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ORAL PRESENTATIONS

Oral Session - Optimizing VAD Performance, O1-O6

O1
SUCCESSFUL FAST TRACK ANESTHESIA IN LEFT VENTRICULAR ASSIST DEVICE IMPLANTATION - IT IS FEASIBLE!

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Introduction: Left ventricular assist device (LVAD) implantation has become a crucial option in end-stage heart failure therapy. Especially postoperative right ventricular failure (RVF) is feared. Fast track procedures have been well established in cardiac surgery and were proven to be effective. We assumed that "fast track" -LVAD implantation is possible in INTERMACS level 3 and 4 patients and might prevent RVF.
Material and methods: From 01/2008 to 11/2012, we implanted 77 continuous flow LVADs. Out of these, 13 patients in INTERMACS level 3 or 4 were treated as 'fast-track' (12 Thoratec Heartmate™ II, 1 Heartware HVAD™). This included extubation in the theatre or up to 6 hours postoperatively. 10/13 patients were male, average age was 61 ± 10 yrs on day of implantation, ITT was DT in 6 and BTT/BTC in 7 cases. The main diagnosis was ICM (10/13). Mean left ventricular EF was 18 ± 4%. 9/13 patients suffered from an impaired RV function.
Results: All operations were done via a standard sternotomy, with use of CPB and a beating-heart procedure. All patients were extubated within 4 hours. The mean stay on ICU was 53 ± 41 hours and the mean stay in hospital after implantation was 23 ± 9 days. We did not record any postoperative RV failure. The 30-day survival was 100%. After one year of support, 11 of 13 patients were alive. The current mean time on device is 413 days.
Discussion: In this pilot study, we demonstrated the feasibility of "fast-track" anesthesia in LVAD implantation in selected patients. Prospective investigations should examine if this approach contributes to sustainable protection of right ventricular function in a larger trial.

O2
USABILITY OF A PATIENT-CENTERED CLOUD-BASED INFORMATION-SHARING SYSTEM FOR HOME MANAGEMENT OF PATIENTS WITH LVAD

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Introduction: Advance detection of life-threatening complications is important in the home management of patients with LVAD. However, patients are often only observed on regular out-patient visits. Therefore, we developed a patient-centered medical information-sharing system for LVAD home management with using the iPad (LVAD@home). Herein, we report a case of successful application of the system.
Material and methods: The following data were sent by LVAD@home: the status of drive line (DL) exit site, infection signs, device operating status, and physical condition. The patient was a 60-year-old man implanted with Heartmate II. The primary caregivers were his wife and daughter, who performed the iPad input. Home health status information from the families were shared everyday with physicians using LVAD@home.
Results: Input records from March 31 to September 25, 2014, were analyzed. During the 178-day home treatment period, 306 items were input. 82% of the data were input by the families, whereas 17% of them were input by a physician. As for the input contents by the families, 35% accounted for physical condition; 25%, pump parameters (PP); 21%, comments; 18%, images of DL exit site. The comments from the families (201 items) included 1) report or questions about PP (81%), 2) concerns about DL such as bleeding (11%) with images, and 3) questions about medication, physical condition (8%). The results of the interview of the families included "Questions to the physicians can be asked easily, which may be difficult over the phone," "I feel relieved when someone checks on my input," and "Input is easy."
Discussion: LVAD@home, a patient-centered medical information-sharing system for home management of patients with LVAD, is useful for advance detection of infection sign at the DL exit site and provides a sense of security not only to patients but also to physicians.

O3
ANTICOAGULATION FOR LVAD PATIENTS: CAN WE IMPLEMENT AN ALGORITHM FOR HOME MANAGEMENT SAFELY?

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Introduction: To implement safely an algorithm to monitor INR ratio's for LVAD patients at home. All patients are instrumented to work with a self-monitoring INR test. The algorithm is based on a week doses of warfarin adapting according INR results. It provides a suggestion for the dose of that day, an indication on when to have the next INR measurement and instructions on how to deal with extreme results.
Material and methods: The algorithm was applied in a cohort of 10 LVAD patients over a total period of 5.4 patient years. We analyzed time within therapeutic INR range (TTR), defined as an INR of 2.0 to 2.5. Secondary endpoints included time in sub/supratherapeutic ranges and median weekly warfarin doses. We calculated the same end-points for a control cohort of 10 LVAD patients (10 patient years) measuring home INR daily and adjusting coumadin dose daily on medical prescription.
Results: Average TTR of patients who followed the algorithm was 49% (range 35%-65%). Average times below and above the therapeutic range were 29% (range 17%-45%) and 21% (range 10%-36%), respectively. The median weekly warfarin dose was 41 mg (range 16 mg- 70 mg). These results are similar to the 53% (range 36%-67%) average TTR of patients who measured INR daily at home (p = 0.359). In this control group, average times in sub/supratherapeutic ranges were 12% (range 1%-27%) and 39% (range 19%-62%), respectively.
Discussion: Anticoagulation home management based on an automatic algorithm is as safe as daily INR monitoring. The algorithm turns out to be more efficient as it reduces the need for finger pricks and the associated testing cost. We currently implement the algorithm in an on-line and mobile application. This will be more user-friendly and allows the hospital to collect automatically the INR data.

O4
INFLUENCE OF INTERMITTENT SPEED CHANGES OF LEFT VENTRICULAR ASSIST DEVICES ON INTRAVENTRICULAR FLOW STAGNATION

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Introduction: Left Ventricular Assist Devices (LVADs) alter blood flow patterns in the ventricle as they change the natural flow pathway. When the aortic valve remains closed during the whole cardiac cycle (full support) the altered flow patterns may introduce potential areas of stagnation and thrombosis. Aim of this work was to investigate the influence of periodical intermittent pump speed changes (washout cycle) on intraventricular flow patterns.
Material and methods: A transparent model of an LVAD assisted heart was developed and bioprosthetic heart valves used to maintain the physiologic flow. Three different cardiac contractility states were created (low, medium, high) and three pump speeds were tested combined with/without a washout cycle (2 sec: -200 rpms, 1 sec: +200 rpms, 60 sec baseline speed) mimicking a broad range of clinical situations. The ventricular simulator allowed visualization of intraventricular flow and the calculation of a stagnation index (SI).
Results: Supported hemodynamics similar to clinically observed ones were measured when setting stroke volumes (SV) and pump speeds (ω) at a constant cardiac output of 5 l/min at a mean arterial pressure of 80 mmHg. Increasing LVAD support resulted in higher SI starting from 1.18 s in the partial support situation (SV 27 ml, ω 2500 rpm), to 1.38 s in the partial support situation (SV 39 ml, ω 2700 rpm) and finally 1.53 s in the full support situation (SV 50 ml, ω 2900 rpm). With the washout cycle the SI was hardly influenced and did not show any positive or negative effect, whereas the mean flow remained unchanged.
Discussion: Intra-ventricular flow patterns are strongly influenced by LVADs as the natural pathways are altered completely. The washout cycle as a method to improve washout of the left ventricle showed some slight alterations but an overall positive or negative performance on the washout of the heart could not be proven in the stagnation index.

O5

MONITORING DURING EXERCISE OF THE ASSISTED CARDIAC HEMODYNAMICS BASED ON PUMP SIGNALS

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Introduction: Due to the lack of hemodynamic sensors, monitoring based on available pump data offers the only way for investigating the cardiac assisted hemodynamics. Here we report results of an ongoing clinical study about pump derived diagnostics in RBP patients with the focus on exercising and physical capacity testing.
Material and methods: To obtain pump data in patients a previously developed recorder device was used to store the data stream of the HVAD (Heartware, Miami Lakes, FL) at a rate of 50 Hz. Algorithms to estimate pump flow with increased frequency content, heart rate, aortic valve opening and suction were applied to the data. From the 12 patients recruited to the study pump data was recorded in 5 patients during cardiac rehabilitation. A total of 24 bicycle ergometry, 19 walking, 11 strength and 17 gymnastic training sessions were analyzed. Intensity for the well documented training was controlled by the subjectively perceived exertion. Furthermore physical capacity testing with ergospirometry (n = 2) and stress-echocardiography (n = 3) was investigated.
Results: Interval bicycle training triggered the highest response of pump derived parameters representing the cardiac function. During bicycle training an increase in heart rate (5 ± 1 bpm), mean pump flow (0.45 ± 0.2 L/min) and pulsatility (0.5 ± 0.2 L/min), contractility and relaxation indices with respect to baseline were observed ($p<0.0004$ in all cases). During ergospirometry and stress-echocardiography maximum increase in heartrate (17 ± 12 bpm), pump flow (1.5 ± 0.9 L/min) and pulsatility (1 ± 1.5 L/min) could be observed. Accept dissimilarities in contractility and relaxation indices developed during ergospirometry in one patient no adverse events could be evaluated.
Discussion: This ongoing study demonstrates that continuous monitoring during exercise provides information that can be used for optimized pump speed adjustments according to the patients demand.

O6

EXERCISE CAPACITY IN VENTRICULAR ASSIST DEVICE PATIENTS: CONSTANT VERSUS INCREASING PUMP SPEED

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Introduction: Exercise capacity in ventricular assist device (VAD) patients is about half of what is expected in normal conditions and the reasons of this are still unclear. In this work we investigated if VAD speed might play a role in improving patient's exercise performance.
Material and methods: Six male Heartmate II patients (age 57 ± 14 years, BMI 28 ± 4 kg/m^2) underwent two maximal cardiopulmonary exercise tests. Both tests were performed on the same day, with an hour of rest in between. Tests were executed on an upright cycle ergometer with a stepwise load increase of 10 W each minute. During one test the VAD speed was kept constant (COST) while during the other test VAD speed was increased by 200 rpm for each 10 W added to the ergometer (INCR). The order of the COST or INCR tests was randomly determined. Heart rate (HR), oxygen uptake, carbon dioxide production were measured continuously during the tests. Peak oxygen uptake (VO2p) was defined as the average VO2 of 30 sec at the highest achieved workload. The ventilatory efficiency slope (VE/VCO2-slope) was calculated. Differences between COST and INCR tests were calculated by paired *t*-tests and Wilkoxon signed-rank test.
Results: HR at rest was 84 ± 13 bpm (83 ± 14 bpm) for COST (INCR) tests. During the COST (INCR) tests patients cycled for 527 ± 154 (511 ± 151) seconds. Maximum HR was 134 ± 29 bpm (129 ± 30 bpm) for COST (INCR) tests. VO2p was 13.2 ± 4.6 (13.1 ± 3.8) ml/kg/min for COST (INCR) tests. VE/VCO2-slope was 48.0 ± 13.3 (46.7 ± 10.0) for COST (INCR) tests. No significant differences were found between the COST and INCR tests.
Discussion: Data collected so far show that patients' exercise performance with and without increment of VAD speed is comparable. Further investigations should be conducted to assess other possible factors limiting VAD patients' performance.

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Oral Session - Apheresis, O7-O12

O7

ADVERSE EVENTS IN APHERESIS IN RELATION TO COLLOID REPLACEMENT FLUIDS. DATA FROM THE WAA APHERESIS REGISTRY

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Introduction: The aim of the study was to clarify what type of colloid replacement fluids were used during the various procedures and to clarify of adverse events can be expected differently in different procedures in relation to the replacement fluid.
Material and methods: Data that is entered into the WAA apheresis registry were analysed for colloid replacement fluid and adverse events in relation to the various procedures. A total of 58345 treatments had been registered and were included in the analyses. Data of substitution fluid was missing in 5.9%. Side effects were graded as none, mild, moderate (needing medication), severe (interrupted treatment due to AE, death due to treatment.
Results: One patient who suffered from severe epilepsia had a seizure during the plasma exchange and died later. The relation to the procedure could not be clarified. No other patient died related to apheresis. The number of procedures that used colloid replacement fluid with plasma were 8867, albumin 15164 and Hydroxyethyl starch (HES) 478. Most of these fluids were given to patients who performed plasma exchange. Thus of all procedures then plasma were used this was for plasma exchange with centrifugation technique (n = 8080) or filtration technique (n = 719). The AE graded mild/moderate/severe were for plasma 1.7/5.8/0.8%, albumin 1.5/2.9/0.6% and HES 2.4/2.9/0.3%.
Substitution was by fresh frozen plasma (FFP: 71%), Liquid stored plasma (LSP: 21%), Octoplasm® (O: 5%), cryoprecipitate poor plasma (CPP: 3%).
The relation of replacement used and severe AE was for FFP 0.7%, LSP 1.3%, CPP 0.7%, Octoplas® 1.1% (n = 375), albumin 0.6% and HES 0.3%.
Significant differences were found between extent of AE and replacement fluid used.
Discussion: The replacement fluid used varies between centres. There are differences in extent of side effects.

O8

MARS AS LIVER SUPPORT THERAPY IN ACUTE-ON-CHRONIC LIVER FAILURE (ACLF): FROM THE LITERATURE TO THE CLINICAL PRACTICE

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Introduction: To establish guide-lines for the use of MARS (Molecular Adsorbent Recirculating System) in the treatment of ACLF, on the basis of both the available literature and our clinical experience.
Material and methods: 115 patients affected by ACLF have been treated with MARS. Grade 1 encephalopathy was present in 12 and grade 2 in 6. Usual parameters pertinent the liver failure have been assessed before, during and after MARS cycle. 40 patients lamented severe pruritus and showed scratch-

ing skin lesions. Treatment modalities: 2-7 daily sessions according to patient's need; session time 5 hours; blood flow 220 ± 20 ml/min, albumin flow 150 ml/min; dialysate flow (in the albumin dialyzer) 500 ml/min; MARS monitor connected with GAMBRO ULTRA machine arranged in hemodialysis mode.
Results: After MARS cycle clinical conditions and liver function improved in 90 patients (group A) and remained unchanged in 25 (group B). The two groups differed at the beginning of MARS treatments only as concerns coagulant activity: INR <3 in group A and INR >3 in group B. The improvement ratio (patients vs primary liver disease) was: chronic hepatitis C 34/41, chronic hepatitis B 9/12, alcoholic liver disease 28/29, primary biliary cirrhosis 6/9, hepatorenal syndrome 7/13, severe cholestasis after graft 2/3, recurrent hepatitis C after graft 1/2, autoimmune cholangitis 2/3, chronic hepatitis B + D 1/3. Coma regressed only in group A; pruritus disappeared in all patients after 3 treatments.
Discussion: Our data, in accordance with those described in the literature, confirm that, among the clinical pictures of ACLF, that secondary to alcoholic liver disease gains more benefits by MARS. All patients affected by ACLF take advantage by a liver support (MARS), except those with high deterioration of coagulation factors (end-stage liver failure, INR >3).

O9
A NANOSTRUCTURED MONOLITH ADSORBENT DEVICE TO AUGMENT HAEMODIALYSIS

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Introduction: A suitable method to address the life-reducing complications associated with poor removal of protein bound and high molecular weight uraemic toxins during haemodialysis has yet to be found. The introduction of adsorbent therapeutics into haemodialysis circuitry is one method by which this may be addressed. It has previously been shown that marker uraemic toxins and inflammatory cytokines which remain in haemodialysed blood samples may be removed by adsorption using phenolic resin derived monoliths with a unique trimodal nanoporous structure. The aim of the following study was to characterise the haemocompatibility of the small prototype adsorbent monolith, scale up the device to a clinically relevant size and assess maintanence of porous profile and efficacy for adsorption of marker toxins.
Material and methods: 7 mm and 30 mm diameter monoliths were characterised by porosimetry and SEM. Small prototype haemocompatibility was assessed by flow cytometry and ELISA, measuring complement, platelet, granulocyte and t-cell activation following perfusion of healthy donor blood samples through the devices over time. Adsorption of biotoxin markers p-CS, IS, IL-6 and TNF was measured in a spiked healthy donor blood perfusion study using clinically scaled 30 mm diameter prototype monoliths and a flow rate of 300 ml/min.
Results: Small prototype monoliths did not stimulate blood activation markers and produced no significant adverse effects on blood biochemistry when compared to tubing only controls. The large monoliths removed protein bound uraemic toxins IS and p-CS to negligible levels and reducing cytokine production by 50% after 90 minutes circulation. Pressure drop across the monoliths was negligible.
Discussion: A phenolic resin derived nanoporous monolith has been scaled up and tested at haemodialyzer perfusion rates. The device was haemocompatible and maintained efficacy for marker biotoxins which are poorly removed by current haemodialysis therapy.

O10
EVALUATION OF NANOPOROUS CARBON MATERIALS FOR UREMIC TOXIN REMOVAL

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Introduction: Patients with kidney malfunction suffer from accumulation of uremic toxins in their blood. One promising concept of blood purification is the use of so-called mixed matrix membranes, which combine filtration and adsorption in one step. An important point there is the selection of the proper adsorptive particles, which can influence the performance of the whole process. In this study, we compared the performance of various nanoporous carbon materials, including home-made mesoporous carbons and commercial Norit A Supra activated carbon, with respect to the removal of the key uremic toxins and cytokines from human plasma.
Material and methods: Structural and porous properties of the nanoporous carbons were characterized by scanning electron microscopy (SEM) and nitrogen adsorption-desorption isotherms at 77 K. The adsorption capacity of all carbons was evaluated for a range of uremic toxins, middle molecules and cytokines. Concentrations of these compounds were analysed by means of UV-vis, HPLC and ELISA.
Results: Activated carbon particles with small diameter and pore size around 2 nm show high adsorption capacity of small water-soluble molecules such as creatinine, and protein-bound toxins, for instance indoxyl sulfate. Additionally, mesoporous particles (pore size >2 nm) can adsorb better middle molecules and cytokines. The home-made mesoporous carbons remove 85% of indoxyl sulfate, 94% of hippuric acid and 55% of p-cresyl sulfate from uremic human plasma with 1:160 carbon to plasma ratio.
Discussion: The new home-made mesoporous carbon seems to be suitable material for removing a broad range of uremic toxins and cytokines from human plasma and would be used for fabrication of new mixed matrix membranes.
Acknowledgement: This work is financially supported by the EU Marie Curie ITN-BIOART Project.

O11
DEVELOPMENT OF BIOACTIVE MEMBRANES FOR BIOARTIFICIAL KIDNEY

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Introduction: The development of cell based Bioartificial Kidney device (BAK) could improve existing dialysis therapies. A key requirement for such device is the formation of a "living membrane" consisting of a tight kidney cell monolayer with preserved functional organic ion transporters, on suitable artificial membrane surfaces. Here, we investigate coating strategies to achieve a tight monolayer of conditionally immortalized human Renal Proximal Tubular Epithelial Cells (ciPTECs) on polymeric membranes.
Material and methods: We investigate the application of L-dopamine and Collagen IV (L-dopa/CIV) double coating (Schophuizen et al, Acta Biomat., 14 (2015), 22-32) and glycosaminoglycan (GAG) based coatings on polyethersulfone (PES) membranes which are suitable for blood/plasma filtration. Several ciPTECs seeding densities and culturing under static and dynamic conditions are studied. The properties of the new bioactive membranes are analyzed in detail, including transport of albumin and immunoglobulinG solutions. CiPTEC monolayer morphology is investigated via expression of tight junction protein Zonula Occludens-1 (ZO-1). The organic cation transporter 2 (OCT2) is evaluated using a fluorescent substrate, 4-(4-(dimethylamino)styryl)-N-methylpyridinium iodide (ASP+).
Results: Both coatings, L-dopa/CIV and GAGs, improve ciPTEC adhesion on the PES membranes. After one week of culture, reproducible cell monolayers are formed, when using L-dopa/CIV, whereas the reproducibility of the cell monolayer seems to be dependent on the type of GAG coating. Preliminary results with L-dopa/CIV coated membranes indicate active ASP+ uptake, most likely, mediated by the OCT2.
Discussion: The application of L-dopa/CIV and/or GAG coatings seems a promising approach to obtain bioactive membranes suitable for BAK device. Future work will include further characterization of ciPTECs function on the membranes and upscaling.
Acknowledgement: This work is funded by the EU Marie Curie ITN-BIOART Project.

O12
EVALUATION OF NEW LEUKOCYTE REMOVAL COLUMN USING A RAT CARDIOPULMONARY BYPASS MODEL

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Introduction: Extracorporeal life support devices, such as the cardiopulmonary bypass (CPB), preserve the patient's life by providing adequate oxygen supply and blood flow to vital organs. However, previous studies have suggested that the interaction of blood and large artificial surface

induces inflammatory response during CPB. As a result of series of chain reactions, the numerous powerful inflammatory mediators, including hormones and autacoids, are formed and released. Therefore, we developed the new leukocyte removal column (LRC) for attenuating the systemic inflammatory response during CPB.
Material and methods: Rats were divided into the CPB group and the CPB with LRC group. CPB pump flow was maintained at 70 ml/kg/min. Blood samples were collected before (baseline), and 30 min and 60 min after initiation of CPB. We measured the differential count of leukocytes, inflammatory markers (TNF-α, IL-6, IL-10) and biochemical markers (LDH, ALT, AST). Moreover, we also measured the wet-to-dry weight (W/D) ratio of the lung 60 min after the initiation of CPB.
Results: In the CPB group, the pro-inflammatory cytokines and increased significantly, reaching a maximum (TNF-α: 1347 ± 75 pg/ml, IL-6: 1763 ± 112 pg/ml) at the end of experiment. In addition, the levels of biochemical markers significantly increased (LDH: 794 ± 85 U/L, AST: 182 ± 32 U/L, ALT: 81 ± 11 U/L) 60 min after the CPB initiation. Moreover, the level of W/D ratio was lower in the CPB with LRC group than in the CPB group (CPB group: 6.02 ± 0.07, CPB with LRC group: 5.49 ± 0.10).
Discussion: The data suggest that the new leukocyte removal column is useful for reducing the inflammatory response and lung edema during CPB. Additionally, this rat model is useful for basic research of extracorporeal circulation device evaluation.

Oral Session - Tissue Engineering of Bone, O13-O18

O13
MULTILAYERS OF POLY-L-LYSINE AND HYALURONIC ACID COMBINED WITH ORDERED NANOSTRUCTURES AFFECT STEM CELL RESPONSE

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Introduction: Topographical and mechanical signals are important regulators of cell behavior in body tissues. This study aims to design a unique system with precise viscoelastic and geometric parameters using laser interference lithography (LIL) and layer-by-layer (LbL) technique to affect stem cell response by mechanical stimuli for potential applications in regenerative medicine.
Material and methods: Round, hexagonally arranged gold nanostructures of different size were obtained by LIL using various angles of incidence. Multilayers of poly-L-lysine (PLL) and hyaluronic acid (HA) were spray-coated on top of the nanostructures. Moreover, their viscoelasticity was tuned by cross-linking using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxysuccinimide (NHS). Pristine and modified nanostructured surfaces were characterized using atomic force (AFM) and scanning electron microscopy (SEM) as well as water contact angle (WCA) measurements. Adhesion, growth, and differentiation of human adipose-derived stem cells (hADSC) was studied to learn about the effect of nanostructures on cell fate.
Results: Initially hydrophobic nanostructured surfaces became hydrophilic after modification with PEM. AFM using colloidal probes revealed the lowest viscoelasticity in PEM cross-linked with the highest EDC concentration. Adhesion and proliferation of hADSC were clearly affected by size and distance of nanostructures and a period of 518 nm was favored. Further, the pitch of the structures had a clear effect on the orientation of cells with more elongated cells on the smallest features. Focal adhesion kinase (FAK) as indicator for mechanical tension on the cytoskeleton was found in the periphery of hADSC and primarily allocated to the nanostructures again with an optimal period of 518 nm. The small GTPase RhoA was evenly distributed within hADSC with no obvious dependence on the feature dimensions.
Discussion: We present a novel technique for reproducible design of nanostructures in combination with viscoelastic surface coatings that can be used in future to control differentiation of mesenchymal and other stem cells.

