate) (PHEMA) and poly-ε-caprolactone (PCL) and the thorough study of the adsorption potential thereof for serum proteins, as key cues for *in vitro* cultures.

Methods: PHEMA was polymerised from 2-hydroxyethyl methacrylate in the presence of a thermal initiator and a high proportion (> 75% wt.) of methanol (MetOH), to prevent physical crosslinking. Thus, the resulting solution was able to be blended with PCL (Mw = 43 – 50 kDa) by adding chloroform (CHCl3) up to a 25:75 MetOH:CHCl3 ratio. Such mixtures could be spun coated to produce thin homogeneous layers of amphipathic polymer blends.

Substrates at 12% wt. of polymer with different PCL:PHEMA ratios were incubated with 10% FBS for short- term (10 s) and equilibrium (30 min) periods in order to analyse the early and stationary adsorption of serum proteins by means of AFM, total protein quantitative assays (Bradford and mBCA) and SDS:PAGE.

Results: The thin layers of polymer blends were homogeneous, and showed the ability of PHEMA to physically cross-link once the solvent of the solution is removed. Thus, monophasic biodegradable hydrophilic- hydrophobic materials could be prepared.

Interestingly, the proteins presented a different adsorption pattern for the PCL:PHEMA blends as compared with either the corresponding pure polymers or bare glass coverslips. This effect was observed for the total amount of proteins, the adsorption kinetics and their spatial distribution over the surface.

Further, the preliminary assays for PCL:PHEMA 90:10 and 80:20 polymer blends showed that higher concentrations (25% wt.) of polymer can be used to obtain fibrous membrane-like structures.

Discussion: The evidences suggest that the amphipathic nature of PCL:PHEMA blends rich in hydrophobic domains produce a synergistic, multiplicative effect on the substrate-protein interaction beyond the features provided by the pure components.

P109

3D CULTURE OF MULTIPLE MYELOMA CELLS ON PROTEIN FUNCTIONALIZED MICROGEL

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Objective: Multiple myeloma (MM) is a hematologic malignancy characterized by monoclonal plasma cells (mPCs) infiltration with heterogeneous localization in the bone marrow compartment. Conventional 2D cell cultures cannot reproduce the development of the disease, and current research is focused on the design of 3D culture systems to

reproduce mPCs behaviour and their susceptibility to drugs mediated by the bone marrow environment (BME). The aim of this work was to demonstrate the ability of a new 3D culture system based on a microgel, on mPCs proliferation, viability and cell adhesion mediated drug resistance (CAM-DR).

Methods: The microgel has been produced by emulsion techniques of a random copolymer of ethyl acrylate (EA) and ethyl methacrylate (EMA), poly(EA-co-EMA). RPMI 8226 multiple myeloma cell line was expanded in suspension in RPMI 1640 supplemented with 5% fetal bovine serum, 1% penicillin/streptomycin, 1% L-glutamine and 0,5 mM MnCl2.

Results: The emulsion was optimized to obtain microspheres smaller than 15 μm. Microspheres were coated with fibronectin (FN) by physical adsorption, using as control microspheres without FN. The cell culture was performed in a transwell system mixing MM cell suspension containing 1x106 cells/mL with different amounts of microgel/cells (30:70, 40:60, 50:50). Proliferation and cell adhesion to FN was assessed using a cell cycle assay by flow cytometry. The fraction of cells arrested in G0 was considered a characteristic of CAM-DR. A MTS assay was done to study cell viability.

Discussion: MM presents a high heterogeneity with very different biological behaviours due to the interaction between the mPCs and the BME. These results allow us to confirm that the developed 3D cultures are more biomimetic and can be used to test "in vitro" the effectiveness of different drugs with mPCs in MM patients oriented to personalized therapy.

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TI6AL7NB ALLOY MODIFIED WITH ATHROMBOGENIC TIN TRYBOLOGICAL BEHAVIOR IN CONTACT WITH ZRO2-Y2O3 IN THE ASPECT OF UTILIZATION IN ROTARY BLOOD PUMP

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Objectives: Rotary blood pump ReligaHeart ROT (RH-ROT) contains passively suspended titanium impeller with athrombogenic layer, and Zirconium pump house walls. The impeller collision with zirconium element of pump housing may damage athrombogenic rotor layers and reduce pump biocompatibility. During preclinical study the pump material properties assessment were performed.