O14
BIOLOGICAL ACTIVITY OF NANOSTRUCTURED HYDROXYAPATITE PARTICLES

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Introduction: In this work we study structural properties and cytotoxic activity of Mg- substituted hydroxyapatite calcium (HA) prepared with Zn and Se ions. The effect of Zn and Se ions addition on Mg, Ca HA formation was investigated. Finally, the processing technique of uniform, spherical HA/Alginate (ALG) microgranules (MG) with encapsulated HA particles distributed throughout the matrix structure were considered.
Material and methods: The suspension of particles was produced from aqueous solutions by co-precipitation method. After separating and annealing at 150°C precipitated powders were investigated by XRD, FTIR, TEM and elemental analysis. HA/ALG MG with diameter ranged from 250 to 1000 μm were produced using Buchi encapsulator. Cytotoxic activity of particles was determined by MTT- test method in range of concentrations from 0.001 to 0.5 wt.% using kidney cells human embryo HEK-243 and cell lines human lung adenocarcinoma A549.
Results: The presence of Mg ions affects the crystallization yield of nanostructured amorphous HA. In general, all samples exhibited an amorphous phase (90-99 wt.%). Although for all samples we detect no significant structural difference, the results of MTT test illustrates the effect of Zn and Se addition. We observed, that Mg, Ca HA nanoparticles are non-toxic both for HEK-243 as well as for A549 cells. For Zn-ions containing nanoparticles we have observed strong inhibition of growth of both A549 and HEK-243 cells. Selective effect on cell growth was confirmed for Se-ions containing nanoparticles. The nanoparticles induce the concentration dependent inhibition of A549 cell growth, however they are non-toxic regarding to HEK-243 cells line. At concentration of 0.5% a slightly toxic effect was observed. This tendency was also detected for HA/ALG MG.
Discussion: Se, Mg, Ca HA nanoparticles proved to selectively effect on cell growth. The effect seems to be related to the presence of Se in HA structure.

O15
ELECTROSPINNING FOR BONE/TENDON TISSUE ENGINEERING, MECHANICAL STRESS INFLUENCE ON DIFFERENTIATION

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Introduction: Electrospinning is a versatile method for polymer fibers production. We investigated here the relevance of several electrospun scaffolds varying by their compositions and structures to rebuilt tendon- and bone-like tissues. Such substitutes with a sheet-like shape could be « tailor made » *in situ*, with a manipulation by surgeons to adapt them to the injured areas constraints, particularly to the geometric complexity of the maxillofacial area. After dynamic cell culture on the fibers, we analyzed biological and mechanical properties of the hybrid tissue.
Material and methods: We studied the influence of various scaffold production parameters: polymer (Polyvinyl Alcohol, Polylactic acid, Polycaprolactone), additional factors (calcium nanoparticles) and fibers' morphology (size, nanostructuration). Preosteoblasts (MC3T3) and mesenchymal stem cells (C3H10T1/2) lines were cultured on scaffolds for 5 days with or without mechanical loading (10 minutes of 1-Hz stretching every 6 hours, Bose Biodynamic) before analysis. We focused on cell differentiation (ALP staining), proliferation and spreading (SEM), cell morphology, viability (fluorescence microscopy) and gene expression (RTq-PCR).
Results: Polymer nature and structure were critical to allow cells to grow and spread. The effect of additional factors appeared to be different depending on the aimed differentiation state (e.g. calcium nanoparticles promoting osteoblast lineage), while some materials enhanced the development of both cell lines (e.g. Polycaprolactone alone). Most scaffolds showed a dry Young Modulus within a range of 0,5-1 MPa, and the mechanical stretching improved the expression of the studied genes (e.g. scleraxis and tenomodulin for tendon, runx2 and osteocalcin for bone) compared to static culture.
Discussion: It is essential to analyze all production parameters in order to define the optimal electrospun scaffold for a specific application. Studying two differentiation lineages was promising for the further development of

multilayer substitutes promoting both bone formation and muscle adhesion on the rebuilt tissue.

O16
PHOTO-CROSSLINKABLE HYDROGEL PRECURSORS FOR TARGETED TISSUE ENGINEERING
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Introduction: The acute lack of available organs for transplantation is a worldwide issue which is even expected to worsen as the world population ages. Tissue engineering aims at bridging this gap by offering a regenerated approach. The present work is situated in this field as it focuses on the development of biomaterials which can be applied as scaffolds to support the adhesion, proliferation and differentiation of adipose-tissue derived stem cells (adMSCs). In addition, bio-active coatings, including fibronectin, were applied in order to investigate their influence on stem cell differentiation.
Material and methods: Photo-crosslinkable gelatin- and starch-based hydrogel precursors and their corresponding networks were synthesized in combination. Subsequently, the materials developed were characterized in depth via HR-MAS ^{1}H-NMR spectroscopy, IR mapping and rheology. adMSCs were derived from adipose tissue through liposuction followed by cell-seeding onto the scaffolds developed. In order to proof both the adipogenesis, as well as the osteogenesis, supporting potential of the materials, the hydrogel films developed were compared regarding material characteristics and behaviour of stem cells *in vitro*. Moreover, fibronectin- and aggrecan-coatings were also applied on the gelatin hydrogel films. The presence of an additional starch phase in the gelatin matrix resulted in a decrease of the cell adhesion, with locally even cell detachment.
Results: The mechanical strength and the cell-interactivity of the scaffolds were achieved by the self-structuring property of the biopolymer gelatin, while starch and the ECM polymers influenced the cell adhesion, proliferation. Moreover, the hydrogels developed allowed *in vitro* adipogenic and osteogenic differentiation of the adMSC.
Discussion: The hydrogels developed were shown to be biocompatible and supported cell adhesion of adMSCs. In addition, by varying the mechanical properties of the gelatin hydrogels developed, both adipogenic as well as osteogenic differentiation could be upregulated.

O17
BIOMIMETIC EVALUATION OF SCAFFOLD PERFORMANCE FOR BONE TISSUE ENGINEERING
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Introduction: The capacity of porous scaffolds for bone tissue engineering (BTE) to promote osteointegration is generally characterized through their microstructural, mechanical and transport properties, and qualitatively compared to hypothetical ideal requirements. Such characteristics of natural bone tissue widely vary with species, anatomical site and age. This makes BTE scaffolds seldom resemble the bone they should replace. In this work, a biomimetic score was developed to quantitatively estimate to what extent a BTE scaffold mimics natural bone, to produce biological substitutes matching the performance of the missing bone tissue.
Material and methods: Samples of two commercial hydroxyapatite scaffolds with different morphometry were characterized and compared with trabecular equine bone tissue from two different anatomical sites. Large mammals are good preclinical models of human therapies and may benefit of BTE therapy. Images of samples were acquired by micro-computed tomography. Morphometric properties related to biological/transport (porosity, average pore size, pore size distribution, permeability) and structural performance (connectivity density, degree of anisotropy) were computationally evaluated. Mechanical properties (compressive Young's modulus, ultimate compressive strength) were experimentally estimated. Biomimetic scores were defined as the weighted 1-p, Eulerian and ∞-p distance between the estimated performance properties of artificial scaffolds and natural tissues.
Results: Properties of artificial scaffolds and natural tissues significantly differed from the common ideal requirements and from one another. The biomimetic score based on the weighted Eulerian performance distance was most effective in identifying scaffolds and tissues exhibiting similar performance.
Discussion: Score values evidenced that commercial artificial scaffolds are available that closely resemble a specific natural bone tissue and may be suitable candidates to replace it, at least in equines. The score may be modified to include biocompatibility parameters.
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O18
DEVELOPMENT OF HYBRID BIO-ARTIFICIAL ANTERIOR CRUCIATE LIGAMENT
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Introduction: To develop a bio-artificial ligament prosthesis as an alternative to current autograft based therapies.
Material and methods: Hybrid bio-artificial ligaments were fabricated using a combination of a titanium spring and a fibrin gel/fibroblast construct. The ends of the ligament prosthesis were incorporated into a brushite cement anchor to allow fusion with the host bone. The ligament constructs were mechanically conditioned in a mechatronic bioreactor using cyclic tensile strain at a magnitude of 2.5%. Cell attachment to the titanium spring was examined using scanning electron microscopy, while tendon development was examined histologically (Masson's Trichrome).
Results: Mechanically conditioned constructs were found to have a significantly higher tensile modulus and a significantly higher failure stress than unstimulated controls. Without reinforcement, constructs were observed to fail at the anchor-ligament junction, while the titanium spring reinforcement was seen to assist in even transmission of the load to the ligament, with no consistent trends in the position at which failure occurred. Cells were seen to be attached to the titanium spring, and fibroblasts on the fibrin gel construct were mostly found on the surface of the contracted gel, without penetrating deeply into the matrix.
Discussion: Unreinforced constructs displayed considerably improved strength as a result of mechanical conditioning compared to static controls, but incorporation of a biocompatible reinforcement gave improved load distribution throughout the ligament construct, and significantly increased strength. The results suggest that the hybrid approach used here shows promise in developing improved therapies for connective tissue injuries.

Oral Session - Development in Mechanical Support I, O19-O24

O19
PRELIMINARY DEVELOPMENT OF CONTROL SYSTEM OF A MINIATURIZED MAGLEV BLOOD PUMP
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Introduction: We are developing a miniaturized magnetically levitated (maglev) rotary blood pump. The Maglev pump enhances the blood compatibility compared to the pumps with contact bearings and its compact system allows less invasive implantation. However, magnetic interferences generated by the actuator coils on the nearby eddy current position sensor coils usually harms the stability of the maglev control system. This work presents development of a control system with anti-interference methods for the miniaturized maglev pump.
Material and methods: A maglev control system was initially built with commercially available self-exciting eddy current position sensors. Transfer function from actuator to sensor coils was measured and analyzed to identify unwanted parasitic magnetic interferences. Several special anti-interference technique were adopted. 1) A new type eddy current signal conditioning circuit with modulation and demodulation method was developed with implemented anti-aliasing filters to remove actuator's harmonics. 2) High power filters in actuator's switch amplifier were designed to suppress harmonics.

3) All clocks, especially actuator's switch clock and eddy current sensor's clock, were synthesized from a single oscillation source and were phase locked with each other. 4) The frequencies of actuator's switch clock and eddy current sensor's clock were chosen to demodulate the actuator's harmonics by eddy current conditioning circuit to zero or far above circuit's bandwidth.
Results: The total power loss in maglev coils was less than 400 mW and the sensitivity of the proposed anti-interference control system was lower than 8 dB which satisfied ISO 14839, demonstrating the stability and freedom from interference.
Discussion: Magnetic interferences in miniaturized blood pumps are so significant that common eddy current conditioning methods would fail. This work has demonstrated the employment of special techniques can successfully remove the interference to guarantee a smooth operation of the maglev pump.

O20
EVALUATION OF THE DOPPLER FLOW CURVE ON CONTINUOUS LVADS IMPLANTED ON NORMAL HEARTS. AN ANIMAL STUDY
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Introduction: To observe the behavior of the continuous wave (CW) Doppler of the inflow cannula in normal pig hearts implanted with a continuous flow LVAD and study its relationships with myocardial contractility and other causes of elevated velocity.
Material and methods: 6 minipigs, mean weight of 43.83 ± 9,0 kg were implanted with Biomedicus centrifugal pump. Cannulas were placed on the ascending aorta and the apex of the LV. Before the implantation LVEF was evaluated with epicardial echocardiography. After implantation the CW Doppler of the inflow cannula was observed on full and partial support. Position of the cannula was controlled by echocardiography. During the experience hemodynamic and analytical measurements were recorded to analyze what influences the behavior of the continuous wave Doppler of the inflow cannula.
Results: None of the subjects presented important obstruction of the LV canula. 5 (83,3%) had a normal LVEF and 1 (17,7%) presented akinesia of the inferior wall of the LV and ST but the LVEF was normal. The mean Doppler velocity found was 3,05 ± 2,0 m/s, range 0,9 to 8 m/s. On partial support the mean velocity was 2,11 ± 0,93 m/s. On total support the mean was 3,98 ± 2,02 m/s. 91% of the Doppler measurements were above 2,0 m/s independent of type of support. The systolic pressure of the inflow cannula was in all cases positive (mean 71,25 ± 36,91 mmHg) while the mean of the diastolic pressure was -102,58 ± 111,44 mmHg.
Discussion: CW doppler velocity of the inflow cannula of continuous flow LVADs tends to be higher than 2,0 m/s in normal hearts. The positivization of the inflow cannula pressure during systole may support a contribution from contractility to the filling of the device. More studies that compare CW velocity with different degrees of myocardial dysfunction are needed.

O21
***IN VITRO* SIMULATION OF ACUTE MYOCARDIAL INFARCTION UNDER MECHANICAL LVAD SUPPORT IN A HYBRID MOCK CIRCULATORY LOOP**
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Introduction: A novel Mock Circulatory Loop (MCL) that combines computer simulations with an electro-mechanically controlled circulation is presented. With the introduction of the Hardware-In-the-Loop (HIL) concept, the presented MCL allows the investigation of interactions between LVADs and the circulatory system under variable hemodynamic conditions.
Material and methods: Acute myocardial infarction was induced using a novel microsphere model in sheep. Prior inducing infarction all sheep were instrumented with ECG and invasive AoP, LVP, CVP and PAP pressure gauges to collect data *in vivo* pre and while LVAD support. Subsequently the LVAD was integrated into the novel MCL. The obtained pressure traces were applied with the MCL to the LVAD to verify MCL dynamic performance.
A lumped parameter cardiovascular computer simulation was implemented in Matlab/Simulink and extended by a myocardial infarction model. The obtained *in vivo* data were used to identify the infarction model. The computer model and the MCL were combined applying the HIL method whereat MCL internal pressures were measured back to complete HIL closed loop control. The LVAD was operated in the MCL while applying computer simulation data to assess the physiologic effects of LVAD support.
Results: The playback of the recorded animal data from myocardial infarction, fibrillation, defibrillation and manual cardiac massage demonstrated excellent MCL dynamic performance. The effect of Impella CP pumps was successfully studied with the HIL Mock Circulatory Loop under various physiologic and pathophysiologic hemodynamic conditions. In particular, the *in vitro* results matched exceptionally to obtained animal data.
Discussion: The novel hybrid Mock Circulatory Loop provides a powerful tool that enables the *in vitro* assessment of mechanical heart support systems under variable hemodynamic conditions. Moreover, it satisfies the recent demand to study the hemodynamic effects of mechanical heart support in reproducible hemodynamic scenarios at the benefit of a significantly reduced *in vivo* study effort.

O22
IMPROVED PERFORMANCE OF NEWLY SHAPED INTRA-AORTIC BALLOONS AT THE SEMI-RECUMBENT POSITION, *IN VIVO*
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Introduction: The major hemodynamic benefits of the intra-aortic balloon pump (IABP) are reduced when the IAB is operated at the semi-recumbent position. We previously tested *in vitro* several novel IAB shapes and showed that this deterioration can be moderated with IABs that deviate from the traditional cylindrical shape. The 2 novel IAB shapes (*Shape_1* and *Shape_2*) with the best *in vitro* hemodynamic performance were subsequently identified, and in this work we aim to compare their hemodynamic results to those of the traditional IAB *in vivo*.
Material and methods: Seven anaesthetised, open-chest Landrace pigs (weight 89 ± 4 kg) underwent coronary artery occlusion for 1 hour, followed by reperfusion. During reperfusion, each animal received, in sequence, IABP support with the cylindrical IAB and with either Shape_1 (Group 1, n = 3) or Shape_2 (Group 2, n = 4). All nominal IAB volumes were 35 cc. Aortic root pressure (Pao) was recorded during IABP support with frequency 1:1 at 0°, 30° and 45°. Diastolic Pao augmentation (Paug) and end-diastolic Pao reduction with respect to baseline (edP) were calculated. Values are presented as mean ± standard deviation.
Results: At 45° there was 97% improvement in edP for Shape_1 and 27% improvement for Shape_2, all compared to the cylindrical IAB. A difference between the novel IAB shapes and the traditional balloon was not as noticeable in Paug, but upon increasing the operating angle, the performance of Shape_1 gradually exceeded that of the cylindrical IAB.
Discussion: In an ischemia-reperfusion animal model, we showed that the hemodynamic performance of 2 novel IABs is superior to the traditional IAB at angled positions. These novel IABs could allow for better efficacy of IABP therapy when patients are nursed at the semi-recumbent position.

O23
IABP SUPPORT IN ISCHAEMIC AND NON-ISCHAEMIC *EX-VIVO* HEARTS
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Introduction: The intra-aortic balloon pump (IABP) induces diastolic blood pressure augmentation and systolic afterload reduction. These blood pressure changes are expected to create clinical improvement in terms of coronary perfusion and myocardial oxygen consumption, but reportedly, the effects are inconsistent and ambiguous in human and experimental studies. The aim of this study was to investigate the influence of persisting ischaemia on IABP efficacy in healthy hearts, and in shock.
Material and methods: Twelve slaughterhouse pig hearts were isolated, prepared, and connected to an external circulatory system. Through coronary reperfusion and controlled cardiac loading, physiologic cardiac performance was achieved. Deteriorating heart function, from normal contractile state to cardiogenic shock, was simulated in hearts 1-6, by step-wise administration

of negative inotropic drugs, while adapting systemic vascular resistance. In hearts 7-12, a large myocardial infarction with different degrees of pump failure was mimicked by gradually creating severe global myocardial ischaemia superimposed on the decreased contractile state. IABP support was applied in all hearts under all conditions and evaluated by measuring coronary blood flow, cardiac output, and myocardial oxygen consumption.
Results: Without ischaemia, the IABP induced a significant increase in coronary blood flow and cardiac output. These effects were strongly augmented in the presence of persisting ischaemia, where coronary blood flow increased by 49 ± 24% ($p<0.01$) and cardiac output by 17 ± 6% ($p<0.01$) in case of ischaemia and severe pump failure. Myocardial oxygen consumption increased in case of ischaemia (21 ± 17%; $p<0.01$), while it slightly decreased without ischaemia (-3 ± 6%; $p<0.01$).
Discussion: In case of progressive pump failure due to persistent myocardial ischaemia, the IABP increased hyperaemic coronary blood flow and cardiac output significantly, and reversed the hemodynamic deterioration instantly. This suggests that IABP therapy in acute myocardial infarction is most effective in patients with viable myocardium, suffering from persistent myocardial ischaemia after adequate epicardial reperfusion therapy.

O24
MINIATURE CARDIOPULMONARY BYPASS FOR RATS TO UNDERGO HYPOTHERMIC CIRCULATORY ARREST

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Introduction: Although hypothermic circulatory arrest (HCA) has been used in pediatric heart and adult aortic surgery, optimal measures for neurological protection has not been fully assessed due mainly to limitation in experimental evaluation. We develop a miniature cardiopulmonary bypass (CPB) for rats to undergo HCA in order to evaluate neurological functions.
Material and methods: A CPB system consists of 1.02 mm (ID) tubing connecting venous and arterial online reservoirs and thermometer, 2.06 mm (ID) roller pump-head and a miniature silicone -membrane lung (80 cm^2, Fuji Systems Corporation). Another membrane lung was connected in line as a heat exchanger and irrigated by a servo-controlled water cooling/heating (c/h) system (core c/h) parallel to a water pad under the animal (surface c/h). The CPB circuit (priming volume 2.0 ml) is connected to a venous catheter (ID1.25 mm with side holes, Hakko, Japan) in the right atrium advanced from the right jugular vein with the arterial return (ID0.41 mm) to the right carotid artery through a neck incision. Rats were orally intubated, ventilated, core- and surface-cooled down to 20˚C (rectal), when HCA is started by induced ventricular fibrillation and cardioplegic arrest with the chest closed. At the end of HCA, rats are rewarmed by CPB until 28˚C (rectal) when the circuit is emptied to terminate CPB.
Results: It takes about 15 min to cool and twice as much to rewarm, resulting in 45 min plus the duration of HCA. Infused volume consists of 2 ml for priming, 1-2 ml for cardioplegia and 0-4 ml from a reservoir, totaling 8 ml at most which is less than half of the circulating blood volume of rats weighing 200 g.
Discussion: Using the CPB system, recovery from HCA is quick and survival is high to allow successive neurological testing.

Oral Session - Biomaterials and Scaffold Engineering, O25-O30

O25
ELECTROSPUN PIEZOELECTRIC PVDF SCAFFOLDS WITH DIFFERENT SOLUTION PARAMETERS FOR NERVE REGENERATION

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Introduction: Polyvinylidinefluoride (PVDF) is a promising biomaterial for nerve tissue engineering because of its proven biocompatibility and piezoelectric properties that can possibly stimulate Schwann cell ingrowth and axonal elongation. Here we report on changed mechanical and physical properties of PVDF-scaffolds using different solvents during their production by electrospinning.
Material and methods: Electrospun scaffolds (flow-rate: 2 ml/h, electrical-field: 1 kV/cm) were produced from PVDF-25% dissolved in DMF 4:1 Acetone (S1), DMSO 4:1 Acetone (S2) and DMAc 6:4 Acetone (S3), respectively. Analysis of scaffold morphology and mechanical properties was performed with SEM and a tensile testing instrument (Electroforce LM1, BOSE), respectively. The presence of the crystalline nonpolar alpha-phase and piezoelectric polar beta-phase was characterized using FTIR and DSC. Neonatal rat Schwann cell viability and growth behaviour on the scaffolds was evaluated *in vitro*.
Results: S1 and S2-scaffolds exhibited a more homogeneous morphology than S3-scaffolds. S2 showed the highest tensile strength (270 kPa) compared to S3 (176 kPa) and S1 (135 kPa). The highest elongation at break was recorded for S1 (186%) compared to S3 (80%) and S2 (33%). The scaffolds hydrophilic nature increased using DMSO: Acetone (110°) and DMF: Acetone (120°) as solvents. All PVDF-scaffolds exhibited a piezoelectric polar beta-phase formation. The beta-phase adsorption ratios were, however, different and most prominent in S1-scaffolds with 70% (at 841 cm^{-1}) in the FTIR-spectrum. Cytotoxicity for Schwann cells could be excluded and the glial cells demonstrated their typical growth behaviour on all scaffolds evaluated.
Discussion: Mechanical and physicochemical properties of electrospun PVDF-scaffolds can be manipulated and their piezoelectric properties can be demonstrated with FTIR and DSC. *In vitro* tests with peripheral glia cells, Schwann cells, reveal their potential as scaffolds for nerve tissue engineering. Future experiments have to evaluate this potential in more detail in organotypic cell culture models *in vitro* and rat sciatic nerve repair models *in vivo*.

O26
DEVELOPMENT OF CHEMICALLY CROSS-LINKED BIOPOLYMER BASED BURN WOUND DRESSINGS WITH ANTIMICROBIAL PROPERTIES

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Introduction: Despite the development of novel diagnostic tools and treatments and the consequential increase in survival rates of burn wound victims, patients still suffer physically, psychologically and financially. Therefore, the aim of the present work is to develop novel, biopolymer based burn wound dressings with antimicrobial properties. For this purpose various UV cross-linking strategies were evaluated as well as different strategies to study the incorporation of the antimicrobial agent.
Material and methods: Gelatin and alginate were modified with cross-linkable moieties using methacrylic anhydride, N-acryloxysuccinimide and 4-pentenoic anhydride. Next, covalently cross-linked hydrogel films were prepared via film casting upon the addition of a photo-initiator and the application of UV-irradiation. Furthermore, thiol-ene cross-linking was tested using multifunctional thiols. The cross-linking kinetics and physico-chemical properties of the resulting films were characterized using rheology, texturometry and swelling experiments.
Interestingly, poly(vinylpyrrolidone)-iodine (PVP-I) was incorporated via incubation to introduce antimicrobial properties. The uptake and release of (PVP-)iodine is currently studied via XRF and electrochemistry. The results will be presented at the conference.
Results: Rheology during *in situ* UV curing and texturometry measurements demonstrated the low efficiency of the pentenoate-thiol cross-linking and the weaker mechanical properties. Acrylamide cross-linking proceeded the fastest, however the final mechanical properties were comparable to the gelatin-methacrylamide hydrogel films. Swelling experiments indicated high gel fractions were obtained for all derivatives.
At present a calibration method for the determination of the iodine content in hydrogel films via XRF has been developed and samples are currently being analyzed. In addition, the potential of applying electrochemistry to study the incorporation of (PVP-)iodine is being evaluated.
Discussion: In the present work, biopolymer-based hydrogels have been synthesized and characterized. The effect of different UV-initiated cross-linking methods on the final hydrogel properties has been evaluated thoroughly.

Additionally, the potential of XRF and electrochemistry to study the incorporation of PVP-I was evaluated.

O27

POLYETHYLENE BARRIER LAYERS TO REDUCE WATER TRANSMISSION OF LOADED MEMBRANES IN A TOTAL ARTIFICIAL HEART

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Introduction: Water transmission through polymer membranes cause undesired effects in medical devices, especially when membranes separate blood and electrical components, like done in total artificial hearts (TAH). Applying common barrier coatings as silicon oxide or amorphous hydrocarbon to a TAH membrane is disadvantages, since it affects hemocompatibility and durability. Therefore, a sandwich construction was chosen as utilized in the food industry as fluid barriers. As barrier material different polyethylene layers (PE) were used in this study.
Material and methods: The original membrane of the ReinHeart TAH is made of three 0.2 mm polyurethane (PU) layers. The structure was replaced by a sandwich construction in which the intermediate layer was changed to PE layer. In this way hemocompatibility of the membrane could be preserved. PE layers of different thicknesses and different degrees of cross-linking density were used to compare the water barrier properties and the mechanical behavior under dynamic conditions. Furthermore the modified membranes have been tested in an accelerated dynamic durability tester. They have been loaded under physiological pressure conditions with a frequency of 8 Hz over 28 million pumping cycles. Water transmission has been determined by long term tests. The results were evaluated against the untreated membranes and those with barrier coatings.
Results: The water transmission was reduced by up to 75% compared to original and by up to 35% compared to coated membranes, respectively. Although the intermediate layer showed some cracks, the barrier properties remain unaltered. Thereby the damage of the PE foils was less compared to coated membranes after the same amount of pumping cycles.
Discussion: Further the results suggest, that sandwich designed membranes are more robust with respect to the coated ones.

O28

REPLICATION OF HUMAN LIVER DEVELOPMENT WITH HUMAN LIVER ORGANOIDS: A NOVEL MODEL FOR DRUG TERATOGENESIS *IN VITRO*?

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Introduction: Bioengineering of hepatic tissues has been hindered with the absence of simultaneous development of hepatic and biliary tissue. This has produced hepatic organoids devoid of biliary ducts, compromising their representativeness of native liver tissue. Hence, the goal of this study was to develop a system that would efficiently recapitulate the liver embryonic development, using decellularized liver extracellular matrix (ECM) as scaffolds with primary human fetal liver progenitor cells (hFLCs).
Material and methods: hFLCs were seeded on decellularized liver ECM discs and were cultured for up to 3 weeks. Immunofluorescence microscopy was used to determine the extent of progenitor cell differentiation into hepatocytes and cholangiocytes. A γ-secretase inhibitor was added to the culture media and bile duct and hepatocyte development was monitored.
Results: hFLCs seeded on acellular liver ECM discs differentiated into hepatocytes and ductal structures. The cells showed predominant albumin expression along with loss of α-fetoprotein expression at 3 weeks. Cells also expressed other mature hepatocyte markers and perform drug metabolism. Cells in ductular structures expressed bile duct specific markers, demonstrating differentiation towards cholangiocyte lineage along with maintaining apico-basal polarity. Ductal structures were also found to precisely mimic the several stages of development of bile ducts of the human liver in the hepatic organoids. The addition of a γ-secretase inhibitor severely impacted the number of bile ducts formed and their maturation, mirroring a biliary atresia model.
Discussion: Our results demonstrate the efficient generation of bioengineered human liver tissue with hFLC that recapitulates stepwise development of hepatocyte and bile duct formation. Altogether, this study demonstrates the potential of this technology to study and mimic human liver development. These models provide novel approaches for liver bioengineering, drug discovery and toxicology (including drug teratogenesis evaluation *in vitro*), and ultimately for the treatment of liver disease.

O29

PHOTO-CROSSLINKABLE POLYSACCHARIDES AS BUILDING BLOCKS FOR ARTIFICIAL EXTRACELLULAR MATRICES

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Introduction: The extracellular matrix (ECM) of mammalian cells is composed of polymeric networks providing mechanical support to the cells and regulating biological functions important for cell growth, wound healing, and fibrosis. It is hypothesized that water-soluble polysaccharides and glycosaminoglycans (GAGs) are potent materials to generate gel-like materials mimicking the native ECM. Photo-initiated network formation and structuring represent a promising approach to create artificial ECM usable in tissue reconstruction.
Material and methods: Photo-crosslinkable polysaccharide and GAG derivatives based on dextran, hyaluronan, and chondroitin sulfate were synthesized by acylation with reactive (meth)acrylate derivatives varying the reaction conditions in order to control the degree and pattern of photoactive substituents. In addition, synthetic routes to crosslinkable GAGs with multiple substitutents (e. g. both sulfate and (meth)acrylate groups) were elaborated. The synthesized macromers were characterized using conventional analytical techniques. Their crosslinking ability was tested employing different photoinitiators. The mechanical properties of the resulting hydrogels were studied and their cytocompatibility was evaluated using an established live/dead viability test and the WST-1 cytotoxicity assay.
Results: Methacrylate-containing macromers of the mentioned biopolymers with varying degree of substitution were obtained by conventional esterification of the biopolymers. A novel procedure was developed to synthesize photocrosslinkable hyaluronan acrylates with controlled degree of substitution using phase-transfer catalysis. Hyaluronan derivatives containing both growth factor sequestering sulphate groups and cross-linkable acrylate functions were synthesized by sulfation of hyaluronan followed by introducing the acrylate groups. The macromers form stable and cytocompatible hydrogels. Using selected examples it will be illustrated that the prepared macromers can be successfully processed via additive manufacturing processes like soft lithography and 3D-printing to fabricate microstructured surfaces or 3D scaffolds soft tissue engineering scaffolds.
Discussion: Photo-crosslinkable polysaccharide and GAG derivatives are promising candidates to fabricate 3D-structured hydrogels which are able to provide, similar to the native ECM, both support and biological activity to cells.

O30

DECELLULARIZED WHOLE PORCINE HEART FOR TRANSPLANTATION

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Introduction: At present, the only treatment for severe heart failure is heart transplantation. However, shortage of donor heart has raised a long waiting list and limited its benefit. As an alternative of heart transplantation, regeneration of heart with organ decellularization technique has been applied. Our ultimate goal is to create a whole beating heart fabricated based on an organ scaffold for human heart transplantation.
Material and methods: A porcine heart was harvested, following cardiac arrest induced by high-potassium solution, which was stored in freezer -80°C for 24 hours. After thawing in 37°C water bath, the porcine heart was completely decellularized with 1% SDS and 1% TX-100 under the control of perfusion pressure, maintaining temperature of 37°C. Decellularized whole heart scaffold was sterilized with gamma irradiation. Finally, the whole-heart scaffold was transplanted in a pig under systemic anti-coagulation treatment with heparin by surgical anastomosis using vessel grafts; an ascending aorta was anastomosed to an abdominal aorta of recipient porcine, and superior vena cava to inferior vena cava of recipient porcine. Angiography of the transplanted heart graft was performed on the operative day and the 3rd postoperative day, respectively.

Results: The scaffold was well perfused without bleeding. Angiography revealed patent right coronary artery and aortic valve regurgitation mildly on the operative day. Injected contrast was appeared 10 seconds later in the right atrium. The transplanted heart scaffold was harvested on day three after transplantation. Histological report showed that blood clot was accumulated in coronary artery. However, blood perfusion was maintained through left to right intra-cardiac shunt.
Discussion: To the best of our knowledge, this is the first study of heterotopic transplantation of decellularized whole porcine heart. It is required to analyze histological features of transplanted decellularized scaffold and optimize the system with recellularization to apply this unique technology for clinical applications.

Oral Session - Vascular Access for Haemodialysis, O31-O36

O31
COMPUTATIONAL FLUID DYNAMIC STRATEGIES FOR THE STUDY OF BLOOD FLOW IN THE VASCULAR ACCESS FOR HEMODIALYSIS

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Introduction: Creation of arteriovenous fistulae (AVF) for hemodialyis has high failure rates. Juxta-anastomotic vein (JAV) stenosis due to neointimal hyperplasia (NH) is the major cause of failure. Previous studies (Remuzzi, *CJASN*2013) have shown development of transitional flow with high-frequency oscillation of shear stress in the JAV. While simulating the transitional flow would be better using turbulence models or direct numerical simulation, recent studies show that "high-resolution" (HR) CFD may detect flow instabilities, not well resolved by "normal-resolution" (NR). Our study was aimed at finding an HR CFD strategy to characterize transitional flow in AVFs.
Material and methods: We used the *Open FOAM* CFD toolbox and a previously used patient-specific computational mesh of an end-to-end AVF. Blood flow was imposed at the inflow, stress-free at outflow and no-slip condition on the walls. NR simulations were run using *icoFoam* solver, setting timestep number per cardiac cycle between 2-6,000 and using the PISO algorithm. HR simulations were performed with the *pimpleFoam*solver and the PISO-SIMPLE algorithm, that automatically adjusted variable timesteps per cardic cycle (Courant number = 1) between 10-30,000. Time discretization used in all cases was first order Euler implicit scheme. We characterized the flow phenotype by means of λ2 criterion, and disturbed flow patterns by hemodynamic wall metrics.
Results: The NR ran with 6,000 fixed timesteps (Δt = 0.15 ms) and CPU time of 6 hrs. The HR ran with a median timestep of 0.09 (range 0.05-0.12) ms and CPU time was 4.75 hrs. Higher resolution of flow phenotype patterns was obtained with HR than with NR CFD, as estimated by λ2 isosurface and shear stress oscillatory index maps (OSI).
Discussion: HR simulation detected more specifically the physics of transitional flow as compared to NR, allowing correct characterization of disturbed flow. This technique may be useful for elucidating the role of hemodynamic forces in the initiation of NH.

O32
SIMULATIONS OF THE UNSTEADY BLOOD FLOW THROUGH MATURE AND IMMATURE ARTERIOVENOUS FISTULAS

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Introduction: The aim of this study is to compare the flow parameters and the wall shear stress (WSS) distribution in mature and immature arteriovenous fistulas used for haemodialysis. Computational fluid dynamics methods were used for an analysis of the blood flow in the patient's specific fistula models.
Material and methods: DICOM images of four well-functioning mature fistulas, obtained from the angio-computed tomography, were the data source used for a reconstruction of 3D geometrical fistula models. Because of the lack of previous investigations, those models were also used for development of the hypothetical virtual geometry of immature fistula models, in which constant typical value of the cephalic vein diameter was assumed. Blood was assumed to be a non-Newtonian fluid and the Shear Stress Transport model of turbulence was employed. Blood vessel walls were assumed to be rigid. Mesh independence tests were conducted.
Results: The simulated pulsating blood flow was disrupted in all anastomoses, in which maximal abnormal values of the blood velocity and the WSS were identified. Flow patterns, velocity fields, WSS and viscosity changes were shown versus time in animations. The WSS was spatially and time averaged in particular fistula regions: artery, anastomosis and cannulated vein.
Discussion: This study shows a strong influence of the mesh precision in the boundary layer region on the results concerning the WSS. High and oscillating values of the WSS were obtained at the anastomoses. It may initiate stenosis that can lead to the vein thrombosis and further dysfunctions of the fistula. The WSS values in the vein receiving blood from the arteriovenous fistula are a few times lower in mature fistulas when compared to the immature ones. The WSS is thought to be an important homeostatic factor in the vein remodelling during the maturation of the fistula.

O33
HAEMODYNAMIC COMPARISON OF METAL NEEDLES AND PLASTIC CANNULAE IN HAEMODIALYSIS

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Introduction: The use of metal needles is standard practice for accessing the vascular system for haemodialysis. Plastic cannulae have been used successfully in Japan for the last 40 years mainly because they have reduced the incidence of over advancing the needle and puncturing the floor of the fistula. The return of blood via the venous needle of a haemodialysis circuit can produce potentially damaging wall shear stresses and recirculating flows in the cannulation segment which may lead to venous stenosis. This study used computational fluid dynamics to compare the haemodynamics of blood flow through metal needles and plastic cannulae.
Material and methods: Transient computational fluid dynamic simulations were conducted on an idealised cephalic vein with a 15 G Gambro metal needle and the Covidien Argyle 15 G cannula. Blood was modelled as a Newtonian fluid with density and viscosity of 1045 kg/m^3 and 0.0035 Pa.s, respectively. Blood flow rates of 200 ml/min, 300 ml/min and 400 ml/min were passed through the venous needle/cannula. The haemodynamics were compared by assessing the wall shear stresses on the blood vessel wall.
Results: Minimal difference was found for the time averaged wall shear stress between the metal needle and plastic cannula in the TAWSS along the floor of the vessel. However, the recirculating flow and particle residence time produced by the high speed exiting venous flow was reduced in the plastic cannula.
Discussion: This study highlights the potential benefits of using plastic cannula over metal needles due to favourable haemodynamic conditions, which occur because of the tapered outlet and additional side holes which reduce the velocity of the high speed venous flow.

O34
TUNNELED HEMODIALYSIS CATHETER OUTCOMES IN ELDERLY PATIENTS

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Introduction: The growing population of elderly and advanced age appears as an exclusive factor negatively influencing dialysis practice. This retrospective study evaluated tunneled catheter outcomes in an elderly patient population (>65 years) and compare them with those in a younger control group.
Material and methods: We looked at the outcome of a group of 170 patients (pts) receiving chronic HD treatment via a 262 tunneled-cuffed catheters (femoral, jugular and femoral). Criteria for catheter removal were (1) persistant bloodstream infection -CRBI (2) catheter dysfunction and (3) elective removal. Catheter-related bloodstream infection rates were calculated per 1,000 catheter days, and Kaplan Meier analysis was estimated for THC cumulative survival between two groups of pts. A Cox proportional hazards regression analysis for sex, comorbidites (diabetes/malignancy), dialysis vintage, catheter site, and total number of prior vascular access was performed between nonelderly (18-64 years) and elderly (>65 years) patients.
Results: Sixty-one tunneled catheters were placed in Group 1 -51 elderly patients (28 men and 33 women; mean age 76.5 years). The mean number of catheters per patient was 1,91 ± 2,1 (range 1-7). Duration of catheter (median) was 155,4 days (range, 6-267). Two hundred and one catheters were identified

in the control group Group 2-119 patients (50 men and 69 women, mean age 50,9 years. Duration of catheter (median) was 185,2 days (range 4-565). There was no statistically significant difference in the mean number of catheters per pts (p = 0,83) between the two groups. There was no significant difference between the two groups in the indication for catheter removal or exchange: CRBI (p = 0,65), malfunction of catheter (p = 0,78) and elective removal of cateheter (p = 0,71).
Discussion: Tunneled catheter outcomes in pts aged 65 years and older undergoing hemodialysis do not vary significantly compared with those in younger cohort.

O35
MICROEMBOLIES OF AIR ARE DEPOSITED IN LUNGS, BRAIN AND HEART IN PATIENTS
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Introduction: Previous studies show that microembolies of air develop in the haemodialysis circuit but also in the fluid infused into patients. The aim of this study was to clarify if such air embolies are immediately adsorbed when they enter blood or if they remain in circulation, to what extent such microembolies may enter into organs such as lungs, brain and heart.
Material and methods: Post-autopsy tissue from a total of 43 autopsied patients were investigated for the presence of microembolies of air. Group 1 consisted of 24 haemodialysis patients while Group 2 consisted of 19 patients who died from amyotrophic lateral sclerosis. To discriminate between air bubbles caused by artificial contamination during autopsy versus *in vivo* deposited microembolies (ME) we stained the tissue with a fluorescent antibody against fibrinogen. If a microbubble of gas is covered by a fibrin embolus it is counted as positive. Twenty-five microscopic fields (600 x) were investigated for each tissue preparation Only one tissue preparation was used for each available organ.
Results: The Table shows ME's found/tissue section, given as median and range. Number of patients (n)
In 2 of 23 of the HD patients and 10 of 19 ALS tissue without ME's were found (p = 0.002).
Significantly more ME's were found in lungs versus heart or brain.
Discussion: Data indicate that many patients are exposed to deposits of ME during hospital stay. In haemodialysis patients the risk is significantly greater for microembolies of gas. Repeated exposure such as 3 times/week in HD patients will result in accumulation of ME over time and add on to tissue injury. We recommend careful handling of infusions and injections as well as using optimal air traps in HD.

TABLE I - Distribution ME deposition in the lungs, heart and brain for patients undergoing haemodialysis and amyotrophic lateral sclerosis patients

	Pulmonary ME	Myocardial ME	Brain ME
Group 1	7, 2-17 (n = 19)	2, 1-5 (n =13)	7, 1-14 (n = 9)
Group 2	3, 0-20 (n = 17)	1, 0-5 (n =19)	2, 0-20 (n = 19)
Total	5, 0-20	2, 0-5	2, 0-20
Mann Whitney P =	0.001	0.17	0.001

O36
MICROBUBBLES IN HAEMODIALYSIS: AN ANALYSIS ON THE PERFORMANCE OF THE AIR TRAP
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Introduction: Due to the chronic nature of the haemodialysis (HD) treatment, minor imperfections in the extracorporeal system may cause significant consequences over time. Clinical studies have highlighted the possibility of small microbubbles travelling through the HD device to the patient. These bubbles lead to further pathophysiological complications (primarily seen in the lungs and brain).
Material and methods: Microbubbles of different sizes can be generated throughout the extracorporeal HD circuit and the size of the bubble is a major factor in the type of complications affecting the patient. The performance of the air trap; the only mechanism for removing air bubbles, is therefore critical. Chronic exposure to various sizes of microbubbles was analysed in detail and the performance of the haemodialysis air trap has been evaluated.
Results: Our results show that bubbles larger than 0.5 mm in diameter are likely to be removed by the air trap, however some of the smaller microbubbles are shown to pass through and enter the bloodstream.
Discussion: While the presence of various bubble sizes before and after the air trap have been investigated in previous studies, these bubbles were only counted and not tracked. The performance of the air trap for removing different bubble sizes is not understood. Here, the performance of the air trap in filtering bubbles and the possibility of different bubble sizes passing through the air trap has been evaluated. The modelled air trap is shown to be ineffective for filtering small micro bubbles.

Oral Session - Tissue Engineering: Cell Therapy, O37-O42

O37
OPTIMIZING IMMUNOSUPPRESSANT'S FOR STEM CELL THERAPY IN MUSCULAR DYSTROPHY MICE MODELS VIA NONINVASIVE IMAGING
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Introduction: Muscular dystrophies are a group of myopathies, characterized by muscle weakness and degeneration. Currently no curative treatment is available. Mesoangioblasts (MABs) have been implicated as a therapy for improving muscle strength (1, 2). To enhance cell survival, different immunosuppressive therapies, like cyclosporine A (CsA) or costimulation-adhesion blockade therapy (costim), can be used. We evaluated the effect of these different immunosuppressants on cell survival with non-invasive multimodal imaging.
Material and methods: Murine MABs were transduced with a lentiviral vector containing firefly luciferase and the human sodium iodide transporter. One million MABs were injected bilaterally in the femoral arteries of α-sarcoglycan knockout ($Sgca^{-/-}$) and nude mice with cardiotoxin damaged muscles. The $Sgca^{-/-}$ mice either received CsA continuously or a short-term regimen (day 0, 2, 4 and 6 post-transplantation) of costim. While nude mice were treated with anti-asialo. Follow-up was done using bioluminescence imaging (BLI) and positron emission tomography (PET). T-cells were isolated from $Sgca^{-/-}$ spleenand analysed via flow cytometry.
Results: We were able to visualize the cells via PET for three days and with BLI until day 21 in the $Sgca^{-/-}$ mice. The first seven days no differences in BLI signal could be observed. From day seven on a steeper decrease in signal could be observed in CsA treated animals. In nude mice, the MABs could be stably visualized for 35 days, indicating T-cell involvement. In cell treated animals there was an increase in cytotoxic T-cells. Furthermore, animals treated with costim had lower cytotoxic T-cells compared to CsA treated animals.
Discussion: We have developed a quantifiable, non-invasive, longitudinal technique to study the kinetics and biodistribution of the MABs *in vivo* using BLI and PET. We demonstrated that T-cells play an important role in cell survival and that costim is a superior immunosuppressant compared to CsA. Stable cell survival could however not yet be achieved.

O38
IMMUNE-MODULATORY CAPACITY OF MESENCHYMAL STEM CELLS (MSCS)
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Introduction: MSCs are multipotential adult progenitor cells with a capacity to differentiate along the mesenchymal lineage to form cartilage, adipose, marrow-stroma, and bone tissue and because of their capacity to secrete trophic factors that contribute to repair via the promotion of vascularization and the inhibition of cell death MSCs have a therapeutic effect in tissue and organ repair. MSCs are hypo-immunogenic and have been successfully

transfused across the human leukocyte antigen barrier to treat autoimmune disease or severe graft-versus-host disease.
Material and methods: MSCs isolated from bone marrow aspirates, cancellous bone, or adipose tissue were cultivated by plastic adherence or in hanging droplets. The immune suppression assay involved purified $CD4^+$ T cells stimulated with OKT3 and CD28 and MSCs or Treg cells as immono-regulators. MSCs were also stimulated with rhTNFa and rhIFNg, or Concanavalin (Con) A, and expression of FoxP3 was determined by FACS, Western blotting and laser confocal microscopy.
Results: MSCs like T regulatory (Treg) cells showed an immune-modulatory capacity to suppress an OKT3-mediated proliferative response of $pCD4^+$ T cells. In this immune-suppression assay 1250-5000 MSCs showed the same capacity to suppress OKT3-stimulated $pCD4^+$ T cells than 25 000-50 000 Treg cells. Immune modulation of MSCs depended on expression of forkhead box P3 (FoxP3) protein, a transcription factor to form transcriptional repression. When MSCs were activated with inflammatory mediators TNFa and IFNg, inducing phosphorylation of signaling molecules STAT1 and STAT3, or ConA no further expression of FoxP3 could be obtained. When MSCs were isolated alternatively from cancellous bone or adipose tissue no detectable foxP3 expression and very little immune modulatory capacity were observed.
Discussion: MSCs from bone marrow have strong immune modulatory capabilities that depend on the expression of the transcription factor FoxP3, which cannot be found in MSCs from other tissue sources.

O39
FLUORESCENCE PROPERTIES OF CURCUMIN-LOADED NANOPARTICLES FOR TRACKING CELLULAR THERAPY

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Introduction: The aim of this study was to analysis the feasibility to use the curcumin nanoparticles for tracking cellular therapy on histophatological analysis.
Material and methods: Curcumin-loaded polycaprolactone nanoparticles (Cur-NP) were prepared using the nanoprecipitation technique as described by Mazzarino et al (2012). Nanoparticle suspensions were characterized in terms of mean particle size, polydispersity and zeta potential using a Zetasizer Nano Series. Curcumin content and entrapment efficiency were determined by UV/VIS spectrophotometry at 420 nm.
In vitro studies were conducted on Vero CCL-81 cell line. Cells were cultured in DMEM high glucose supplemented with 10% FBS, 100 U/mL penicillin, and 0.1 mg/mL streptomycin. Cells were incubated with DMEM containing 40 µM Cur-NP in a 24-wells plate for 72 hours. Subsequently, wells were washed with PBS and photomicrographswere taken with the DAPI fluorescence filter.
In vivo studies, Cur-NPs were injected in the *substantia nigra* of the adult rat by stereotaxic surgery using the followings coordinates from the bregma (anteroposterior -5.0 mm, dorsoventral 7.7 mm, mediolateral ± 2.1 mm). It was injected 2.0 µL of Cur-NP (0.426 mg/mL) using a Hamilton syringe. After 24 h, the rat was euthanized by a lethal dose of anesthetic and the brain removed and frozen in liquid nitrogen. Tissue sections were cut using cryostatic microtome and analyzed by fluorescence microscopy Zeiss Axio Vert. A1.
Results: Nanoparticles displayed a mono disperse distribution with a mean particle size around of 200 nm, and zeta potential close to zero. Cur-NPs showed a drug content of 426 µg/mL and high entrapment efficiency, demonstrating their suitability in the encapsulation of curcumin. The Cur-NPs could be identified in Light optical and by fluorescence microscopies with the DAPI fluorescence filter *in vitro* as well in tissue biopsy after transplantation.
Discussion: Cur-NPs have a natural fluorescence and could be used for tracking cellular therapy on histopathological analysis.