Methods: Impeller is made of Ti6Al7Nb, modified by TiN+Ti2N+αTi(N) layer of roughness Ra=80nm, created utilizing plasma level glass discharge nitriding process. Zirconium part was made of composite ZrO2-Y2O3 with roughness Ra=40nm. Following investigations were performed: microstructure and surface morphology (HITACHI S3500-N SEM), TiN adhesion (diamond Rockwell indenter, 6mm; 1-50N), material hardness and wear-resistance (scratch test), on-pump hemolysis test (performed on human blood, circulation: 100Hg, 4.5l/min) and microscopic examination of pump surface (Keyence VHX-6000).

Results and Discussion: TiN+Ti2N+αTi(N) layer parameters: thickness ~1 μm, homogenous surface morphology, hardness ~710, HV=0,02. TiN layer had improved friction coefficient in comparison to Ti6Al7Nb, for contact with ZrO2. TiN scratch test revealed flashover by the load=44N. No acoustic emission was observed with confirmed no nitrating layer delamination. Transverse cracks were observed very fast what evidence low cohesion of nitrating layers due to low diffusion layer thickness and low nitride diffusion in titanium alloy.

First blood test (n=1) revealed high hemolysis (NIH=0.2916g/100l). Detailed microscopic assessment revealed that zirconium and TiN parts were seized up and zirconium part was distorted (153um) due to mechanical influence of magnetic bearing. Zirconium part was modified and hemolysis test were repeated (n=3). Significant NIH decreasing was observed (from 0,01 to 0,09g/100l).

Conclusion: Mechanical features of Ti6Al7Nb coated by TiN+Ti2N+αTi(N) and ZrO2-Y2O3 commonly with its high biocompatibility make that materials suitable to apply in construction rotary blood pump RH-ROT intended for long term contact with blood.

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POSTER SESSION PF07: BIOMATERIALS FOR BONE & CARTILAGE

P112

INTERACTION OF OSTEOBLASTS AND PROTEIN-COATED SUBSTRATES: INTEGRIN-MEDIATED ADHESION STUDIED BY ATOMIC FORCE MICROSCOPY

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Objectives: The nature of cell adhesion plays and important role in modulating cell response. This process takes place through adhesive proteins, such as fibronectin (FN) and vitronectin (VN), which are recognized by integrins, a family of surface proteins that mediate cell adhesion. In this work, we aim to determine the relationship between the mechanical properties of osteoblasts and specific integrins during adhesion on FN and VN- coated substrates by means of atomic force microscopy.

Methods: FN and VN was adsorbed on glass covers (10 μg/mL-1h). Additionally, antibody HFN 7.1 and mAb 1937 were incubated on FN-coated substrates in order to block FNIII9, FNIII10 domains or both. MC3T3 cells were seeded at low density (5000 cells/cm2) onto the protein-coated substrates and placed in the AFM cell chamber. The elastic modulus was measured for 3 h after adhesion. Cell morphology was analysed by immunofluorescence.

Results and Discussion: Specific binding domains were exposed to cells, depending on the protein-coated substrate employed. The Young modulus is significant higher for FN-coated substrates, increasing with time from 2 to 4.2 kPa. When cells adhered on substrates with FNIII10 domain blocked (i.e. FN-RGD motif), in which recognition by α5β1, αv-class and αIIbβ3 integrins are hindered, the Young module decreases dramatically. Similar behaviour was found in cells adhered on substrates with FNIII9 blocked (i.e. FN-synergy site) which leads to an impaired recognition by integrins α5β1 and αIIbβ3. Finally, in VN-coated substrates, recognized mainly by αvβ3 and αvβ5 integrin, the Young modulus was found to be lower than in FN-coated substrates, increasing with time from 0.5 to 1.5 kPa. Cell morphology was related to mechanical properties; a low Young module leads to smaller and more rounded cells. These results show the close dependence between cell mechanical properties and integrin interaction during cell adhesion.

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P113

PURIFICATION PROCESSES OF XENOGENEIC BONE SUBSTITUTES AND THEIR IMPACT ON TISSUE REACTIONS AND REGENERATION

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Xenogeneic bone substitute materials are widely used in oral implantology. Prior to their clinical use, a purification of the former bone tissue has to be conducted to ensure the removal of immunogenic components and pathogens. Different physicochemical methods are applied for the purification of the donor tissue and temperature treatment is one of these methods. Differences in these methods and especially the application of different temperatures for purification may lead to different material characteristics, which may influence the tissue reactions to these materials and the related (bone) healing process. However, little is known about the different material characteristics and their influences on the healing process. Thus, the aim of the present mini-review is to summarize the preparation processes and the related material characteristics, the safety aspects, the tissue reactions, the resorbability and the preclinical and clinical data oftwo widely used xenogeneic bone substitutes that mainly differ in the temperature treatment, i.e., sintered (cerabone) and non-sintered (Bio-Oss) bovine-bone materials (BBM). Based on the summarized data from the literature a connection between the material-induced tissue reactions and the consequences for the healing processes are presented with the aim for translation into their clinical application.