O40
EFFECTS OF LIPOSOME-ENCAPSULATED HEMOGLOBIN ON SKIN WOUND HEALING IN DIABETIC DBDB MICE

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Introduction: Liposome-encapsulated hemoglobin with extremely high O_2-affinity (h-LEH, $P_{50}O_2$ = 10 mmHg) has been reported to accelerate skin wound (ulcer) healing in normal mice. We examined the effects of h-LEH in wound healing of diabetic dB/dB mice which exhibit severe wound-healing impairments as in human diabetics.
Material and methods: Full thickness dorsal wound of 6 mm in diameter with surrounding silicone stent (Fuji Systems Corporation, Yokohama, Japan) was created in diabetic dB/dB mice (Day 0, n = 14). Two days after wounding (Day 2), animals were randomized to receive intravenous h-LEH (10 mL/kg, n = 7) or saline (n = 7) as the 1st dose, which was repeated on Day 4 as the 2nd dose. The size and healing of the ulcer were analyzed by digital photometry, Laser-Doppler flow detection and blood sampling for cytokines, repeated on Day 2, Day 4 and Day 7 post wounding, when animals were sacrificed for histological studies.
Results: The ulcer size reduction was significantly retarded in dB/dB mice compared to normal mice. While ulcer size reduction remained retarded in saline-treated dB/dB mice, wound healing was significantly accelerated in h-LEH-treated dB/dB mice on Day 4 as well as on Day 7, when the level was equivalent to the normal mice treated with saline. Blood perfusion as detected by Lazar-Doppler flowmeter was significantly improved in mice treated with h-LEH. These differences became significant on Day 7, when the cytokines, IL-6 and IFNγ were suppressed significantly in h-LEH-treated dB/dB mice. Histological examination favored for the mice treated with h-LEH, which showed less inflammation and more granulation.
Discussion: The results suggest that h-LEH (10 mL/kg, hemoglobin 600 mg/kg) early after skin excision may accelerate wound healing in diabetic dB/dB mice equivalent to the normal mice. The mechanism(s) of action appeared to be more related to the early suppression of inflammation rather than accelerated aerobic metabolism.

O41
3DISCO AS THE METHOD OF CHOICE FOR CLEARING BIO-ARTIFICIAL MUSCLE

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Introduction: Recently, several clearing techniques have been published or revisited, aiming at 3D visualization of unsectioned tissue. The efficacy of these methods is mostly demonstrated for brain tissue, which has a different structural and biochemical composition compared to skeletal muscle. Therefore, we evaluated the effect of four clearing methods, Sca*l*eA2, Clear^{T2}, CLARITY and 3DISCO, on both native and bio-artificial muscle (BAM).
Material and methods: Native skeletal muscle was obtained from eGFP-positive mice. BAMs were made by mixing human myoblasts in a fibrin hydrogel, which was cast into custom-made silicone rubber molds with end attachment sites to stimulate myofiber alignment. After seven days, BAMs were fixed and cleared with four different methods. Myofibers were imaged by confocal fluorescence microscopy.
Results: Clear^{T2} did not improve visualization depth while Sca*l*eA2 performed significantly better with a visualization depth of ~300 µm versus ~150 µm for uncleared tissue. The best results were obtained with 3DISCO and CLARITY, both allowing imaging over 400 µm deep, making the microscope hardware a limiting factor rather than the transparency of the tissue. With the main objective reached, other issues determined the best clearing method for skeletal muscle. First, cleared tissue was obtained much faster with 3DISCO than with CLARITY. Second, the tissue became softer and therefore more difficult to handle during CLARITY. A hardening was observed during 3DISCO, which also better preserved the original shape of the tissue. Third, the tissue respectively expands or shrinks during CLARITY and 3DISCO. Although ideally, the clearing does not change the dimensions of the tissue, shrinkage results in an even deeper visualization.
Discussion: The above observations all point to 3DISCO as the method of choice when clearing (bio-artificial) skeletal muscle. Using 3DISCO, the full impact of further structural improvements can be evaluated, providing a unique 3D perspective in the way engineered tissues are formed.

O42
EFFECTS OF LIPOSOME-ENCAPSULATED HEMOGLOBIN ON CARDIOPULMONARY EXERCISE TESTING IN THE RAT

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Introduction: Since liposome-encapsulated hemoglobin (LEH), cellular artificial oxygen (O_2) carrier, is known to increase O_2 content in the plasma fraction,

LEH may supply extra O_2 for enhanced exercise tolerance at cardiopulmonary exercise testing (CPE).
Material and methods: Eight rats implanted with a telemetry underwent CPE [rest (5 min), 5 m/min run (5 min), 10 m/min run (10 min) and rest (5 min)] on a metabolic treadmill to monitor heart rate (HR), blood pressure (BP), whole-body O_2 consumption (VO_2) and CO_2 production (VCO_2). After the 1st run, each animal received infusion of one of, LEH with high O_2 affinity (ℓ-LEH, $P_{50}O_2$ = 10 mmHg), LEH with low O_2 affinity (h-LEH, $P_{50}O_2$ = 45 mmHg), homologous blood (RBC), saline or none as the control. The animals were returned to their cage for 2 hours, when each rat underwent the same CPE as the 2nd run to compare the difference. Animals underwent the CPE-set (1st run + medication + 2nd run) one week apart to test each treatment in a random sequence, 5 CPE-sets over 4 weeks.
Results: While VO_2 increased in response to CPE, it increased more after treatment with h-LEH or RBC in response to 2nd run while HR decreased compared to the 1st run in animals treated with h-LEH or RBC. As the result, VO_2/HR increased significantly after treatment with h-LEH or RBC compared to the other treatments. BP, VCO_2 or lactate level did not differ significantly among treatments.
Discussion: While O_2-content increase in the unit of blood is supposed to be equivalent among rats treated with h-LEH, RBC or ℓ -LEH, h-LEH may act as an "artificial O_2 carrier" better than ℓ -LEH, suggesting enhanced aerobic metabolism and improved tissue perfusion, resulting in attenuated sympathetic response or suppressed HR response to the CPE.

Oral Session - Development of valves and robots, O43-O48

O43
TAILORING EXPERIMENTAL SET-UP TO COMPARE DIFFERENT TECHNOLOGIES OF VALVE PROSTHESES

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Introduction: Sutureless bioprostheses for aortic valve replacement have been recently introduced as an effective option to expedite the implantation procedure compared to the standard, sewed-in counterparts. However, understanding of how their hydrodynamic performance compares with standard solutions is still limited. *In vivo* post-operative data, as acquired with ultrasound techniques, cannot accurately capture small differences of velocity and pressure. *In vitro* tests can replicate conditions which might be too ideal compared to physiological contexts. Aim of this study is therefore improving an experimental set-up to assess bioprosthetic valves' performance by taking into account more representative conditions as device anchoring and patient-specific geometry.
Material and methods: A sewed-in (Carpentier-Edwards Magna Ease) and a sutureless (EDWARDS INTUITY) valve of same size were included in this study. The two prostheses, commercially available, are identical in the design of the valve frame and leaflets, but they differ in the proximal anchoring system, with the sutureless device including a balloon-expandable stent in the proximal position. The hydrodynamics performance of the two devices was assessed in a pulse duplicator system (ViVitro Labs Inc, Canada), under standard operating conditions (i.e. ISO 5840). The sewed-in valve was tested with and without pledget-armed sutures. All set of tests were performed using an idealised and a patient-specific aortic root.
Results: Pressure gradients and effective orifice areas were measured for each tested valve and condition. Standard experiments showed an overall equivalent performance of the two valves tested under identical and ideal conditions. The presence of pledget-armed sutures, however, worsened the performance of the sewed-in valve. Finally, the new patient-specific block was successfully manufactured and integrated within the system, providing results comparable to clinical scenarios.
Discussion: This study confirms the importance to adapt the standard tests to include settings which are more representative of the *in vivo* working conditions.

O44
ENDOSCOPIC INVESTIGATION OF A HEART VALVE IMPLANTATION IN AN ISOLATED PIG HEART

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Introduction: The isolated heart apparatus recently has become a method to investigate cardiovascular devices or hemodynamic mechanisms *ex vivo*. In principal a pig heart is arrested by cardioplegia and explanted. The heart is then reperfused either with blood or a crystalloid physiologic solution (Krebs-Henseleit buffer), both tempered and oxygenated. The purpose of this study was to investigate the implantation procedure of a TAVI heart valve prostheses in an isolated pig heart with video endoscopy.
Material and methods: After euthanasia of a pig from an animal trial, the thorax has been opened and 1l of cold cardioplegic solution (HTK) has been administered to the coronaries. The heart was transported, cannulated and prepared under cardioplegic and cold conditions (0-4°C). After preparation the vessels were connected to a custom made isolated heart apparatus and reperfusion was achieved with Krebs-Henseleit buffer. Hemodynamic parameters, like heart rate, pressures and flow rates have been recorded. A flexible endoscope was inserted to the heart and a TAVI heart valve prostheses was implanted in aortic position.
Results: The reperfusion of the pig heart with Krebs-Henseleit buffer was successful and the hemodynamics were in an acceptable range. Endoscopic videos of the implantation procedure could be recorded, due to the transparent solution.
Discussion: The isolated heart apparatus is a suitable platform to investigate heart valve prostheses implantation with endoscopy. It provides new insides to the implantation procedure and valve behavior, which usually only can be observed under x-ray imaging.

O45
TELEOPERATION CONTROL SYSTEM FOR REMOTE SURGERY WITH PIONEER, TOUCHLESS USER INTERFACE

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Introduction: A novel control system supporting long-distance teleoperation by means of Robin Heart surgery robot used in presented project was equipped with functionality allowing connection of multiple type man-machine interfaces (MMI) both contact and touchless. Most existing motion capture systems relay on markers worn by the object during motion recording, which complicate the measurements, is not very precise and can interface with the object natural movements. The aim of described project was to develop an optimal, user friendly, touch-less interface for polish Robin Heart® surgery robot, based on new, available on the marked LeapMotion® controller to compare it to earlier MMI-s like e.g. hand or foot Master controllers.
Material and methods: Presented project uses a touch-less 3D object capture technology provided by Leap Motion and patented by David Holz. A special software was developed by authors to integrate it with control system of polish surgery telemanipulator Robin Heart. A whole master-slave control system with a surgeon gesture reading interface works in a loop repeating with 200-1000 [Hz], which controls a 4 DOFs robotic arm RHVision® for endoscopic camera holding.
Results: A special testing stand with prepared tracks to follow, for remote robot arm, with landmarks to reach was used to verify time and precision of given task realization and compare it with other man-machine interfaces like medical joystick and foot-controller. For a testing group of novice subjects, who carried out the test three times, learning rate was evaluated, where average progress of task time performing was on the level of 30% between 1st and 2nd trial and 10% from 2nd to 3rd one. Comparable best results was reached for hand joystick and gesture MMI.
Discussion: Presented system, positively verified touchless MMI, integrated into main telemanipulator control system, what can be especially useful e.g. in the environment of sterilize operation room.

O46

DEVELOPMENT OF AN AUTOLOGOUS VALVED CONDUIT (TYPE IX BIOVALVE) USING A CAGED MOLD

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Introduction: Pediatric patients with congenital heart disease would benefit from replacement heart valves. We developed an autologous valved conduit (Biovalve), formed by in-body tissue architecture technology (IBTA) using subcutaneously embedded plastic molds. Biovalves might potentially serve as pediatric replacement valves because they are composed of mainly autologous fibroblasts and collagen fibers. However the small-diameter Biovalve required for pediatric patients generally tends to be thin connective tissue which need careful surgical handling. Accordingly, we aimed to develop a caged mold with a paling structure to enhance IBTA for producing small-diameter Biovalves with robust conduits.
Material and methods: The caged mold consisted of a two-layer structure. The inner part (outer diameter, 14 mm), which mainly formed the leaflets, was surrounded by the paling (width, 2 mm) that lined the conduit at equal intervals of 1.0 mm (total length, 20 mm). A 1 mm space was designed between the inner and outer parts as the conduit wall. After the embedding period, the space for the conduit wall was completely filled with connective tissue from outside the mold via the palings. After trimming the excess peripheral tissues and removing the mold, completely formed Biovalves with approximately 1 mm conduit walls (inner diameter, 14 mm) were obtained.
Results: There was a smooth and clear boundary between the conduit and leaflets, which consisted of mainly fibroblasts and collagen fibers. The mold allowed maintenance of the structure, including the lumen, and greatly improved handling of the Biovalves.
Discussion: The paling structure facilitated the formation of approximately 1-mm thick conduit wall and leaflets through a small aperture inside the inner portion. The caged mold with a two-layer structure enabled better handling of the Biovalves, and may eventually lead to clinical applications. We hope that Biovalve with robust conduits wall will be clinically used in heart valve replacement even in pediatric patients.

O47

ANALYSIS OF THE FLOW FIELD BEHIND A MEDTRONIC COREVALVE PROSTHESIS IN THREE DIFFERENT IMPLANTATION HEIGHTS VIA PIV

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Introduction: The flow field behind a TAVI Medtronic corevalve prosthesis was investigated in three different implantation heights (normal, too high, too low) to analyze the impact of the implantation height on the flow field and on the flow through the coronary arteries.
Material and methods: A silicon model of the aorta, including the sinuses of Valsalva and both coronary arteries was manufactured. The prosthesis was inserted in the correct implantation position and then approximately 8 mm higher and lower. For the flow measurements, the CVE pulse duplicator was used to produce physiological flow and pressure curves (5 L/min and 120/80 mmHg) through the prosthesis. The flow field was investigated by particle image velocimetry technique. Two high-speed cameras recorded the particles (ILA GmbH, Jülich, Germany) in the fluid (water/glycerine mixture with a viscosity of 3.6 m Pas at 37°C), illuminated by a laser (Nd: YAG, Pegasus, New Wave Research Inc.). The flow field was divided into six planes with 5 mm distance to each other. The recorded data was post-processed using the software dynamic studio (Dantec, Denmark) and Tecplot (USA).
Results: The analysis showed that for each position, a central jet of the same maximum velocity developed in early systole. Depending on the implantation height, a different amount of fluid passed through the coronary arteries over one heart cycle. Furthermore, the inflow direction of the fluid in the near proximity of the pulmonary arteries inside the sinuses of Valsalva varies depending on the implantation height.
Discussion: The amount of flow through the coronary arteries and the inflow direction highly depends on the implantation height of the prosthesis.

O48

IMPROVEMENT AND EVALUATION OF A BIOVALVE WITH STENT FOR TRANSCATHETER PULMONARY VALVE IMPLANTATION

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Introduction: We are developing an autologous heart valve-shaped tissue with a stent (stent-biovalve) for transcatheter pulmonary valve implantation by using 'in-body tissue architecture' technology. In previous study, the leaflet shape of the developed stent-biovalve remains basically open form (OF-SBV), since the stent-biovalve was fabricated using a simple cylinder-shaped acrylic mold. As a result, the leaflets of open form could not close rapidly and it was involved in increasing the regurgitant volume.
In this study, we designed a novel mold for fabricating the stent-biovalve with closed form leaflet (CF-SBV) to reduce the regurgitant volume and evaluated the hydrodynamic performances of developed CF-SBV in *in vitro* testing for its application to the pulmonary valve (PV).
Material and methods: A specially designed, self-expandable, stent-mounted, acrylic mold with three projections for CF-SBV was placed in a dorsal subcutaneous pouch of a goat, and the implant was extracted 2 months later. Only the acrylic mold was removed from the implant, and a tubular hollow structure of membranous connective tissue impregnated with the stent strut was obtained. Half of the tubular tissue was completely folded in half inwards. Here, the acrylic mold was designed such that the half of the tubular tissue which is folded inwards becomes the closed form leaflets. The 3 commissure parts were connected to form 3 leaflets, resulting in the preparation of the CF-SBV (25-mm ID).
The CF-SBV was fixed to a specially designed pulsatile mock circulation circuit under pulmonary circulation conditions using 37°C saline.
Results: The leaflet shape was found to significantly affect the hydrodynamics of stent-biovalve. The leaflet of the CF-SBV closed more rapidly compared to the conventional OF-SBV, and reduced regurgitation rate was obtained under pulmonary circulation conditions.
Discussion: The developed completely autologous CF-SBV may be useful for PV replacement.

Oral Session - Mechanical support outcome, O49-O54

049

VENO-VENOUS ECCO2-REMOVAL: A PILOT STUDY

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Introduction: Patients with Acute Respiratory Distress Syndrome (ARDS), should be treated with lung protective mechanical ventilation (MV). Lung protective MV includes lowering of tidal volume (V_T) and plateau pressure (P_{PLAT}). It is less harmful for the lungs and associated with better outcomes. However, it is also associated with decreased lung clearance of CO_2, resulting in respiratory acidosis. Extracorporeal CO2-removal (ECCO2-R) is a new veno-venous therapy allowing CO_2 clearance. The aim of this pilot study was to evaluate whether this therapy was able to treat respiratory acidosis allowing reduction of P_{PLAT} and V_T.
Material and methods: In this single centre trial, we included patients who met the Berlin definition of ARDS and who had respiratory acidosis. The first 2 hours blood flow was at 300 ml/min, after which it was increased to 400 ml/min. During ECCO2-R (Abylcap®, Bellco) we aimed at lowering P_{PLAT} and V_T.
Results: We included 9 patients, 4 female, with a median age of 50 y [22.8; 66.5]. All patients showed a decrease of pCO_2 after 2 hours of treatment, median reduction was 28.2% [11. 6; 31.0]; p = 0.008. Five patients (56%) achieved a decrease in pCO_2 of more than 20%. The median reduction in P_{PLAT} after 5 days (D5) of treatment was 8.5 cmH_2O [5.3; 12.5]; p = 0.012. Median reduction in V_T at D5 was 1.52 ml/kg predicted body weight [0.65; 1.85]; p = 0.017. In all patients pH could be corrected to normal range values, the median difference of pH at D5 was 0.23 [0.21; 0.27]; p = 0.012. Three patients needed a blood transfusion because of bleeding.

Discussion: Veno-venous ECCO2-R is a very promising extracorporeal technique to remove CO2, allowing MV of ARDS patients with lung protective strategies. An explanation for the inter-patient variation in efficiency of CO_2 removal could not be found in our patient cohort.

O50
THE CURRENT SITUATION OF RESEARCH AND DEVELOPMENT OF PEDIATRIC VAD IN JAPAN: A CASE STUDY
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Introduction: A clinical trial for the pediatric ventricular assist device (VAD), which has already been approved worldwide, is underway in Japan. To extract regulatory issues on clinical trials of pediatric ventricular assist device and discuss the current situation of research and development (R&D) of pediatric VAD in Japan.
Material and methods: We extracted regulatory issues from one case: Japanese government eased the selection criteria for the trial after a pediatric patient died, who was excluded from the trial because she had not been registered for heart transplantation. After the patient expired, her family published a message in the media, in which they sincerely hoped for early approval of the pediatric VAD in Japan. Consequently, an academic society submitted an official request to the government for early approval of pediatric VADs. Originally, the participants in the trial must be registered for heart transplantation, however, according to the new government's instructions, patients who were not registered for heart transplantation may be enrolled in the trial based on the physicians' decision. We also discussed other issues surrounding R&D of pediatric VAD in Japan.
Results: Fundamental issue is that no pediatric VAD is approved in Japan. While easing the selection criteria of the trial could expand an access to investigational devices for patients with severe heart failure who do not have other treatment options, it violates the rigidness of clinical trial protocols. Furthermore, the access to the investigational device is strictly limited. According to the demand of pediatric VADs, our center has decided to reproduce a pediatric VAD which was approved in 1990 and out of production due to the small number of pediatric patients suitable for the device.
Discussion: The best way to ensure widespread access to investigational pediatric VAD is to shorten the time to make the device clinically available.

O51
SURVIVAL OUTCOMES IN CHILDREN LESS THAN 10 KG BRIDGED TO TRANSPLANT WITH THE BERLIN HEART EXCOR
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Introduction: Although the remarkable advances with the use of ventricular assist devices (LVAD) in adults, and the well established experience with adolescents, pneumatic pulsatile support in small children is still limited. The aim of this work is to report a retrospective review of our experience on the use of VADs in very small children (<10 kg of body weight).
Material and methods: Data of 30 consecutive children weighing less than 10 kg undergoing mechanical support with Berlin Heart (Berlin Heart AG, Berlin, Germany) as a bridge to heart transplant from March 2002 to March 2015 were retrospectively collected.
Results: The mean patient age was 12.7 ± 10.8 months. The mean patient weight was 6.5 ± 1.7 Kg. Prior to VAD implantation, all children were managed by multiple intravenous inotropes or extracorporeal membrane oxygenation (13%). Three patients required biventricular mechanical support (among patients implanted before 2010) and two patients had single ventricle physiology. The mean duration of VAD support was 115.8 ± 64.7 days and increases over the time from 2002 to 2015. Eight (27%) deaths occurred. However, in the last 20 patients (implanted between 2010 and 2015), mortality decreased to 4 patients (20%). Cause of death was neurological complication (13%) and sepsis (7%). Sixteen patients (53%) were successfully bridged to heart transplantation and six other patients (20%) are still on VADs waiting for heart transplantation. Two (7%) patients required surgical revision for a large haematoma around the aortic cannula, while 16 patients (53%) required at least one pump change.
Discussion: Mechanical support in smaller children with end-stage heart failure is an effective strategy for bridging patients to heart transplantation.

O52
RUSSIAN AXIAL-FLOW LEFT VENTRICULAR ASSIST DEVICE: RESEARCH, TECHNICAL SPECIFICATION AND CHARACTERISTICS
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Introduction: At the terminal stages of heart failure medications and therapeutic methods are useless, and there is only one way of patient's life saving-heart transplantation (only 100 operations per year in Russia annually) or implantation of a left ventricular assist device (LVAD). Actual problem of the severe heart failure treatment on the one hand and international experience of using VADs on the other hand formed the basis for the development of the Russian LVAD.
Material and methods: Rotor type blood pump is designed to provide blood flow to help left ventricle of patient's heart. The implantable pump continuously transmits fluid's energy flowing through it. The pump consists of moving parts-the impeller (rotor with three blades) and stationary parts-straight device. Blade's geometry creates profiled impeller, and the straight device is behind it. The pump is driven by an external source of power supply (two rechargeable modules in a portable version of LVAD) by electric cable going through a percutaneous lead in the patient's skin that is protected with a membrane connected to electronic control unit.
Results: From 2009 to 2014 there were consistently conducted development of the prototype, *in vivo* and *in vitro* tests, there was carried out a full cycle of certification and clinical testing. The Result is the implantation of ten LVADs in Russia (December 2014).
Discussion: The results, obtained in the research process and the positive clinical experience of LVAD's implantation is the basis for further research of the VADs development and improvement. National Research University of Electronic Technology (MIET) conducts research to develop the circulatory support system that provides adaptive changes in flow characteristics depending on the intensity of blood pumping by the heart that allow personalizing treatment of acute heart failure and increase survivability and life expectancy with implanted circulatory support system.

O53
SINGLE CENTER EXPERIENCE: 100 HEARTMATE II IMPLANTATIONS; WHAT DID WE LEARN?
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Introduction: Continuous flow ventricular assist devices have gained their place in treatment of end-stage heart failure in the last decade. Over the last years the outcomes have improved significantly with one year survival reaching 80%. When reaching the 100th consecutive HeartMate II (HM II) implant in our hospital we conducted a review of our own series. Goal was to identify key points for improved survival.
Material and methods: Between 2007 and 2014, one hundred HMII assist devices were implanted in the University Hospital Leuven, Belgium. 83 male and 17 female patients with a mean age of 50,3 ± 14,0 years (range 11,7-72). All patients were classified according to the INTERMACS classification, 34% were in class I and 66% class II or higher. Eight patients were on ECMO before receiving a HM II.
Kaplan Meier survival analysis and Cox proportional Hazard regression analysis were done.
Results: Overall one year survival was 75,3%. A significant lower survival could be found for the time of pump implantation (first 20 patients versus next 80; ($p = 0.006$)), prior ECMO support ($p = 0.04$), the age at the time of assist implantation ($p = 0.03$) and the preoperative level of creatinine ($p = 0.01$). Even after correction for ECMO support, age and preoperative creatinine time of implant remained a significant risk factor for death. The number of reinterventions for bleeding was higher in these first 20 patients (40% vs. 18%; $p<0.05$).
Discussion: We observed an explicit learning curve in our patient series. Retrospective analysis of our data show that the patient demographics of early versus late implantation was not different. There was however a significant reduction in the number of reinterventions for bleeding. We believe that optimizing our perioperative anticoagulation protocol played an essential role in optimizing patient survival.

O54
EXERCISE CAPACITY IN FULL SUPPORT AND PARTIAL SUPPORT PATIENTS: A COMPARATIVE ANALYSIS
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Introduction: Ventricular assist device is a consolidated therapy for end-stage heart failure, but some questions about patients' quality of life still remain. In this work we compared the exercise capacity of full support (FS) and partial support (PS) patients.
Material and methods: 27 FS patients (24 Heartmate II and 3 HeartWare HVAD) and 7 PS patients (Circulite Synergy Micropump) underwent maximal cardiopulmonary ergometer tests. Maximum heart rate (HRmax), heart rate reserve (CR), peak oxygen uptake (VO2p) and ventilatory efficiency slope (Ve/VCO2) were calculated for each test. Data were expressed as percentage of expected values (%HRmax, %CR, %VO2p and %Ve/VCO2) calculated according to patient's gender, age and weight. Student *t*-test and Wilcoxon test were used to compare FS and PS groups.
For each patient, the slopes %HRmax/time, %CR/time, %VO2p/time and %Ve/VCO2/time were calculated with a regression between the values of these variables at different exercise tests and the time these tests were performed (days after VAD implantation). One sample *t*-test and Wilcoxon test were used to evaluate if these slopes were different than zero, that would indicate a change of these variables over time.
Results: The analysis of slopes reveal that all variables do not change over time for both FS and PS. Only %CR/time for FS that is significantly different than zero (0.043 ± 0.129, p<0.05). No significant differences were found between FS-PS for %VO2p (48 ± 13%-45 ± 7%), %Ve/VCO2 (154 ± 38%-133 ± 22%) and %CR (59 ± 26%-42 ± 24%). %HRmax was statistically different in the two groups (77 ± 14%-65 ± 16%, p = <0.05). A correlation analysis of PS and FS data together showed a relationship %CR-%VOp2 (r = 0.531, p<0.01) and %HRmax- %VO2p (r = 0.448, p<0.01).
Discussion: FS and PS patients show a comparable exercise performance. Further analysis should be conducted in a larger population to better evaluate the role of HR and the impact of FS and PS on it.
Acknowledgement: This work was supported by Marie Curie Scholarship (PIEF-GA-2013-624296).

Oral Session - Tissue Engineering: Modelling, O55-O59

O55
PROBE MOLECULES LOADING INTO RED CELLS TROUGH HYDRODYNAMIC FOCUSING: A COMPUTATIONAL EVALUATION
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Introduction: This work aims at studying the fluid-dynamic conditions allowing the encapsulation of probing molecules (PM) into Red Blood Cells (RBCs) by applying shear stresses (τ) on their membrane. Indeed, it is well-known in the literature that this process enhances the opening of the pores, thus allowing the diffusion of solutes. In our microdevice τ were applied through a single passage in a sheath flow focuser, designed to drift the cells to a controlled τ solicitation zone.
Material and methods: A computational model using Comsol Multiphysics was developed; the geometry is a cross-shaped microchannel (MC) with 50*50 µm cross-section and 87 mm length. Velocity (v), volume fraction of dispersed phase (rd) and τ for a suspension of RBCs and PM (FITC-Dextran) in a Phosphate Buffer were evaluated, varying the flow rate of RBCs suspension (Qb), sheath flow (Qf) and Ht. When the pair of τ values and time results subhaemolytic (according to Tillman Diagram (TD)), and the RBCs transit time is higher than the time required for PM diffusion into RBCs, encapsulation can be promoted. A dedicated efficiency index was used to evaluate the flow conditions (v, rd, τ) that are thought to increase the encapsulation rate.
Results: Taking into account the efficiency index, the position on TD and the overall pressure drop, suitable fluid-dynamics conditions were: Qb = 40 µl/min, Qf = 7 µl/min, PM 2 mM for Ht = 5% or Qb = 33 µl/min, Qf = 5,5 µl/min, PM 4 Mm, and Ht = 10%. In these conditions the area occupied by RBCs is the 75% of the channel section. The resistance of the MC and their connections to the pumping system to the high pressure evaluated through CFD (respectively of 4 and 3 atm) was verified.
Discussion: The model allows the characterization of RBCs fluid-dynamic in simple microfluidic devices and to identify the optimal conditions to promote PM encapsulation. This model will be used to define appropriate test conditions.

O56
MODELLING AND QUANTIFYING THE FLUID TRANSPORT THROUGH POLYLACTIC ACID SCAFFOLDS
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Introduction: As part of our research on understanding the determinants of intraperitoneal (IP) chemotherapy, we are developing controlled environments in which tumor cells can be seeded and cultured in order to test the therapeutic effects of cytotoxic drugs. In this work, we aim to mimic tumor tissue by developing scaffolds, of which the permeability characteristics can be theoretically predicted based on its printing parameters.
Material and methods: Three polylactic acid (PLA) scaffolds were printed using a target filament thickness of 400 µm and an interfilament distance of 500 µm. To measure the scaffold permeability experimentally, a gravity-based setup was built to perfuse the scaffold with a constant fluid height of 20 cmH_2O (ΔP) and measure the resulting flow (Q). The Darcy permeability k [m^2] was calculated based on the Darcy equation for porous media as follows for a cylindrical scaffold with length l [m], area A [m^2] and μ the dynamic viscosity [Pa.s]:
$k = -(Q \cdot l \cdot \mu)/(A \cdot \Delta P)$
Next to the experimental approach, a virtual 3-dimensional scaffold model was created in pyFormex using the printing parameters and meshed in ICEM. Subsequently, CFD simulations were performed to calculate the theoretical permeability, allowing comparison with the experimental results.
Results: The experimentally measured permeabilities of the scaffolds are $7.27 \pm 0.10 \cdot 10^{-10}$, $6.89 \pm 0.05 \cdot 10^{-10}$ and $7.70 \pm 0.14 \cdot 10^{-10}$ m^2, respectively, resulting in an overall average of $7.29 \pm 0.36 \cdot 10^{-10}$ m^2. The theoretical permeability obtained from the CFD simulation was $7.85 \cdot 10^{-10}$ m^2.
Discussion: In this work, a framework is presented for developing scaffolds of which the permeability characteristics can be predicted based on their printing parameters. Comparison of the experimental and virtual permeability values showed that values were in the same order of magnitude, but virtual permeability was slightly overestimating the experimental values.

O57
DESIGN CRITERION FOR RADIAL FLUX UNIFORMITY IN RADIAL-FLOW PACKED BED BIOREACTORS FOR BONE TE BASED ON A 2D FLOW MODEL
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Introduction: Osteogenic cells cultured in clinical-scale annular porous scaffolds in radial flow packed-bed bioreactors (rPBBs) may be effectively used to engineer clinical-scale bone tissue substitutes. Although generally neglected, the distribution of radial flux depends on the design of rPBB void spaces and construct transport properties. Uniform radial flux distribution along the construct length is essential to enable uniform cell survival, proliferation, differentiation and tissue formation. Criteria for the optimization of rPBB geometry (its inner hollow cavity, construct and peripheral annulus) to ensure flux uniformity are not yet available. In this study, a model-based criterion is proposed to optimize rPBB geometry to ensure uniform radial flux distribution for steady operation.
Material and methods: A 2D mathematical model was developed to describe stationary medium transport in the three compartments of axisymmetric rPBBs according to the Navier-Stokes and Darcy-Brinkman equations. Conservation equations were solved numerically for construct geometries and conditions typical of bone tissue engineering. Flux uniformity was assessed in terms of the average difference between model-predicted local and length-averaged fluxes.
Results: Model predictions showed that radial flux distribution along the construct depends on construct length and permeability, inner hollow cavity radius and peripheral annulus thickness as well as on operating conditions. Geometries giving total axial pressure drop along the rPBB void spaces lower than 10% of that radial across the construct at any operation yield less than 10% deviation from ideally uniform radial flux distribution.

Discussion: We conclude that meeting this pressure drop requirement is a feasible criterion to design rPBB geometries yielding a uniform radial flux distribution along the construct length under any operating condition.
Acknowledgement: Study co-funded by the Italian Ministry of Instruction and University (MIUR) (Project PRIN 2010, MIND). DD and GFDL were supported by grants of the European Social Fund and ARUE, respectively.

O58
PERSONALIZING BONE TISSUE ENGINEERING TREATMENTS: FINDING AN OPTIMAL TIME WINDOW TO ENHANCE BONE HEALING
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Introduction: In this study we improved an existing computational model of bone regeneration to correctly predict the vascularized fibrous tissue that is formed in the central callus area of a non-healing large segmental defect. In addition, we explored the efficacy of a delayed injection of mesenchymal stem cells (MSCs) and/or osteochondrogenic growth factors to enhance bone healing.
Material and methods: In order to improve the correspondence of the computational predictions with the histological data, the following parameter values were altered: increase of VEGF production by fibroblasts, increase of the duration of fibroblast invasion and increase in the rate of fibroblast proliferation. An adapted logistic growth function was used to account for limitations on available space for cellular growth and matrix deposition. Chemotaxis was the only driving force for endothelial cell migration.
Results: The novel model correctly predicted the formation of vascularized fibrous tissue in the central callus area. Next, we investigated the optimal timing for a single injection of MSCs and/or growth factors. We found that the injection of only growth factors did not improve bone formation. The injection of MSCs was found to be morebeneficial between post fracture day (PFD) 21 and 35 since by that time the vasculature in the interfragmentarygap was already partially restored, in this way sustaining the viability of the injected cells. Similar conclusions could be drawn for the combined injection. At later time points, injection did not have any positive effect, because of the presence of excessive (vascularized) fibrous tissue that prevented bone formation.
Discussion: Our simulation results suggest that there is an optimal time window for cellular injections to enhance bone regeneration, which seems to be related to (partial) revascularization and absence of excessive fibrous tissue formation. Future work will focus on the validation of the existence of such a window and its dependence on the patient-specific host environment.

O59
MODELLING MASS TRANSFER IN AN EXTRACORPOREAL BIOARTIFICIAL LIVER DEVICE
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Introduction: Development of extracorporeal bioartificial liver devices is often hindered by hepatocytes' peculiar requirements. High oxygen uptake and wide range of metabolic functions in turn necessitate enhanced mass transfer rates. Unfortunately, local concentrations of nutrients and cellular products are currently impossible to measure. In this study, mass transfer modelling is employed to evaluate the cellular microenvironment in a hollow fiber membrane bioreactor (HFMBR).
Material and methods: In our convection-enhanced HFMBR, provision and removal of culture medium is realized through separate hollow fibers (HFs) in a crossed configuration, mimicking the blood capillary network. Numerical analysis of the mass transfer model for dissolved oxygen concentration (DOC) was performed using COMSOL Multiphysics. Two types of cellular compartments were considered: spheroids trapped between HFs, and a cellular layer surrounding the HFs. Advection was limited by the maximum shear stress tolerated by hepatocytes.
Results: Sufficient oxygen supply to a mass of cells depends on the number of constituent cells, represented here by the spheroid diameter and the layer thickness. Preliminary results indicate sufficient oxygen supply to large spheroids (400 µm diameter) with DOC dropping 60% to 106 µmol/L at the center, i.e. higher than DOC in periportal zone *in vivo.* However, investigation of DOC in the cellular layer suggests that the thickness should not exceed 100 µm ($D_{layer}/D_{membrane}$ 1.4).
Discussion: The model provides deep insight into DOC in an HFMBR. It significantly facilitates optimization of the operative culture conditions, spheroid size, and seeded cell density in each system. Consequently, an *in vivo*-like microenvironment can be achieved to prolong viability/functionality of hepatocytes.
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Oral Session - Development in Mechanical Support II, O60-O65

O60
AN ANATOMICAL MOCK HEART CIRCULATION LOOP WITH CONTRACTING SILICONE VENTRICLES AND AN ANATOMICAL AORTA
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Introduction: Mock circulation loops (MCLs) are often used as *in vitro* test bench to investigate VAD assisted heart circulation systems. To investigate the effect of different assisting methods on the flow distribution in the ventricle/aorta, the MCL should reproduce important natural characteristics. Besides auto regulation also contraction of the ventricles, anatomical shape of the aorta and clinical inflow/outflow cannulation method of a VAD are of interest.
Material and methods: A MCL with systemic and pulmonary side was developed and tested. Ventricle molds were produced based on MRI data and cast with silicone, likewise for the anatomical aorta. Aramid fibers on the silicon ventricle forced the ventricle torsion. Both apexes were connected to a rotating hollow shaft enabling the rotation of the ventricle and the connection of a VAD. Each ventricle was placed in a tank filled with water and air simulating a definite compliance while the connected linear motor was expanding the ventricles throughout diastole. During that, the torsion angle (α_{min}, α_{max}) was measured at the apex and a pressure-volume loop was measured by a catheter inserted in the left ventricle.
Results: The aramid fibers (E-modulus: 105 GPa) could partially prevent dilation of the silicon ventricle during diastole, and a contraction of the ventricle was achieved. The torsion angle had a value of α_{min} = 3' and α_{max} between 30'-45' depending on the type of ventricle (aramid fiber angle, density and ventricle silicon thickness). Physiological pressure-volume loops with clear four phases were reached with and without connected VAD (inflow: apex, outflow: ascending aorta).
Discussion: An MCL with a contracting Mock-Heart and an anatomical aorta was constructed enabling clinical cannulation methods of VADs under physiological and pathophysiological conditions. The transparent design enables following the catheterization process offering a good method for clinical training of the pressure-volume measurement system. Furthermore, detailed investigations of flow characteristics inside the ventricle/aorta become possible.

O61
PIV FLOW MEASUREMENTS IN AN ELASTIC MODEL OF THE AORTIC ARCH WITH ADJUSTABLE COMPLIANCE
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Introduction: The Particle Image Velocimetry (PIV) is a common optical measurement technique to perform *in vitro* flow investigations with a high spatial and temporal resolution. In order to provide optical accessibility the measurements have to be carried out in transparent models. These models usually lack of elasticity, which is an important property, especially of the aorta. The purpose of this study was to build a transparent elastic aortic model with an adjustable compliance, fulfilling the requirements to PIV models and to perform flow measurements on this model.
Material and methods: A transparent silicone replica of the aorta has been manufactured and fixed in a fluid filled box of Plexiglas. A mock circulation loop was connected to the aorta, in order to simulate the pulsatile heart inflow. An adjustable air chamber was connected to the fluid filled box, enabling an adjustable aortic compliance. A particle seeded transparent blood analogue fluid was used (water-glycerol). A laser light sheet illuminated the

aortic outlet cross section. A camera positioned orthogonal to this plane recorded particle images and wall movements. Pressure was recorded simultaneously. The recorded images have been analyzed, regarding compliance and 2D flow fields.
Results: Time-resolved flow fields behind the aortic mechanical valve could be measured. Pressure curves and diameter changes of the aorta were recorded simultaneously. Herewith, the compliance could be calculated and was found to be in a range of 0.13-0.17%/mmHg, which is comparable to a person of 55-65 years (literature data).
Discussion: PIV flow measurements could be performed in a fully transparent model of the aortic arch with an adjustable compliance, overcoming present limitations in the field of aortic *in vitro* flow investigations regarding compliance.

O62
PROTOTYPE DEVELOPMENT AND HEMODYNAMIC ANALYSIS OF A FULL-JACKET CARDIAC ASSIST DEVICE FOR DILATED CARDIOMYOPATHY
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Introduction: Ventricular assist devices including total artificial hearts are potent alternative or bridge therapy to heart transplants for dilated cardiomyopathy patients. However, ventricular assist devices have problems of biocompatibity, hemocompatibility, and thromboembolic events especially in younger patients. The present study examined jacket-type direct cardiac compression device using artificial rubber muscles to determine hemodynamic effects in young swine models of dilated cardiomyopathy.
Material and methods: Dilated cardiomyopathy was established in 6 pigs (6-8 weeks of rapid right ventricular pacing, average weight of 22.6 ± 2.1 kg). The device was designed using pneumatic rubber muscle (Fluidic Muscle, FESTO, Esslingen, Germany). The device can be synchronized swine hearts by sensing atrial amplitude through atrial pacemaker electrodes. Hemodynamic parameter was monitored under baseline conditions, after the assistance, and after inducing ventricular fibrillation. The device was implanted through median sternotomy. Hemodynamic data was acquired using PiCCO2, left ventricular pressure monitoring, and epicardiac echo.
Results: The device worked powerfully, coordinating with native hearts' movements. Direct epicardiac assistance showed significant improvement in hemodynamic data. Cardiac output improved from 1.39 ± 0.24 L/min to 1.96 ± 0.46 (p = 0.02). Stroke volume (14.5 ± 3.2 ml versus 20.1 ± 4.3 ml, p = 0.04) and ejection fraction (25.2 ± 3.6% versus 47.7 ± 7.8%, p<0.01) were also improved after assistance. Left ventricular end-diastolic volume and pulmonary arterial wedge pressure didn't significantly change with treatment. After inducing ventricular fibrillation by ejection of potassium chloride, cardiac output maintained 1.33 ± 0.28 L/min and systemic arterial systolic pressure maintained 74.5 ± 21.7 mmHg.
Discussion: Jacket-type direct epicardiac assistant device demonstrated improvement in hemodynamic data in dilated cardiomyopathy model. Although there are still needs for improvements in device component, direct cardiac assistance may be a good alternative to recent heart failure device therapies.

O63
GASTROINTESTINAL BLEEDING AND CONTINUOUS BLOOD FLOW: COULD HYPOPERFUSION EXPLAIN THIS RELATIONSHIP?
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Introduction: It is recognized the relationship of gastrointestinal bleeding events and the loss of pulsatility of the blood flow, as seen with continuous blood flow VADs and severe aortic stenosis. What still remains unknown is the physiopathological mechanism. One of the hypothesis coined is the associated hypoperfusion of the small intestine with the consequent hypoxia and the development of angiodysplasias. In this experimental model, we analyze and compare the perfusion of the small intestine with pulsatile and non-pulsatile blood flow.
Material and methods: 22 minipigs with a mean weight of 29,5 +/- 9,6 kg were assigned to receive one LVAD. We used two types of pulsatile VAD (Berlin Heart EXCOR® and a Tubular Pump designed in our laboratory), and one type of non-pulsatile device (BIO-MEDICUS®). For analyzing the small intestine perfusion we used coloured microspheres. Once the pig was anesthetized and intubated, a median sternotomy was carried on. The aorta and the left ventricle apex were cannulated. Three kinds of coloured microspheres were delivered in the left atrium in three moments: before initiation of assistance (white), after 30 minutes of total assistance (orange) and after another 30 minutes of partial assistance (violet). Finally, the pig was sacrificed and biopsies of the small intestine at the terminal ileum were taken.
Results: After comparing the quantity of microspheres in partial and total assistance with the quantity of microspheres before initiation of assistance (basal conditions), no statistically significant differences were observed. Moreover, comparing the quantity of microspheres between the different pumps did not find any difference. Results are expressed as a percentage relative to basal conditions (Tab. I).
Discussion: Attending to our results, non-pulsatile blood flow is not associated with hypoperfusion of the small intestine Therefore, the greater incidence of gastrointestinal bleeding events in patients with continuous blood flow cannot be explained by this situation.

TABLE I - Percentage of microspheres relative to basal conditions with the different LVAD in the small intestine

Bomba	Media	Error St.
Biom	110,0	33,7
BT	113,7	36,4
BH	180,8	29,7

O64
TURBULENCE LENGTH SCALES IN A HEARTMATE II ROTARY BLOOD PUMP
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Introduction: Corpuscular components of blood can be damaged or activated when exposed to external forces caused by shear. Typical fluid dynamic based models for the prediction of blood damage in artificial organs consider the mean flow shear whereas the proper incorporation of turbulence remains unclear. It is believed that the ratio of the size of turbulent structures to the size of the corpuscular blood components affects the transmission of force. Thus the objective of this work is to find out which eddy sizes are found in a clinically used rotary blood pump, which is the HeartMate II (HM II).
Material and methods: As the original HM II rotary blood pump does not permit turbulence measurements, a 3:1 up-scaled model with an acrylic housing is used for the research. This enables the use of a two component laser Doppler anemometry system to measure the time resolved velocity fluctuations inside the pump. Measurements were taken up- and downstream of the rotor blades. The turbulence spectrum in terms of wavenumber and turbulence energy were then evaluated at the center of the flow in order to obtain information on the size of turbulent structures or so called turbulent eddies.
Results: The Kolmogorov length scale represents the size of the smallest turbulent eddies. It was estimated to be ≈70-80 µm corresponding to ≈25 µm in an original sized HMII pump model. Additional data on mean flow profiles and rms-velocity fluctuations were obtained.
Discussion: Turbulence length scales were measured in an up-scaled model of a HM II rotary blood pump. The size of turbulent eddies is found to be larger than the largest corpuscular blood components in the center of the flow. The existence of a universal equilibrium range could be shown. Information about the length scales inside the boundary layers of the experimental model was not obtained.

O65

ESTIMATION OF LEFT VENTRICULAR PRESSURE WITH THE PUMP AS 'PRESSURE SENSOR' IN PATIENTS WITH A CONTINUOUS FLOW LVAD

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Introduction: Long-term ventricular support with Left Ventricular Assist Devices (LVADs) requires intensive and frequent monitoring of the patient. To date, ventricular function is measured through echoscopic examination of ejection fraction. This yields limited information on the remaining functionality of the ventricle with the supporting pump. In this study, we aim to assess ventricular function by determining left-ventricular pressure (p_{lv}), using the LVAD as a sensor.
Material and methods: The input parameters of this method are pump flow, aortic pressure and properties of the outflow graft (resistance and inertance). Pressure drop was estimated over the outflow graft ($dp_{outflow\ graft}$). Pressure head (dp_{lvad}) was estimated from pump flow with a static and a dynamic pump model. The estimated $dp_{outflow\ graft}$ and dp_{lvad} and measured aortic pressure were used to calculate left ventricular pressure. Moreover, the parameters dp/dt_{max} and mean, minimum and maximum left ventricular pressure were derived. The method was validated with a porcine *ex-vivo* beating heart model, instrumented with a continuous flow VAD. Measurements were done on four hearts supported with a Micromed DeBakey VAD and three hearts supported with a Heartmate II. Data were collected at the baseline, without LVAD support and with an increasing level of LVAD support. During each measurement aortic and left ventricular pressure (p_{ao} and p_{lv} in mmHg), pump flow (Q_{lvad} in L/min) and outlet pressure of the LVAD (dp_{out} in mmHg) were recorded.
Results: The estimation of left ventricular pressure was accurate for both pumps. Mean and minimum pressure were estimated with high accuracy. The degree of accuracy of the estimated p_{lv} was proportional to the degree of accuracy of the pump model.
Discussion: With the model, left ventricular pressure in LVAD supported patients can be monitored sufficiently reliably in case pump flow, aortic pressure and the properties of the outlet graft are determined accurately.