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TREATMENT OF SEVERELY RESORBED MAXILLA DUE TO PERI-IMPLANTITIS BY GUIDED BONE REGENERATION USING A CUSTOMIZED ALLOGENIC BONE BLOCK: A CASE REPORT

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The objective of this case report is to introduce a customized CAD/CAM freeze-dried bone allograft (FDBA) block for its use in Guided Bone Regeneration (GBR) procedures for severely deficient maxillary bones. Additionally, a special newly developed remote incision technique is presented to avoid wound dehiscence. The results show optimal integration behavior of the FDBA block after six months and the formation of new vital bone. Thus, the results of the present case report confirm the use of the

customized CAD/CAM bone block for augmentation of complex defects in the maxillary aesthetic zone as a successful treatment concept.

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BIOCOMPATIBLE 3-D NANOSCAFFOLDS FOR BONE AND CARTILAGE RESTORATION

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Objectives: As part of new biocompatible implant materials development, 3-D nanoscaffolds were created by layer-by- layer laser prototyping. The creation of 3-D nanoscaffolds is aimed at obtaining the possibility of defects replacing and restoring the functions of damaged bone-cartilage connections. The paper presents the results of in vitro and in vivo biocompatibility studies of the 3-D nanoscaffolds.

Methods: When creating 3-D nanoscaffolds we used carbon nanotubes of high purity, albumin and chitosan, acting as a matrix for nanotubes. Three-dimensional printing of nanoscaffolds with given shape and size was performed using a laser installation. 3-D nanoscaffolds were incubated with bone and cartilage cells - osteoblasts and chondroblasts. Cell proliferation was evaluated by fluorescence microscopy. To evaluate the biocompatibility of 3-D nanoscaffolds in vivo, they were implanted in an artificially created bone defect of a laboratory animal (rabbit). The morphology of biological tissues in the implantation area was studied histologically in 2 months after the operation.

Results: The fluorescence microscopy showed that cells form a dense network, both fixed cells and cells that have just begun fixing were observed on the surface. After 3 days of incubation, the osteoblast cell line formed a monolayer on the surface of 3D nanoscaffolds, and the chondroblast line was unable to form a single monolayer, but it was capable to form large focal clusters and areas of the monolayer. Tissue histology in the area of 3D nanoscaffolds implantation showed the presence of a newly formed bone tissue with an adjacent implanted nanoscaffold without signs of inflammation.

Discussion: The studies have shown the biocompatibility of the 3D nanoscaffolds, the ability to support the growth of bone and cartilage cells in vitro and to provide restoration of these tissues in vivo. Therefore it is advisable to continue studies of the 3D nanoscaffolds properties and to prepare for their clinical trials.

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THE CHONDROGENIC POTENTIAL OF NANOCELLULOSE-ALGINATE IN COMBINATION WITH NASOSEPTAL CHONDROCYTES FOR TISSUE ENGINEERING PURPOSES

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Objectives: Contemporary reconstruction of cartilage defects relies on autologous tissue or synthetic implants. Our strategy involves a natural biomaterial in combination with tissue specific cells, to replicate native tissue micro- and macro architecture.

Methods: Primary human nasal progenitor cells (NP) were isolated by fibronectin adhesion assay, while non-adherent cells were cultured as differentiated nasal chondrocytes (DNC) and the original cell population containing both subpopulations, cartilage derived cells (CDC) served as a control. DNC cells were mixed in sterilised nanocellulose with 2.5% alginate (NA) or alginate (AG) on its own to confirm which biomaterial encourages chondrogenesis as alginate is known to have chondrogenic properties. DNC and NP with the different biomaterials were cultured for 14, and 21 days followed by gene expression analysis and histological analysis.