Oral Session - Build-up of Vascularized Tissue by 3D-Printing Technologies: ArtiVasc 3D, O66-O71

O66

ARTIFICIAL BLOOD VESSEL SCAFFOLDS MADE BY 3D PRINTING

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Introduction: For the development of multi-layered soft tissue, e.g. full-skin equivalents vascularization for cell nutrition is one of the main challenges in tissue engineering. Today most tissue engineering approaches develop tissue, which needs no vascularization like cartilage or thin cell layers. ArtiVasc 3D uses Additive Manufacturing (AM) technologies, inkjet printing and stereolithography to build up branched, porous blood vessel structures which should provide cell nutrition supply.
Material and methods: The inkjet printing and stereolithography combination are under investigation to position photocurable materials and to build up larger vessel structure with an inner diameter of approximately 2 mm by inkjet. Process parameters which allow photocuring either by a UV-lamp or by laser based stereolithography (STL) have to be evaluated. The STL process allows structuring of thin vessel walls with a thickness of approx. 10 µm. By STL pores can be structured in the vessel walls which allow the nutrition exchange between the blood and the surrounding cells.
Results: It was shown that porous blood vessels can be structured in the given design just using the single STL process. Combination experiments with the inkjet printing and STL show that linear tube structures can be build.
Discussion: Linear and branched elastic scaffolds for blood vessels can be build. Those vessels will be used to build up a multilayered vascularized tissue.
Acknowledgement: The ArtiVasc 3D project is funded by the European Commission under the grant agreement no 263416.

O67

DEVELOPMENT OF A THREE LAYERED SKIN MODEL CONSISTING OF A FATTY TISSUE LAYER WITH DERMIS AND EPIDERMIS

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Introduction: *In vitro* engineering of autologous full-skin equivalents is still a major challenge for the treatment of congenital deformities, tumor resections or high-graded burns. To date, no suitable replacement is available. Here, we evaluated the suitability of mature adipocytes and adipogenic differentiated stem cells in co-culture with fibro-blasts and keratinocytes for the composition of a full-skin equivalent.
Material and methods: Cells were isolated from human skin tissue. Full-skin equivalents were built up by encapsulating mature adipocytes or stem cells into an extracellular matrix like hydrogel. This layer was overlaid by a dermis consisting of fibroblasts and an epidermis consisting of keratinocytes. Cells in the full-skin equivalents with stem cells were differentiated into the adipogenic lineage for 14 days. Subsequently, cultivation under airlift conditions for 14 days allow a stratification of the epidermis. To determine tissue morphology H&E staining was performed and compared to native skin. The expression of cell-specific markers was evaluated. To test functionality, release of several adipokines was measured.
Results: Current results demonstrate that adipocytes and differentiated stem cells are suitable for the composition of full-skin equivalents. Under optimized media conditions, all cells stayed morphologically stable and a successful differentiation of the epidermal layer was possible. The tissue morphology was comparable to native skin. Mature adipocytes and stem cells differentiated into the adipogenic lineage released specific adipokines. Cells in the full-skin equivalent expressed cell specific markers.
Discussion: The composition of a full-skin equivalent is possible when using mature adipocytes or adipogenic differentiated stem cells for the composition of the subcutaneous fatty tissue. Our long-term goal is the composition of large vascularized full-skin equivalents supplied by a vascular system and cultured in a bioreactor.
Acknowledgement: The ArtiVasc 3D project is funded by the European Commission under the grant agreement no 263416.

O68

ADDITIVE MANUFACTURING (AM) BASED VASCULARISED SCAFFOLD DESIGN FOR SOFT TISSUE ENGINEERING

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Introduction: The aim is for modelling and design of an additive manufacturing based vascular system that effectively delivers nutrients from blood to the surrounding tissue. Detailed aims can be divided as:

1. To investigate the nutrient permeation within the vascular system to the cells.
2. To identify the requirements for the blood flow through the system and provide an informed design specification.
3. To develop design tools for generating highly complex 3D CAD models of optimum vascular systems.
4. To translate 3D models into an appropriate data format for the latter additive manufacturing processes.

Material and methods: In order to obtain an optimised vascular vessel network in which nutrient can permeate and be consumed by cells sufficiently, simulations were carried out avoiding time consuming experiments. Simulation division established two main models which are 1) nutrient diffusion and 2) CFD in vascular vessels. Design criteria were obtained thanks to simulations which will guide the design work. A 2D vascular vessel topology was obtained and transferred into its 3D form ready for manufacturing using computer aided design techniques. Further customised data format are obtained from the 3D model and will be used for various manufacturing processes such as ink jetting

or SLA. Printed samples were available for either biological or physical testing. A feedback would available helping optimising the simulations and parameter selections.
Results: Output from design and modelling work includes an established CFD model for vascular branching, a diffusion model for porous vascular wall; an automatic 3D modelling tool; and a direct slicing tool.
Discussion: Simulations carried out in this project played an important role to guide designing the vascular vessel network in the skin patch. Optimised 3D vascular vessel network were obtained which gave sufficient and distributed nutrient profile.

O69
NOVEL POLYMERIC SCAFFOLDS FOR SOFT TISSUE ENGINEERING
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Introduction: ArtiVasc 3D is a multinational, interdisciplinary project aiming to develop an artificial vascularized skin substitute. The three layered-skin model consists of dermal and epidermal cell layers completed with vascularized bioartificial fatty tissue. The generation of such a complex tissue substitute sets high demands for material syntheses, properties and processing. The scaffold material should fulfil the requirements for soft tissue engineering and serve as a framework for cell co-culturing and proliferation. A material for 3D printing of a functional vascular network is needed.
Material and methods: Polymeric biomaterials play an important role in engineering of tissue constructs. In this new approach vascularized soft tissue scaffolds are produced of hydrogels combined with electrospun meshes and 3D printed vascular structures. First screening of suitable materials was based on their chemical, physical, thermal and mechanical properties followed by studies related to processability, stability and cytocompatibility. Further studies on biofunctionalization, cell cultivation and *in vivo* behavior are ongoing.
Results: Hydrogel formation of a variety of photochemically crosslinkable biopolymers crylated/methacrylated hyaluronic acid and methacrylated gelatin) and their stability is proven. Electrospinning parameters for many biodegradable thermoplastic polymers have been clarified and materials processed into fleeces. Typically the fleeces consist of fibers with micrometer scale fiber diameters. Photocurable materials have been developed with tailored viscosity profiles and crosslinking rates for 3D printing of elastic vessel structures. Cytocompatibility has been evaluated for the most promising materials.
Discussion: Within ArtiVasc 3D project we have been able to successfully produce materials for each scaffold component, i.e. vascular structure, hydrogel and surrounding fleece, with respect to processing methods. These materials will be further optimized to build up a multilayered vascularized tissue.
Acknowledgement: The ArtiVasc 3D project is funded by the European Commission under the grant agreement no 263416.

O70
BIOPLOTTING OF INTERCONNECTED HYDROGEL SCAFFOLDS BASED ON MODIFIED PLURONIC F-127
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Introduction: Hydrogels composed of Pluronic® F127 derivatives were investigated as possible HepG2 cell supports to assess their applicability for tissue engineering purposes. To enable the production of complex three-dimensional and fully interconnected scaffolds, the Bioplotter™ technology was applied.
Material and methods: For the synthesis of photo-polymerizable Pluronic® F127-BMA and F127-Ala-L, methacryloyl chloride was applied, thereby introducing methacrylate end-groups. For the bio-inspired enzymatic pathway, phenolic end-groups were introduced (F127-SATA and F127-PNCTA). The macromonomers were characterized for their micelle formation and gelation behaviour. The hydrogels were characterized for their sol/gel fractions, their temperature-dependent swelling properties, their mechanical properties (i.e. texturometry) and drug release profiles. The 3D construction of the scaffolds occurred in a laminar fashion through a computer-controlled deposition of the material. Finally, the hydrogels were applied as encapsulation matrices for HepG2 cells and cell viability studies were performed.
Results: The Pluronic® derivatives were successfully synthesized, showing a high degree of substitution (>90%). The hydrogels developed were characterized in depth and were suitable to be applied as starting materials to fabricate 3D scaffolds using the Bioplotting™ process. Preliminary biocompatibility and cell viability studies using HepG2 indicated that the enzymatic crosslinking strategy showed a significant positive effect on the cell viability of the HepG2 cells.
Discussion: The results indicated that 3D scaffolds can be successfully developed starting from various Pluronic® F127 derivatives and by applying different crosslinking strategies. At present, the potential of the scaffolds developed to function as cell carriers is further evaluated. Future work will focus on the fine-tuning of the biocompatibility as well as on the 3D Bioplotting of hydrogels containing encapsulated cells.
Acknowledgement: The authors would like to acknowledge the research Foundation Flanders (FWO-Flanders) and the IWT (Agency for Innovation by Science and Technology, Belgium, IWT-SBO HEPSTEM project) for the financial support.

O71
ADDITIVE MANUFACTURING OF CERAMICS-BASED BIOMATERIALS FOR APPLICATIONS IN BONE TISSUE ENGINEERING
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Introduction: Due to their high precision and accuracy, additive manufacturing (AM) technologies based on photopolymerization have gained increasing interest for the application in tissue engineering (TE). Because of the nature of photopolymerization, scaffolds based on this fabrication technology were usually based on polymers. Nonetheless, due to the similarity to native bone tissue, compounds based on bioresorbable ceramic materials such as tricalcium phosphate (TCP) would have preferable properties for this application.
Material and methods: This work presents results regarding the shaping of TCP-based materials by means of the recently introduced Lithography-based Ceramic Manufacturing (LCM) technology, which is a slurry-based process that relies on the selective curing of photosensitive ceramic suspension.
Results: The layer-by-layer principle of this method enables the fabrication of highly intricate structures with virtually no limitations regarding geometrical complexity and enables the fabrication of highly complex architectures. Features like defined channels with diameters around 200 µm or a wall and strut thickness of down to 150 µm can already be realized. By using newly developed non-toxic photocurable monomers it is also possible to produce highly biocompatible and bioresorbable composites based on TCP. By treating the fabricated composites at elevated temperatures it is also possible to remove the organic matrix and sinter the TCP particles together to give the neat ceramic bodies. By optimizing the slurry preparation und adding various dopants it was possible to achieve improved bending strength of 33 MPa while still maintaining the same level of microporosity of 15% for the neat TCP. Results of currently ongoing *in vitro*- and *in vivo*-studies show good biocompatibility of these new materials and underline the potential of this new manufacturing paradigm for TE applications.
Discussion: Scaffolds, cellular structures or parts with defined macroporosity can be shaped by means of LCM in order to provide environments for cells to adhere, migrate and proliferate throughout the structure.

Oral Session – Modelling VAD's, O72-O77

O72
VERIFICATION OF A NUMERICAL MODEL TO SIMULATE THE CAVO-PULMONARY ASSISTANCE IN FONTAN CIRCULATION
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Introduction: The use of ventricular assist devices (VAD) for the cavopulmonary assistance in Fontan is challenging. The lack of an established experience leads to the needs of dedicated VADs development and animal experiments. A dedicated numerical model could support clinical and experimental strategies

design and new VADs testing. This work aims at performing a preliminary verification of a lumped parameter model of the cardiovascular system to simulate Fontan physiology and the effect of cavo-pulmonary assistance using experimental data reported in literature.
Material and methods: Echocardiographic and haemodynamic data of 4 pigs were used to simulate animals baseline, Fontan circulation and cavo-pulmonary assisted condition to compare measured (Me) and simulated (Sim) data.
Results: Numerical models can well reproduce experimental data (cardiac output [l/min]: Me = 2.8 ± 1.7, Sim = 2.8 ± 1.8; ejection fraction [%]: Me = 57 ± 17, Sim = 54 ± 17; arterial systemic pressure [mmHg]: Me = 41.8 ± 18.6, Sim = 43.8 ± 18.1; pulmonary arterial pressure [mmHg]: Me = 15.4 ± 8.9, Sim = 17.7 ± 9.9; caval pressure [mmHg]: Me = 6.8 ± 4.1, Sim = 7 ± 4.6). In addition, the model permits to evaluate the trend of some haemodynamic variables: the diastolic elastance remains quite constant, whilst the systolic elastance, the arterial systemic and the arterial pulmonary resistances increase (10%, 69%, 100%) passing from the biventricular circulation to the Fontan physiology and then decrease (21%, 39%, 50%) once the VAD was implanted. From energetics point of view the ventricular external work decreases (71%) passing from the biventricular circulation to the Fontan physiology and it increases three times after the VAD implantation in parallel with the VAD power consumption.
Discussion: A numerical model could support clinicians in an innovative and challenging field as the use of VAD to assist the Fontan physiology and, in particular, it could be helpful to personalize the VAD insertion on the base of ventricular systo-diastolic function, circulatory parameters such as peripheral and pulmonary resistances and energetic variables such as ventricular external work and VAD power consumption.

O73
INFLUENCE OF A FLEXIBLE INLET VALVE ON THE FLOW PATTERN INSIDE THE PAEDIATRIC VENTRICULAR ASSIST DEVICE

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Introduction: In the present study, a new flexible valve for the Paediatric Ventricle Assist Device (PVAD) is shown and evaluated. A tilting artificial mechanical valve has been replaced by a specially designed flexible one in the form of an elliptical petal. Mechanical artificial valves generate usually relatively high shear stresses and cause an excessive blood backflow. The new valve has to solve these problems, especially in the paediatric device. An evaluation of this new flexible valve by means of an estimation of the blood backflow, as well as a determination of potential blood stagnation areas are the main aims of the conducted analysis. Advanced numerical simulations have been used to visualize the flow pattern inside the PVAD.
Material and methods: Numerical simulations under unsteady conditions in the time domain have been used to model a pulsating character of the artificial ventricle operation. A combination of three techniques has been used to simulate the flow pattern inside the chamber. A controlled deformation of the mesh has been used to obtain volume of the chamber changing in time. An Immersed Body technique has been implemented to simulate the motion of the outlet valve. The Fluid Structure Interaction (FSI) method has been used to model the operation of the newly designed flexible inlet valve. The viscosity of blood has been modelled versus shear rate.
Results: A combination of three methods-mesh deformation, Immersed Body technique, and FSI-has allowed one to visualise the real operation of the PVAD. The designed flexible valve strongly influences the flow pattern inside the chamber.
Discussion: The results of conducted simulations have shown that the newly designed flexible inlet valve has improved the flow structure inside the chamber. The obtained areas of stagnation zones have significantly lower values. The valve applied in the PVAD has decreased the blood backflow.

O74
TOWARDS A BETTER UNDERSTANDING OF HEMOLYSIS: PARTICLES' SHEAR STRESS HISTORIES IN A VENTRICULAR ASSIST DEVICE (VAD)

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Introduction: Hemolysis is an important risk factor that leads to increased morbidity and mortality of patients with artificial organs. Hemolysis has been associated with shear stress, but little is known about the exact impact of these fluid stresses on erythrocyte survival. This is in part due to the large parameter space, with its relevant shear stress levels and temporal variations; too large to be probed experimentally. Using the example of a continuous flow VAD, we show how computational flow modeling coupled with systematic analysis of possible erythrocyte flow paths through the device can be used to reduce this parameter space, enabling subsequent experimental analysis.
Material and methods: Transient flow fields inside the VAD under normal operating conditions were simulated in StarCCM+, a commercial computational fluid dynamics code, using a rotation speed of 4500 rpm and 100 mmHg adverse pressure gradient. To probe possible erythrocyte paths, 5700 particles were seeded at the inlet and passively advected by the flow. Particle location, velocity and shear stress were extracted at each time step.
Results: The shear stress history of erythrocytes is inherently related to their paths. Identified parameters of interest include shear stress magnitude, temporal gradients, number of exposures to mid or elevated stresses and frequency of these exposures. A finite number of levels is defined for each parameter based on all recorded particle histories, setting ranges for experimental investigations, while correlations between parameters (e.g. absolute vs. temporal shear stress gradients) provide a probability measure for these events.
Discussion: Our analysis allows for a device-specific assessment of the shear stress patterns that are actually experienced by erythrocytes flowing through a VAD. Such analysis sets the frame for future experimental investigations, and might ultimately help us to identify the exact conditions leading to hemolysis.

O75
CFD BASED OPTIMIZATION OF A SEMI-OPEN IMPELLER CENTRIFUGAL PUMP FOR CIRCULATORY SUPPORT

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Introduction: In many cases, the use of rotary circulatory ventricular assist devices is followed by mechanical blood trauma. It has been demonstrated that both the exposure magnitude and time affect the haemolytic effect of shear stress. The optimization of a semi-open impeller of the centrifugal pump is presented. The objective function is the red blood cell plasma rupture minimization by means of the CFD model correlating the exposure time and shear stress. It is to be obtained by modification of main impeller geometrical parameters.
Material and methods: A parametrized geometrical model of a semi-open impeller of the centrifugal pump was used to generate a series of model variants. A mesh was generated and a CFD analysis was conducted in each geometrical variant. A multiobjective optimization procedure was used to minimize the shear stress vs. the time of blood cell exposition. Stagnation areas, recirculation zones, excessive velocity gradients and cavitation were minimized. The quasi-Newton gradient method enabled an application of the Implicit Filtering algorithm in the case of the objective function characterized by some noise.
Results: A sensitivity study was performed and variables having the highest influence onto the objective function were selected on the basis of the results of numerical simulations. Knowing these variables, the optimization procedure was divided into levels. In the first step, optimization was performed for selected variables having the highest impact onto the objective function. In the next step, other variables were used to minimize the objective function.
Discussion: It has been shown that through the selected optimization procedure, it was possible to improve flow parameters. The multilevel approach allowed one to shorten significantly the computational time needed to obtain the final solution.

O76
OPTIMISATION OF CFD HAEMOLYSIS MODEL COEFFICIENTS TO ENABLE ACCURATE PREDICTION OF HAEMOLYSIS PERFORMANCE IN VADS

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Introduction: Previously our CFD model was able to provide an estimate for haemolysis that showed a good relative correlation to lab data, but it was inaccurate in absolute terms, one order of magnitude greater. This study aimed

to investigate a numerical haemolysis formulation capable of an improved absolute blood damage prediction across a range of operational conditions and in VADs with significant geometrical differences.
Material and methods: The normalized index of haemolysis (NIH) was computed using a scalar transport model and a particle tracking model (PT). Mathematically, haemolysis was modelled as a power law function of shear stress (τ) and exposure time (Δt). The model parameters are determined from fitting the VADs experimental haemolysis values. Haemolysis experiments were carried out at different flow rates and pump speeds. It was found that the model coefficients are dependent on the operating conditions. Fitting was carried out in two stages: fitting flow rate dependency followed by fitting pump speed dependency. The fitted haemolysis equation, below, includes a scaling factor that is a function of flow rate (m) and pump speed (Ω), and it was used in conjunction with CFD PT, $NIH = C' \cdot (\Omega^n/m) \cdot (\sum \Delta t \cdot \tau^{\beta/\alpha})^{\alpha}$. The scalar transport method used a formulation described by Taskin et al (2012) with a modified source term (S), $S = \rho \cdot (Hb \cdot C' \cdot (\Omega^n/m) \cdot \tau^{\beta})^{1/\alpha}$, Hb = plasma free hemoglobin.
Results: So far we had significantly improved the absolute haemolysis estimate [g/100L] when modelling the Centrimag:

1 l/min; 2250 rpm- $NIH_{LAB} = 0.001817$; $NIH_{PT} = 0.001775$;
5 l/min; 2250 rpm- $NIH_{LAB} = 0.000300$; $NIH_{PT} = 0.000299$; $NIH_{ST} = 0.000229$;
5 l/min; 3300 rpm- $NIH_{LAB} = 0.003250$; $NIH_{PT} = 0.003250$; $NIH_{ST} = 0.002723$;
10 l/min; 2250 rpm- $NIH_{PT} = 0.000161$; $NIH_{ST} = 0.000098$;

Discussion: This work is currently ongoing. The absolute haemolysis estimate has been significantly improved compared to our previous CFD model. The PT is predicting absolute haemolysis to within 5% of the lab value and the ST within 25%. Next steps are to expand the geometries of pumps tested including Calon new MiniVAD.

O77
HAEMODYNAMIC EFFECTS OF VAD IMPLANTATION ON NORWOOD, GLENN AND FONTAN CIRCULATION: A SIMULATION STUDY

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Introduction: The growing population of failed single ventricle (SV) patients might benefit from VAD support as a bridge to heart transplantation. However, the documented experience is limited to isolated case reports. Considering the complex and different physiopathology of Norwood, Glenn and Fontan patients and the lack of established experience, the aim of this work is to realize and test a lumped parameter model of the cardiovascular system able to simulate SV haemodynamics and VAD implantation effects to support clinical decision.
Material and methods: Haemodynamic and echocardiographic data of 30 SV patients (10 Norwood, 10 Glenn and 10 Fontan) were retrospectively collected and used to simulate patients baseline. Therefore, the effect of VAD implantation was simulated.
Results: The numerical model can well reproduce patients baseline. Simulation results suggest that the implantation of VAD: (a) increase the cardiac output and the mean arterial systemic pressure in all the three palliation conditions with the highest increment in the case of Norwood palliation (Norwood 41.8% and 31.6%, Glenn 27.6 and 24% and Fontan 18.7% and 15.3%); (b) decreases the SV external work with the highest decrement in the case of Fontan physiology (Norwood 13.1%, Glenn 27% and Fontan 44.5%); (c) decreases the pressure pulsatility index more evidently in the Norwood palliation (Norwood 82.7%, Glenn 69.9% and Fontan 67.8%); (d) increase the pulmonary arterial pressure in particular in the Norwood circulation (Norwood 31.6%, Glenn 11.5% and Fontan 5%).
Discussion: The use of numerical models could be helpful in this challenging and innovative field to study the effect of VADs implantation on SV physiology patients and in particular to support patient and VAD selection to optimize the clinical outcome.

Oral Session - Uremic Toxicity, O78-O83

O78
A NOVEL, HUMAN, *IN VITRO* MODEL TO EVALUATE TOXICITY OF UREMIC RETENION SOLUTES (AND DRUGS)

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Introduction: Substances retained in the body of patients with chronic kidney disease are denominated uremic retention solutes (URS). Since not all may cause toxic effects their biological effects have to be evaluated. The aim of this study was to develop an "*in vivo*" method, using human spermatozoa, to estimate toxic effects of various URS.
Material and methods: Semen from healthy donors were used as well as ultrafiltrate derived from the blood of uremic patients performing hemodialysis. The semen was diluted to optimal concentration of spermatozoa to allow investigation of the motility and vitality of the spermatozoa under various conditions. The motility over time of spermatozoa was counted using a Bürker chamber and video recording. Incubation was performed to evaluate the effect of the buffer and the URS. Vitality was analyzed at different time intervals, using a Sperm VitalStainÔ kit. Adjustment calculations for the time-effect on motility and vitality were used.
Results: The semen was investigated for spermatozoa function in the presence of various buffers used for dilution. The buffer maintaining the best motility over time was selected. Vitality was similar for all tested buffers. The ultrafiltrate obtained from dialysis patients was prepared with sepharose into 6 different fractions. The more hydrophobic fraction 5 exhibited an overall significant toxic effect while such effect was not obvious for the first more hydrophilic fractions. Additional investigation was performed in the presence of four different drugs, at concentrations that are administered to uremic patients. Drug A resulted in a significant reduction of spermatozoa motility but not vitality, while such negative effect was not found with the other drugs.
Discussion: This novel "*in vivo*" model consistently demonstrated toxic/non-toxic effects on motility and vitality of spermatozoa. It is useful to investigate biological effects of URS but also of various drugs.

O79
PLASMA ADROPIN LEVEL IS ASSOCIATED WITH RESIDUAL DIURESIS AND PROTEIN-ENERGY WASTING IN HEMODIALYSIS PATIENTS

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Introduction: Adropin is a recently identified protein that has been implicated in the maintenance of energy homeostasis and insulin resistance in subjects with preserved renal function. In end-stage renal disease, nutritional status and the insulin requirement are associated with residual diuresis (RD). We aimed to check whether plasma adropin is involved in mentioned relationships in hemodialysis (HD) patients.
Material and methods: HD patients (n = 50, age 65 ± 12 years, 27 M, 25 with type 2 diabetes mellitus-T2DM, dialysis vintage 36.6 ± 29.4 months) were assigned into groups according to the tertiles of RD (mL/24 hrs): RD <250, RD 250-799, and RD ≥800. Anthropometric measures were taken. Plasma samples were collected for adropin (enzyme-linked immunosorbent assay) and for routine biochemistry. Insulin resistance was assessed by the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR).
Results: In whole HD group, there was a correlation (r = -0.339, p = 0.015) between plasma adropin level (3.38 ± 1.84 ng/mL) and RD (657 ± 635 mL/24 hrs). HD patients showing RD <250 mL/24 hrs had plasma adropin concentration higher (4.43 ± 2.05 ng/mL) than that (2.74 ± 1.7 ng/mL) shown in subjects with RD ≥800 mL/24 hrs (p = 0.018), whereas their mean annual plasma albumin concentration was lower (3.57 ± 0.32 vs 3.89 ± 0.23 g/dL, p = 0.011). There was no significant difference (p = 0.7) in plasma adropin level between

T2DM group (3.34 ± 1.78 ng/mL) and non-diabetics (3.33 ± 1.93 ng/mL), but only in the latter group plasma adropin level showed correlations with plasma insulin level (r = -0.460, p = 0.02), HOMA-IR (r = -0.414, p = 0.039), body dry weight (r = -0.410, p = 0.041), and borderline with BMI (r = -0.390, p = 0.053).
Discussion: In HD patients, plasma adropin concentrationis inversely related to RD associated protein wasting. In non-diabetic HD patients, higher plasma adropin concentrations additionally indicate lower insulin resistance and anthropometric nutritional indices.

O80
VISCERAL ADIPOSITY AS A RISK FACTOR FOR HYPOGONADISM IN MALE CHRONIC KIDNEY DISEASE PATIENTS
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Introduction: Testosterone deficiency (hypogonadism) is a common endocrine disorder among patients with chronic kidney disease (CKD) that associates with comorbid complications and increased mortality. The risk factors underlying this condition in CKD are still not well characterized. In the general population, visceral adiposity is proposed to contribute to testosterone deficiency via aromatization to estradiol and leptin-effects on testosterone production. We here tested whether visceral adiposity is associated with low testosterone levels in male patients with CKD.
Material and methods: Cross-sectional study including 172 consecutive non-dialyzed men [median age 61 (45-75) years] with CKD stages 3-5, and serum testosterone assessment. Hypogonadism was defined as testosterone <10 ng/ml. Visceral adiposity was quantified by abdominal CT scanning, and indirectly by the measurement of waist circumference.
Results: Median testosterone level was 11.7 (7.3-18.4) nmol/L. As many as 52 (30%) patients had hypogonadism. Hypogonadal men presented higher BMI [29 (24-38) vs 28 (22-34) kg/m^2; p = 0.03], waist circumference [101 (85-122) vs 97 (83-112) cm; p = 0.03]; and visceral adiposity [200 (65-356) vs 166 (39-287) cm^2; p = 0.01) than patients with testosterone >10 ng/ml. In linear multivariate regression analysis controlling for known confounders, testosterone levels were independently associated with both visceral adiposity and waist circumference. Further adjustment for estradiol as a mediator did not materially modify this, while the statistical significance was lost after adjustment for leptin concentration.
Discussion: Higher visceral adiposity was associated with lower testosterone levels in men with chronic kidney disease, suggesting that factors linked to obesity may reduce circulating levels of testosterone. This association was independent of levels of circulating estrogen implying that conversion of testosterone to estrogen in the adipose tissue may not be a main mechanism.

O81
THE NEW UREMIC TOXINS DIADENOSINE PENTAPHOSPHATE AFFECTING THE GLOMERULAR FILTRATION RATE
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Introduction: Mechanisms and participating substances responsible for the reduction of glomerular filtration (GFR) rate in contrast induced acute kidney injury (CI-AKI) are still matter of debate. Here we hypothesize that diadenosine polyphosphates are released by the action of contrast media and may act on glomerular arterioles thereby reducing GFR.
Material and methods: Rat tubules were freshly isolated using a modified iron oxide sieve technique and treated with iodixanol (47 mg iodine/ml) at 37°C for 20 min. The supernatant was analyzed regarding the content of ApnA (n = 3-5) by using reversed phase chromatography, affinity chromatography and Maldi-MS. Concentration response curves for ApnA (n = 3-5, 10^{-12}-10^{-5} mol/l) were measured in isolated perfused glomerular arterioles. The GFR was obtained in conscious mice by inulin clearance.
Results: Treatment of tubules with iodixanol increased the concentration of ApnA (n = 3-5) significantly in the supernatant. Ap_nA (n = 3-5) reduced afferent arteriolar diameters dose dependent, but did not influence efferent arterioles. Ap_5A acted strongest; its effect weakened with time. Suramin blocked the Ap_5A effect. Further, application of Ap_5A in conscious mice significantly reduced the GFR.
Discussion: The data indicate that contrast media induced release of Ap_5A act differentially on glomerular arterioles resulting in the reduction of the GFR. This mechanism may add to the reduced GFR in CI-AKI.

O82
WHAT POROSITY IS REQUIRED FOR OPTIMAL MIDDLE TO LARGE MOLECULAR WEIGHT AND ALBUMIN BOUND URAEMIC TOXIN MARKERS REMOVAL?
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Introduction: Standard medical grade activated carbons (ACs) with micropores (<2 nm) and small mesopores (2-10 nm) cannot adsorb many of the high molecular weight and protein bound biotoxins most detrimental to health. The removal of these molecules remains one of the key challenges in the optimisation of haemoperfusion devices. This study aims to explore the impact of increasing the porosity of polymer resin derived AC beads on haemocompatibility and adsorption profile in order to optimise the porosity of these beads for use in haemoperfusion.
Material and methods: A selection of AC beads synthesised with varying pore size distribution ranging from 75 to 560 nm mean diameter were characterised using SEM and mercury porosimetry. The impact of increasing pore size distribution and dextran coating on dust formation and adsorption efficacy were investigated for biotoxin size markers bilirubin, vitamin B12, IL-6 (1 ng/ml), TNFα (1 ng/ml), p-CS (250 µM) and IS (125 µM) using spiked human plasma. Platelet activation and fibrinogen adsorption were measured in healthy blood donor studies using flow cytometry and coagulometry, assessing platelet activation and fibrinogen adsorption.
Results: Increasing the pore size distribution of the AC beads into the macroporous range increased dust formation and reduced adsorption of marker biotoxins. A slight reduction in fibrinogen occurred with increased macroporosity. No platelet activation was observed. Coating reduced dust formation, did not affect biotoxin adsorption, fibrinogen adsorption or platelet activation.
Discussion: The nanoporous AC beads with a mean diameter of 75 nm were optimal haemoadsorbents, showing low dust formation, high adsorption capacity and good haemocompatibility. Surprisingly, increasing porosity into the macroporous range (>100 nm) reduced adsorption efficacy for large biomolecules and increased dust formation. Dust formation was reduced by dextran coating without effecting haemocompatibility.

O83
EXPLORING PROTEIN BINDING OF URAEMIC TOXINS IN CHRONIC KIDNEY DISEASE AND HAEMODIALYSIS PATIENTS
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Introduction: Several protein-bound uraemic toxins are known to accumulate in patients with chronic kidney disease (CKD). As protein binding is not well understood neither in CKD progression, nor during a haemodialysis session, we studied protein binding in two cross-sectional studies.
Material and methods: Ninety-five CKD2-5 patients were included from Amiens University Hospital (France), and ten stable haemodialysis patients from Ghent University Hospital (Belgium). Blood samples were taken during routine ambulatory visit (CKD patients) and from inlet blood line at 0, 30, 60, 120, and 240 min and from outlet blood line at 30 and 120 min during dialysis (HD patients). Total and free concentrations were determined of *p*-cresylglucuronide (pCG) (only in HD patients), hippuric acid (HA), indole-3-acetic acid (IAA), indoxyl sulphate (IS) and *p*-cresylsulphate (pCS). Percentage protein binding (%PB) was calculated from measured total and free concentrations.
Results: Over the stages of CKD, %PB was in the range 38-43% (HA), 60-68% (IAA), 77-92% (IS), and 93-94% (pCS). For the highly bound IS, %PB was inversely correlated with renal function (R = -0.64; P<0.001). During an HD session, %PB of the weakly bound pCG was not changing, while it was increased after 120 min for HA, and after 240 min for the highly bound IAA, IS, and pCS. During one-pass through the dialyser, %PB for pCG was again not changing, while it was increased at 120 min for HA, and at 30 and 120 min for IAA, IS and pCS.
Discussion: Percentage protein binding of IS was higher in more advanced CKD. %PB was also increased during one-pass through the dialyser as well

as during the dialysis session, most pronounced for the highly bound solutes IAA, IS, and pCS. These findings imply that there is a slow release of bound solute from the ligand-protein, resulting in fast exhaustion of free (dialysable) solutes and hampered removal.

Oral Session - Tissue Engineering: Cardiac Tissue and Blood Vessels, O84-O89

O84
MACROSCOPIC MODIFICATIONS OF ELECTROSPUN VASCULAR GRAFTS TO AVOID KINKING

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Introduction: A major challenge in vascular tissue engineering is to develop a graft which avoids a life-threatening stenosis induced by graft kinking. In general, mechanical properties of electrospun scaffolds are stiffer compared to the surrounding native tissue. This study aims to develop a method to modify macroscopic scaffolds structure in order to fabricate a highly flexible vascular scaffold.
Material and methods: Tubular scaffolds were spun from polycaprolactone (170 mg/ml) dissolved 2,2,2-trifluoroethanol. Mandrel collectors were structured using four different screw-like patterns (30°-, 60°-, 90°-, 120° V-thread). A flow-bending test setup had to be developed to measure decrease in volume flow at different bending angles. In addition, macroscopic graft structure, fiber deposition and mechanical properties were determined using scanning electron microscopy and uniaxial tensile testing.
Results: Scaffolds fabricated with a 30°-90° collector showed great appearance of gap-spinning whereas a homogeneous fiber deposition leading to a perfect matching part of the collector could be observed for the 120°. Force at break and strain at break increased with the increase of flank angle, showing comparable results between the 120° collector (31.8 N and 4.99 mm/mm) and the unstructured control scaffold (35.6 N and 3.94 mm/mm). The volume flow through unstructured grafts reduced to more than 50% after bending to an angle of 55°, which demonstrated the low flexibility of commonly used electrospun grafts. The use of a 90° or 120° collector lead to decrease of only 15% or 45% when bended to 140°.
Discussion: Structured collectors were successfully used to fabricate grafts with different shapes and a high flexibility. Finally the results pointed out that grafts fabricated with the 120° collector showed a homogeneous fiber deposition and an appropriate mechanical strength combined with a high resistance to kinking.

O85
HIGH PATENCY OF AN *IN VIVO* TISSUE-ENGINEERED MICROVASCULAR GRAFT (MICROBIOTUBE) IN A RAT MODEL

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Introduction: As presented in the past ESAO congresses, Biotubes, autologous tubular connective tissues formed by in-body tissue architecture technology, a novel and practical approach in regenerative medicine based on the tissue encapsulation phenomenon, have high performance potential as vascular replacement grafts with a diameter ranging from several mm to cm. In this study, MicroBiotubes with a diameter less than 1 mm were firstly developed, and their patency was evaluated in a rat model by optical coherence tomography (OCT) and magnetic resonance angiography (MRA) for several months.
Material and methods: MicroBiotubes was prepared by subcutaneous embedding the molds, assembled with stainless wires (length 30 mm; diameter 0.5 mm) covered with silicone tubes (length 22 mm; internal diameter 0.5 mm; outer diameter 0.6 mm), into rats. After 2 months, the molds were harvested and MicroBiotubes (length 20 mm; internal diameter 0.6 mm) were obtained as tubular connective tissues by trimming the excessive connective tissues and removing the molds. MicroBiotubes (10 mm) were implanted in bilateral femoral arteries (0.6 mm) of rats by end-to-end anastomosis.
Results: Cross-sectional OCT (Panasonic Healthcare) imaging noninvasively demonstrated the patency of MicroBiotubes immediately after implantation. Histological examination performed 1 month after implantation showed no thrombi in the lumen of the MicroBiotubes. Neovascularization developed from the native arteries to the MicroBiotube walls, and entire endothelialization occurred on the MicroBiotubes' luminal surfaces. In follow-up 7-Tesla MRA 1 month after implantation, high patency (75%, n = 4) was obtained without any transformation.
Discussion: Biotubes had high patency for several months even in ultra-small caliber of 0.6 mm. Biotubes may be useful also in neurosurgery and plastic surgery areas in addition to cardiovascular surgery area.

O86
A TWO-LAYER ELECTROSPINNING APPROACH TO ENHANCE CELL ADHESION AND INFILTRATION OF VASCULAR GRAFTS

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Introduction: Scaffolds for vascular tissue engineering need to fulfil manifold requirements. They have to mimic the morphology of the extracellular matrix, match biomechanical properties appropriate for the implantation site and exhibit high compatibility to blood cells and vascular tissue. Pore size and porosity are known to strongly influence cell adhesion and seeding. This study aims to use a multi-layer fabrication concept to promote an efficient endothelial cell adhesion and smooth muscle cell infiltration.
Material and methods: Grafts were spun from polymeric solutions with a total concentration of 100 mg/ml and 200 mg/ml. Lower concentrations were used for the inner and higher concentrations for the outer layers. Pure polycaprolactone (PCL) as well as a blend of PCL and polylactide (PLA, w/w = 2:1) were dissolved in 2,2,2-trifluoroethanol. A custom-made nozzle enabled a gradual polymer shift to avoid layer separation. Fiber diameter, pore size, cross-section (scanning electron microscopy) and mechanical properties (uniaxial tensile testing) were analyzed. Fluorescence staining was used for multi-layer visualization.
Results: Fiber diameter and pore size decreased with polymer concentration as well as with the addition of PLA. Layers consisting of the PCL/PLA (100 mg/ml) had an average fiber diameter of 0.8 µm and a pore size of 5.6 µm while values of 2.1 µm and 13.7 µm were measured for PCL (200 mg/ml). Tensile tests revealed higher values of Young's modulus (22 N/mm² to 7 N/mm²), tensile strength (7.2 N/mm² to 3.5 N/mm²) and strain at break (6.0 mm/mm to 2.2 mm/mm) for scaffolds spun from pure PCL. High concentrations of PCL/PLA lead to instabilities in the electrospinning process causing a layer separation, which was proved by fluorescence imaging.
Discussion: Our results show that a combination of PCL/PLA (100 mg/ml, inner layer) and PCL (200 mg/ml, outer layer) presents the best morphological structure to enhance endothelial and smooth muscle cell adhesion.

O87
GROWTH POTENTIAL OF *IN VIVO* TISSUE-ENGINEERED 'BIOTUBE' VASCULAR GRAFTS

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Introduction: In pediatric surgery, size mismatch between implanted vascular grafts and native vessels is problem that occurred after the growth of patients. Biotubes are autologous connective tissue tubes formed by "in body tissue architecture" technology, which is regenerative medicine based on tissue encapsulation phenomenon in living bodies. Several months after implantation, biotubes can be reconstructed to vascular structure, therefore the growth potential of biotubes was expected. However, the rapid growth of animals prevents evaluation in animal models. In this study, allogenic biotube implantation of pre-prepared biotubes was performed in adult to juvenile beagles. And then, evaluated the growth potential of biotubes by examining their caliber adaptation to growing native arteries after implantation.
Material and methods: Biotubes (internal diameter; 3 mm) were prepared in adult beagles (age, 1 year; body weight; 10 kg) subcutaneous embedding silicone molds (outer diameter; 3 mm) for 8 weeks. After treatment with argatroban, allogenic biotubes were implanted into carotid arteries (internal diameter; 2 mm) of juvenile beagles (age; 12 weeks, body weight; 3 kg, n = 6) by end-to-end anastomosis.

Results: After 1 month, implanted biotubes showed a tendency to reconstruct vascular structure. Angiographic observation performed every month, that revealed diameter of the host arteries were gradually dilated 3 mm, however, little change was observed in diameter of implanted biotubes in 3 months. Thereafter, biotubes were continuously expanded in diameter, similarly to native arteries with little size-mismatching. At 6 months, juvenile beagles achieved to adult size (body weight; 10 kg) and implanted biotubes and host arteries diameter reached approximately 4 mm.
Discussion: Several months after implantation, biotubes were vascular reconstruction, and then they could be dilated according to the growth of native arteries. This is the first study to confirm the growth potential of biotubes, and this result showed they have a high potential usefulness in pediatric surgery.

O88
DEVELOPMENT OF A NOVEL AUTOLOGOUS BIOPROSTHESIS FOR A TAILOR MADE VALVE SURGERY

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Introduction: We are developing a novel autologous heart valve prosthesis (Biovalve) with a unique in-body tissue engineering method. This enables us to select a tailor made valve replacement to fit the each patient's shape and keep biocompatibility. In this study, we made 3 types of heart valve and tested their feasibility in a large animal model.
Material and methods: We made many designs and sizes of molds for Biovalves by plastic rods using 3D printer easily and quickly considering the recipient character. In this study, we selected 3 types (a conventional type, a full-root type and a valve with a metalic stent for transcatheter implantation) and embedded them in the subcutaneous spaces of adult goats for 1-2 months. After extracting the molds and capsulised tissue en bloc and removing the plastic rods 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, 8 cases of full-root type were implanted in the apico-aortic bypass, and 24 stent valve type were implanted with transcatheter technique into *in situ* the aortic and pulmonary valves (17 and 7, 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 2 months in fullroot type and 6 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.
Discussion: The Biovalves have a potential to be used for tailor made therapy in valve surgery and satisfy the higher requirements of the systemic circulation maintaining the histological character as autologous tissues.

O89
CELL SEEDING ON GRGDS-BIOFUNCTIONALIZED PDMS FOR APPLICATION AS ARTIFICIAL BLOOD GAS BARRIER IN A BIOHYBRID LUNG

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Introduction: Patients suffering from severe lung diseases can be supported by extracorporeal membrane oxygenation (ECMO) based on hollow fiber membranes. Unspecific protein adsorption, resulting in a decrease of gas transfer and other side effects limit the application to short-term. However, as a bridge-to-decision or a bridge-to-transplant a system applicable for weeks to months is needed. Relevant biocompatibility can be obtained with a physiological gas-exchange surface made of an endothelialized flat membrane. Cell coating requires cell adhesive surfaces with high gas permeability, e.g. binding of pentapeptide GRGDS on PDMS.
Material and methods: Human endothelial cells were isolated from umbilical veins and cultivated in EGM-2 medium (Lonza). PDMS surfaces were prepared from ELASTOSIL (Wacker Chemie) in 96 and 24 well plates. Two approaches were followed to covalently bind the peptide sequence Gly-Arg-Gly-Asp-Ser (GRGDS, Bachem): a) A solution of Sulfo-SANPAH (Pierce) in DMSO/H_2O at different concentrations was added to PDMS surfaces and exposed to UV light (320-500 nm, 30 min). After washing of PDMS, GRGDS in PBS was added and incubated for 24 h. Surfaces were characterized by IR and contact angle measurement; b) Glas cover slips were coated with PDMS, surfaces activated in ammonia plasma and functionalized with star shaped polyethylene glycol (starPEG) by spin coating and subsequent reaction with an aqueous GRGDS solution. HUVECs were seeded on the surfaces, characterized by CD31, vWF (van Willebrand factor) and CD 29 staining, XTT test and cell density determined with CellProfiler 2.2.1 software by nuclei staining with 4',6'-Diamidin-2-phenylindol (DAPI).
Results: Both biofunctionalisation approaches and subsequent seeding with HUVECs was successfully performed. Cell proliferation and density was higher as on untreated PDMS and showed similar values as on gelatin.
Discussion: GRGDS-biofunctionalized PDMS may serve as suitable membrane in an endothelialized oxygenator (Endoxy). Further tests require HUVEC cultivation under static and dynamic conditions under relevant shear stress.

Oral Session - Cardiac Reversed Remodelling in Clinical Practice, O90

O90
PARTIAL RIGHT VENTRICULAR SUPPORT INDUCES REVERSE REMODELING IN THE CHRONIC PRESSURE OVERLOADED RIGHT VENTRICLE

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Introduction: Supporting the failing right ventricle (RV) can be a life-saving option in patients with pulmonary arterial hypertension. Therefore we assessed the effects of long-term RV support on the chronic pressure overloaded RV.
Material and methods: The pulmonary artery was banded in 16 sheep. Eight weeks later, heart function was assessed by MRI. Subsequently a Synergy® micro-pump was implanted in 8 sheep, draining blood from the right atrium to the pulmonary artery. Hemodynamics were recorded before and after pump implantation. Eight weeks later, heart function in all animals was assessed by the same means. At sacrifice, RV and left ventricular (LV) weight were measured and samples were taken for histology.
Results: Although total cardiac output (CO) did not change significantly during 8 weeks of support, the RV contribution to the total right sided CO significantly increased from 21 ± 11% to 43 ± 10% ($p<0.001$). Ejection fraction and stroke work of the supported RV improved from 20 ± 7% to 41 ± 25% ($p<0.05$) and from 96 ± 60 ml. mmHg to 531 ± 226 ml. mmHg ($p<0.01$), respectively. After pump explantation, MRI analysis showed significant decreases of RV end diastolic and end systolic volume (from 129 ± 33 to 101 ± 24 ml and from 88 ± 29 to 62 ± 20 ml, respectively, $p<0.05$ in both) and significant increases of LV CO and ejection fraction (from 2.8 ± 0.9 L/min to 3.6 ± 1.2 L/min and from 45 ± 8% to 57 ± 10%, respectively, $p<0.05$ in both). RV pressure-volume analysis showed an increased end systolic elastance. Comparison with the control group at 16 weeks showed a significant lower ratio of RV/LV weight (0.47 ± 0.13 vs 0.65 ± 0.14; $p<0.05$) and significant lower diameters of RV myocytes (34 ± 4 vs 37 ± 3 µm; $p<0.0001$).
Discussion: Long term partial support of the chronic pressure overloaded RV has a favorable effect on RV and LV hemodynamics and on RV contractility. Our findings indicate a good recovery of the chronic pressure overloaded RV after long term mechanical support with the potential of reverse remodeling.

Oral Session - Blood Trauma, O91-O95

O91
DEVELOPMENT OF A TWO-STAGE ROTARY BLOOD PUMP WITH LOW BLOOD TRAUMA

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Introduction: Implantable left ventricular assist devices (LVAD) became the therapy of choice in treating end-stage heart failure. Although survival improved substantially, complications related to blood trauma as a result of high shear stresses are still frequently observed. Aim of this project was to

develop a rotary blood pump with lower blood trauma. With two impeller stages blood velocities are lower so that lower shear stresses result.
Material and methods: Using the principles of turbomachinery, a diagonal impeller with an outer diameter of 22 mm was designed to be employed as two stages of a rotary blood pump. The first stage starts with a flow straightener and terminates with a diffusor, while a volute casing behind the second stage is utilized to guide flow to the outlet. Stabilizing of the rotor is realized by cup-socket ruby bearing. With the help of computational fluid dynamics (CFD) using the STAR CCM+ package (Adapco) the pump was analyzed and optimized.
Results: A two-stage blood pump with a flow straightener, diagonal impellers, a diffusor and a volute casing was developed resulting in a priming volume of 10.7 mL. The pump is capable of generating a physiological pressure head of 70 mmHg and a flow rate of 5 L/min at 3300 rpm with throttle curves similar to centrifugal pumps. CFD results reveal smooth flow fields without critical areas of recirculation or swirls and low shear stresses (0.1 vol% above 150 Pa, 0.03 vol% above 200 Pa).
Discussion: The two-stage blood pump achieves similar operating points at lower circumferential velocities compared to current one-stage rotary blood pumps on the market. These lower circumferential velocities yield lower shear stresses in the gap between the rotating impeller and static housing which is the critical region for blood trauma. Hence, blood trauma with the design may be reduced.