Results: qPCR data comparing CDC, DNC, and NP in NC or AG have shown NC to enhance chondrogenic potential of all cell subpopulations in comparison to AG most significantly seen in collagen type II at 14 days (CDC 15.7-fold, $p<0.001$; DNC 166-fold, $p<0.001$; PC 22.5-fold, $p<0.001$). Overall the highest expression of chondrogenic marker was observed in the CDC population embedded in NC than the AG counterpart as indicated by the up-regulation of matrix genes at 14 days (aggrecan ~2.3-fold, $p<0.01$; SOX9 ~2.4-fold, $p<0.05$; collagen type II ~15.7-fold, $p<0.001$) and 21 days (collagen type II ~6.9-fold, $p<0.001$). These results are confirmed at the protein level by histological staining indicating enhanced GAG synthesis after 21 days in culture in comparison to CDC in AG and DNC and NP in NC.

Discussion: CDCs are shown to form cell clusters surrounded by territorial matrix recapitulating a similar distribution as in native cartilage tissue. These results indicate that NC is a promising biomaterial for cartilage tissue engineering.

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MECHANICALLY CONDITIONED BONE LIGAMENT BONE CONSTRUCTS

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Objectives: In this project, we aim to create a tissue engineered bone ligament bone construct and then subject the construct to mechanical conditioning to optimize the cell alignment and collagen production and organization, thereby increasing the strength of the construct. This will be done through improvement of the thickness of the hydrogel substrate, creation a sinew structure, development of the bone anchor, and manufacture of a bioreactor all using cost effective materials.

Methods: Fibroblasts were sourced from female English Mule sheep by excising the cruciate ligaments, cleaning thoroughly, digesting the tissue, and culturing the fibroblasts. The cells were kept at low passages to maintain their robustness. The hydrogel substrate was created using chitosan and gelatin and proanthocyanidin as the crosslinker. Anchors were cast using calcium carbonate and dicalcium phosphate incorporated into the hydrogel and poured into a cylindrical mold. Fibroblasts were seeded onto the hydrogel with anchors attached. The fibroblasts were then allowed to proliferate, causing the gel to contract into a sinew shape around the anchors. Cell proliferation was measured by alamar blue assay.

Results and Discussion: Hydrogels with thickness between 0.5mm-2.5mm in 0.5mm increments were created to optimize fibroblast proliferation. The 0.5mm and 1.0mm hydrogels showed greatest proliferation. In order to allow the contraction of the hydrogel into the sinew shape, the adhesion of the gel to the well plate was prevented using a premade silicone elastomer cut to the shape of the well. A 1.5 molar ratio of CaCO3:CaHPO4 proved to be most effective in terms of pliability and stiffness in creating the anchors. Modifications to the bioreactor were necessary to maintain a sterile environment and reduce any debris from moving parts without compromising the ability to apply tension. When assembled, the bioreactor accommodates a 6 well plate allowing the visualization of the maturing construct.

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BONE TISSUE SUBSTITUTES WITH TAILOR-MADE OSTEOINDUCING PROPERTIES AND MULTI-LAYERED CELLULAR INTERFACE

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Objectives: This work was aimed to develop a modelled tissue-engineering construct able to reproduce the phenotype of bone tissue in its native state. This was approached by the combination of osteoinducing properties with a multi-layered biointerface. Functional elements of the designed hybrid constructs included polylactide scaffolds and mesenchymal stromal cell sheets.

Methods: As building blocks for the construct fabrication we employed polylactide microparticles. This material meets the criteria demanded for an ideal scaffold including biodegradability, biocompatibility and mechanical stability. In order to render the particles hydrophilic we modified them with hyaluronic acid. The modified microparticles were then structured using the surface-selective laser sintering method with water as the photosensitizer. Finally, the scaffolds were reinforced via photo-crosslinking with Irgacure 2959. The structural, mechanical, osteoinducing properties and biocompatibility of the resulting scaffolds were investigated using a set of cutting-edge materials testing techniques.

Results: The scaffolds had porous structure and rough surface and exhibited temperature-depended surface mechanics. Human bone marrow mesenchymal stromal cells seeded on the scaffolds were highly viable and promoted calcium deposition associated with osteogenic differentiation. An innovative approach to graft the scaffolds with multi-layered cell sheets precultured on spin-coated thermolabile polymer layers exhibited contiguous morphology and high viability.

Discussion: Surface-selective laser sintering method proved to be effective in designing 3D porous scaffolds with osteoinducing properties suitable for the delivery of multi-layered cell sheets. The confluence of unique properties including osteoinduction, biodegradability, biocompatibility, high-resolution 3D structure, and the feasibility of tissue-like biointerfacing is expected to significantly improve the host tissue- implant integration.

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