O92
INVESTIGATION OF SHEAR-INDUCED INTERFERENCE ON PRIMARY HEMOSTASIS BY ROTARY BLOOD PUMPS
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Introduction: In the last years continuous flow left ventricular assist devices (LVADs) have evolved from short time therapy into permanent or destination therapy. One complication in long term usage is bleeding, which is presumably attributed to shear-induced interference on the coagulation system. In our study, we investigated the impact of shear stresses similarly occurring in rotary blood pumps on the primary hemostasis. For these Investigations a novel shear device was designed. It simulates typical shear stresses in rotary blood pumps, which are very high, of short duration and repeatedly occurring. The PFA-100 (Platelet Function Analyzer) test device was chosen to evaluate the clotting ability of the blood.
Material and methods: With the novel shear device blood is sheared in an 180 µm gap between a static inner and a rotatable outer cylinder. The blood was exposed to sine half-wave shaped shear stresses in a range of 40-200 Pa maximum with exposure times of 25-65 ms and up to 25 repetitions. 74 samples of citrate human whole blood were taken from 4 different donators.
Results: A damaging model of the PFA closure time based on the power law including shear stress and exposure time could be established. Even after few repetitions a significant decrease of the blood clotting ability could be determined. Furthermore a dependency of the integral of shear stress over time and the increased closure time has shown of maximum stresses above 20 Pa.
Discussion: The shear device enables investigations of shear stresses occurring in rotary blood pumps on blood under controlled conditions. In this case the reduction of the clotting ability could be estimated using the PFA closure time. In 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.

O93
***IN VITRO* HEMOLYTIC PERFORMANCE EVALUATION OF A NEW IMPLANTABLE CENTRIFUGAL HEART PUMP WITH AN OPTIMIZED DESIGN**
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Introduction: Heart failure is one of the most common disease causing death in the developed countries. The left ventricular assist devices (LVAD) are used to support heart failure patients by providing enough blood flow to the human body. A new centrifugal type LVAD is under development as an alternative to heart transplantations. This study presents the results of the validation process including designing, manufacturing, analyzing and *in vitro* blood tests.
Material and methods: 3D pump geometries were designed in the CAD environment and analyzed with CFD method. In CFD analyses, hemolytic performance of the device has also been simulated by calculating the shear stress affecting to red blood cells. The design has been optimized by CAD-CFD iterations. Optimized model is manufactured in our high-precision 5-axis CNC machining facility after conducting CFD analyses. *In vitro* blood tests were conducted in various conditions with different prototypes according to the American Society for Testing and Materials (ASTM) F 1841-97 standards.
Results: Four different prototypes have been tested with *in vitro* experiments. Last prototype presented the most promising results in terms of hemolysis. It provided sufficient output up to 7 l/min and maximum pressure 200 mmHg. *In vitro* blood tests were conducted up to 12 hours with adequate pump performance. The N.I.H. result of the prototype was near 0.003 g/100 L which is considered as antitraumatic.
Discussion: The prototype pump indicates sufficient pump performance. CFD studies provide a good estimation in terms of hemolysis before conducting *in vitro* blood test. The N.I.H. result shows that the prototype does not cause clinically significant hemolysis. These promising results also raise great hope for the next stage, *in vivo* experiments. However, validation studies will be continued first by including Cardiovascular Mock Loop to investigate the dynamic pump performance under realistic physiologic flow-pressure conditions.

O94
***IN VITRO* BENCHMARKING STUDY OF VENTRICULAR ASSIST DEVICES**
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Introduction: The aim of this study is to develop a blood damage profile of ventricular assist devices (VADs) in current clinical use including the HVAD (HeartWare), HeartMate 2 and CentriMag (HM2; CMAG; both Thoratec) in comparison to a new VAD in development, the MiniVAD (Calon Cardio-Technology).
Material and methods: Several explanted HVADs and HM2s were carefully cleaned and inspected and tested *in vitro* against the MiniVAD in a standard 500 ml mock circulatory loop using bovine blood. The CMAG was used as a control pump due to its low blood damage profile. Pump flow was maintained at 5 L/min and pressure at 100 mmHg. Samples were collected at regular intervals and complete blood counts were analysed: automated haematology counts; haemolysis by Harboe assay; leukocyte microparticles (MP) and platelet activation by flow cytometry; and von Willebrand factor by immunoblotting. We recognise that the use of explanted pumps is a limitation of the study.
Results: This study is ongoing with a targeted completion date in June 2015. Preliminary results show plasma-free haemoglobin (g/L) & NIH (g/100 L) at 360 min of 1.4 ± 0.32 & 0.02 ± 0.006 (HM2, n = 7); 0.34 ± 0.02 & 0.006 ± 0.0006 (HVAD, n = 3); 0.07 ± 0.02 & 0.001 ± 0.0003 (MiniVAD, n = 3); 0.06 ± 0.019 & 0.001 ± 0.0005 (CMAG, n = 16). Leukocyte MP levels expressed as fold change to static control are 30.6 ± 6.9 (HVAD); 27.3 ± 5.5 (HM2); 13.7 ± 6.9 (MiniVAD); 4.3 ± 1.9 (CMAG).
Discussion: These preliminary results indicate that it is possible to observe differences between different pump designs during *in vitro* testing that might translate to clinical performance. This study shows the importance of developing standard *in vitro* testing methods against which device developers could report data to progress the overall research field.

O95
THE ROLE OF ACQUIRED VON WILLEBRAND SYNDROME IN OCCURRENCE OF BLEEDING EVENTS IN PATIENTS ON A CONTINUOUS FLOW LVAD
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Introduction: Left ventricular assist devices (LVADs) have become a valuable treatment option in end-stage heart failure. However, bleeding is one of the most common adverse events post-implantation and is a major cause of morbidity in these patients. Though the use of anticoagulation therapy is undoubtedly a contributing factor, there is increasing evidence that an acquired von Willebrand syndrome (AVWS) exists in all patients with LVADs. We sought to analyse whether there was a correlation between the bleeding events and AVWS in our patients.
Material and methods: Ninety-eight patients received a continuous flow LVAD implantation (HeartMate II; Thoratec) between 2007 and 2014. Since 2011, von Willebrand factor antigen (VWF:Ag) and von Willebrand factor ristocetin (VWF:Rco) activity were recorded prospectively both before implantation and

at fixed timepoints throughout the first year on LVAD. As found in literature, a vWF Rco/vWF Ag ratio <0.8 was considered diagnostic for AVWS. Mean age was 49.9 ± 13.9 years (81 male, 17 female).
Results: 53.06% of patients experienced at least one type of bleeding. The most common types of bleeding were: epistaxis (39.5% of bleeding events), surgical bleedings needing revision (30.6%), GI bleeding (13.9%). Of 63 patients with vWF measurements, 88.89% had a vWF Rco/vWF Ag ratio <0.8 (criterium for AVWS). No correlation was found between bleeding events and levels of vWF antigen, vWF ristocetin, or pump speed.
Discussion: Bleeding events are common after LVAD implantation. AVWS is present in almost all LVAD patients. Analysis of our data shows that the absolute values of routinely available biochemical parameters to test for the presence of AVWS are of no predictive value towards the occurrence of bleeding events.

Oral Session - Renal Assist: Dialysis, O96-O101

O96
EVODIAL PLUS CITRATE CONTAINING DIALYSATE IS NON-INFERIOR TO REGIONAL CITRATE ANTICOAGULATION

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Introduction: Heparin is widely used to prevent clotting of the extracorporeal circuit during hemodialysis. In patients at high risk of bleeding, heparin-free hemodialysis can be achieved using either regional citrate anticoagulation (RCA), heparin-grafted dialyzers or saline flushes. In some centers citrate containing dialysate is used, as citrate containing dialysate also provides a modest local anticoagulant effect. RCA is hampered by technical complexity and labor intensiveness. Other heparin-free dialysis techniques frequently lead to premature clotting. We studied the efficacy of the combination of a heparin-grafted dialyzer and a citrate-containing dialysate for prevention of circuit clotting in comparison to conventional RCA.
Material and methods: We performed a prospective, open-label randomized trial including 25 chronic hemodialysis patients. Patient characteristics are summarized in Table I. Regional anticoagulation was achieved using either RCA (Polyflux 170® membrane; n = 13; 367 sessions) in the control arm versus the combination of a heparin-grafted AN69ST dialyzer (Evodial®) and a citrate-containing dialysate (SelectBag Citrate®; n = 12; 331 sessions) in the treatment arm. At the end of each four hour dialysis session, the dialyzer was scored semiquantitatively for visible signs of thrombus formation (0, no clotting, to 4, severe clotting).
Results: Clotting necessitating premature termination of the dialysis treatment, was encountered in 8.99% of sessions using RCA and in 4.23% of treatments using Evodial plus SelectBag Citrate (p = 0.01). Mean dialyzer clotting scores were 1.58 ± 0.70 (RCA) and 1.18 ± 0.69 (treatment arm) (p<0.01). A Cox proportional hazard analysis of premature clotting supported non-inferiority of the combination treatment to conventional RCA (p = 0.12).
Discussion: For prevention of extracorporeal circuit clotting during intermittent hemodialysis, combining a heparin-grafted dialyzer with a citrate-containing dialysate is non-inferior to conventional RCA. The incidence of circuit clotting in the RCA group was comparable to previously published data.

TABLE I - Patient characteristics (values given as mean ± SD unless indicated otherwise)

	Control	Treatment
No. of patients	13	12
No. of sessions	367	331
Sex m/f	13/0	3/9
Age	72.2 ± 8.8	70.3 ± 15.5
Access (central line vs. fistula)	3/10	2/10
Hemoglobin (g/dL)	10.7 ± 0.5	10.3 ± 0.9
Anti-platelet therapy	69.2%	91.7%
Premature clotting	32/367 (8.99%)	14/331 (4.23%)
Clotting score at 4 h	1.58 ± 0.70	1.18 ± 0.69

O97
WHERE AND WHEN TO INJECT LOW MOLECULAR WEIGHT HEPARIN IN HAEMODIAFILTRATION?

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Introduction: Low molecular weight heparins (LMWHs) are small enough to pass large pore dialysis membranes. Removal of LMWH if injected before the start of the session is possible during high-flux dialysis and haemodiafiltration. The aim of this study was to determine the optimal mode of tinzaparin administration during postdilution haemodiafiltration.
Material and methods: In 13 patients, 3 approaches of injection were compared: i) before the start of the session at the inlet blood line filled with rinsing solution (IN_0), ii) 5 min after the start at the inlet line filled with blood (IN_5) and iii) before the start at the outlet blood line (OUT_0). Anti-Xa activity, thrombin generation, visual clotting score and reduction ratios (RR) of urea and beta2microglobulin were measured.
Results: Anti-Xa activity was lower with IN_0 compared with IN_5 and OUT_0, and also more thrombin generation was observed with IN_0. No differences were observed in visual clotting scores and no clinically relevant differences were observed in solute RR. An anti-Xa of 0.3 IU/mL was discriminative for thrombin generation. Anti-Xa levels below 0.3 IU/mL at the end of the session were associated with worse clotting scores and lower RR of urea and beta 2 microglobulin.
Discussion: Injection of tinzaparin at the inlet line before the start of postdilution haemodiafiltration is associated with loss of anticoagulant. An anti-Xa above 0.3 IU/mL at the end of the session is associated with less clotting and higher dialysis adequacy.

O98
THE EFFECT OF LOCAL HEMATOCRIT AND HEMATOCRIT CHANGES ALONG THE FIBERS ON PRODUCING HEMOLYSIS IN A DIALYZER

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Introduction: Blood flowing through artificial organs is exposed to different types of mechanical stress causing blood trauma. Specifically, uremic patients frequently undergoing dialysis treatment (approx. three times a week) are confronted by the potential accumulation of various blood trauma consequences, such as free plasma hemoglobin. In the case of dialyzers, two important phenomena take place, both affecting the concentration of erythrocytes. On one hand, hematocrit increases along the fibers because of ultrafiltration. On the other hand, velocity profile influences the distribution of RBC leading to the existence of "local" Hct values. The aim of this study is to evaluate the effect of local hematocrit and to examine the way hematocrit changes along the fibers, in order to determine the hemolysis level in a dialyzer which was achieved by means of an innovative Couette flow system.
Material and methods: A setup consisting of two dialyzers in a series configuration was prepared and samples were taken to measure hematocrit and free plasma hemoglobin. The sequential arrangement of the two dialyzers enables 3-point sampling, which enhances filtration visualization by demonstrating the course of hematocrit along the fibers' length. Conditions in the Couette system were adjusted to match those of the dialyzer circuit and the hemolysis level were compared. Freshly drawn heparinized pig blood was used in both cases and inlet hematocrit values were adjusted.
Results: This study enables us to investigate the changes of hematocrit inside the dialyzer. It was clearly shown that hematocrit will sharply increases in the point where backfiltration starts. At this point hematocrit is significantly higher than inlet and even outlet. Since the impact of increasing of hematocrit in heightening of viscosity and consequently enhancement of hemolysis.
Discussion: The results demonstrate this method delivers more realistic hemolysis results by investigating hematocrit changes in dialyzer as well as local hematocrit values.

O99

EFFECTS OF MARATHON CYCLING ON CYTOKINES AND ADIPOKINES IN KIDNEY TRANSPLANT RECIPIENTS

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Introduction: The clinical-laboratory frame of transplant recipients is characterized by chronic inflammation affecting cardiovascular outcome. Physical activity seems to improve health and inflammatory status, but the role of intense training has not been fully elucidated. We evaluated the effect of a 130 km road cycling race on inflammatory cytokines and adiponectin in kidney transplant recipients (KTR).
Material and methods: Serum levels of TNF-α, IL-6, IFN-γ, and adiponectin were assayed one day before race, at the end and after 18-24 hours, in 81 healthy *vs* 22 transplanted cyclers, all male and matched for age, BMI and previous preparation workout. KTR had stable renal function (creatinine: 1.25 ± 0.40 mg/dL; eGFR: 61 ± 25 mL/min).
Results: Renal function parameters showed a significant increase after race, returning back to baseline levels after 18-24 hours. Circulating TNF-α was unaffected by training in both groups. Conversely, IL-6 levels were 6 to 8-fold increased at the end of race in all participants, but at a significantly greater extent in KTR, and it dropped, without returning to basal levels, the day after. Circulating IFN-γ was similar in healthy subjects and KTR before race. Marathon triggered a greater increase in KTR compared to healthy cyclists, but it declined to levels very close to the baseline within 18-28 hours following performance. The trend in adiponectin variations was fairly similar to that of IFN-γ in healthy subjects and TR at all the 3 measurements of the competition.
Discussion: Our data show that TR in good clinical conditions and properly trained can benefit from physical activity, even at a competitive level. The changes in renal function inflammation parameters were transient and rapidly with no remarkable differences with the healthy cyclists. Our succeeding analysis intends to clarify whether the long-term benefits of sport after transplant might counterweigh these temporary modifications of some parameters during acute exercise.

O100

EXTENDED MULTIPASS VERSUS STANDARD HAEMODIALYSIS IN THE HOME SETTING

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Introduction: Single-pass haemodialysis modalities, requiring large amounts of prepared dialysate, are less suitable for home use. Multipass haemodialysis (MPHD) on the contrary consumes only a small volume of dialysate (50% of estimated body water) which is repetitively recycled. Dialysis regimes of 6 × 8 h/week resulted in an increased removal of small water soluble solutes and middle molecules compared to standard haemodialysis (SHD). Since protein-bound solutes (PBS) exert important pathophysiological effects, we investigated whether MPHD results in improved PBS removal as well.
Material and methods: A cross-over study was performed in nine HD patients with, at midweek, a single session of either 4 h SHD (dialysate flow 500 mL/min) or 8 h MPHD. Blood and dialysate samples were taken hourly to determine concentrations of p-cresylglucuronide (PCG), hippuric acid (HA), indole acetic acid (IAA), indoxyl sulfate (IS), and p-cresylsulfate (PCS) (%binding in the range 10-99%), and dialyser extraction, reduction ratio, and solute removal were calculated.
Results: Already at 60 min, dialyser extraction ratio was a 1.4-4 × lower with MPHD versus SHD, resulting in significantly smaller reduction ratios and lower solute removal during one session. Even when extrapolating our findings to 3 times 4 h SHD and 6 times 8 h MPHD per week, the latter modality was at best similar in terms of total solute removal for most protein-bound solutes, and worse for the highly protein-bound solutes IS and PCS. However, when efficiency was calculated as solute removal/litre of dialysate used, MPHD was found superior to SHD.
Discussion: A treatment regime of 6 × 8 h/week MPHD is an acceptable alternative for 3 × 4 h/week SHD, with more efficient use of dialysate, but at the expense of a lower removal of highly protein-bound solutes. This new method can thus successfully be used when high water consumption is a concern.

O101

A NEW METHOD TO PERSONALIZE DIALYSIS THERAPY

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Introduction: Health conditions and quality of life of uremic patients treated with hemodialysis could be improved by tailoring the treatment on each patient, whereas dialysis is usually based on standard not patient-specific parameters. This work aims at adapting a mathematical model, describing fluid and solutes kinetics to single patient's characteristics, in order to simulate the patient reaction to the therapy and allow the clinician an offline evaluation of the settings and prescriptions to improve the treatment outcome.
Material and methods: A multi-compartmental model was adopted and data from 70 patients (recorded both at Ospedale Regionale di Lugano and at A.O. della provincia di Lecco, Italy) were used to estimate each patient's parameters. A Bayesian approach was used. The parameters are related to the mass exchange across the patient-specific cellular and capillary membranes and to the dialyzer membrane efficiency. Parameters were computed using a MCMC (Markov Chain Monte Carlo) algorithm.
Results: Solutes concentrations and volume profiles simulated in about 400 dialysis sessions by the kinetic model optimized through the Bayesian method, show to better fit clinical data, than using the non-optimized model. The effects of different parameter settings are highlighted in terms of different molecules removal efficiency. The simulation error of the model, estimated in the preliminary tests, comparing the output to the clinical trends, is 6 ± 0.5% for the solute concentrations (urea and the most important plasmatic electrolytes were considered) and 7 ± 0.5% for the blood volume trend.
Discussion: The kinetic model, coupled with a robust method to identify patient-specific parameters, allows a better prediction of electrolytes and fluid transfer during dialysis, and the possibility of evaluating the effects of different therapy settings. These results will be beneficial to improve dialysis therapy planning.

Oral Session - Fibrogelnet, O102-O106

O102

PROTEIN ORGANISATION TO ENGINEER THE HEALING MICROENVIRONMENT

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Introduction: We aim at engineering the cellular microenvironment by a combination of synthetic materials, extracellular matrix proteins and growth factors which are organized to direct stem cell differentiation and promote tissue healing.
Material and methods: MSCs will be seeded on the engineered matrices and characterized for the short-term (adhesion, signaling) and long-term phenotypic expression (PCR). The organization of proteins at the material interface will be assessed using AFM.
Results: Most cells assemble rich protein matrices via an integrin-dependent mechanism that incorporates e.g. fibronectin (FN) molecules into matrix fibrils. The process involves integrin binding and activation of cell contractility to extend FN and expose cryptic domains that promote protein-protein interactions. We have shown that this process can occur by simple adsorption of individual protein molecules onto particular surface chemistries-in absence of cells. FN-material interactions would induce exposure of self-assembly sites to drive FN assembly, a process that we have named material-driven fibronectin fibrillogenesis. This FN matrix assembled at the material interface involves conformational changes of FN upon adsorption and enhanced FN-FN contacts on the material surface. The resulting material-driven FN matrix assembled at the material interface consists of a protein network with enhanced biological activity: it supports cell adhesion, matrix remodeling, and trigger cell differentiation. Moreover, it provides a

robust platform to engineer advanced microenvironments in combination with growth factors to tune stem cell differentiation and promote tissue repair.
Discussion: We have shown the organisation of ECM proteins directed by the material interface to enhance cellular processes relevant for tissue healing, including osteogenesis and vascularisation.

O103
INJECTABLE COMPOSITES OF LOOSE MICROFIBERS AND GELATIN FOR SOFT TISSUE ENGINEERING
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Introduction: Enzymatically gellable gelatin hydrogels from tyramine conjugates have been proposed for soft tissue regeneration due to their injectability. Their low mechanical properties limit their application. Our aim was to prepare injectable gelatin composites reinforced with poly-L-lactid acid (PLLA) loose fibers with a hydrophilic grafting to enhance interfacial interaction with the hydrogel.
Material and methods: Loose PLLA microfibers were obtained by injecting a PLLA solution into highly agitated cold ethanol and subsequent hydrophilic grafting was performed by UV irradiation. Two series of 3% w/v hydrogel composites with different quantities of grafted and non-grafted fibers were prepared using gelatin tyramine conjugates. Hydrophilic grafting was characterized by FTIR and ^{1}H-RMN, mechanical properties and morphology of the composites by rheometry and SEM. Cell viability, distribution and shape of encapsulated mouse L929 fibroblats were evaluated by MTS and fluorescence microscopy.
Results: FTIR and ^{1}H-NMR show successful grafting. All hydrogel composites are porous, with pores of about 20 µm. The storage moduli of the gels increased proportionally to the quantity of grafted fibers. No significant increase in storage modulus is observed in the non-grafted fiber composites. L929 viability increased until the 7th day of culture for the gelatin and until the 14th day for the composites. Fibroblasts in the composites are more dispersed and have a more elongated shape than in pure gelatin.
Discussion: Reinforced gelatin composites with a very good interfacial interaction between the PLLA microfibers and the gelatin were obtained. Fibers do not compromise injectability, cell encapsulation and proliferation, making these materials promising *in situ* hydrogels for the regeneration of soft tissues.
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O104
HUMAN MESENCHYMAL STEM CELLS BEHAVIOR IN NANOFIBROUS ENVIRONMENT
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Introduction: In a series of recent studies we strive to learn how mesenchymal stem cells (MSCs) respond to spatially organized signals from the extracellular matrix (ECM) culturing them in an artificial nanofibrous environment.
Material and methods: Here we report on the development and characterization of new type hybrid fibrinogen/poly- L, DL-lactic acid (FBG/PLA) nanofibers combining the good mechanical properties of PLA with the excellent cell recognition of native FBG. For biological characterization we were particularly interested on the dorsal and ventral response of human mesenchymal stem cells (MSCs) of adipose tissue origin to the nanofibers organization, namely: randomly deposited and aligned nanofibers.
Results: Upon ventral contact with random nanofibers the cells developed a stellate-like morphology expressing multiple projections onto the differently oriented fibres. Well-developed focal adhesion complexes suggest successful cellular interaction. Time-laps analysis, however, shows significantly restricted cell movements on random nanofibers resulting in relatively short distance that they traverse in multiple directions. Conversely, an elongated cell shape and significantly increased cell mobility were observed on aligned nanofibres. To follow the dorsal cell response artificial wounds were created on confluent human MSCs layers and either random or aligned nanofibers were dorsally applied. Time-laps analysis showed significantly faster wound coverage (within 12 h) of MSCs on aligned samples versus almost absent of directional migration on random ones. No significant difference in cell growth was observed, however, qPCR data for the expression of Collagen 2, Collagen 10 and SOX9 at 35th day of culture in chondrogenic medium shows that MSCs possess lowered cartilage production on aligned NFs apart from random were the expression of differentiation markers was relatively higher.
Discussion: Collectively, our studies show that randomly organized nanofibers support the differentiation of MSCs into chondrogenic lineage while aligned configuration favours directional cell locomotion that could be used for guided colonization of implants.

O105
CHONDROGENIC RESPONSE OF HUMAN MESENCHYMAL STEM CELLS TO THE GEOMETRY OF ELECTROSPUN NANOFIBERS
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Introduction: We seek to understand how mesenchymal stem cells (MSCs) respond to the spatially organized signals from the extracellular matrix (ECM) and one way to learn this is to expose them *in vitro* to a synthetic nanofibrous environment. Electrospinning is a technique capable of producing nanofibers (NFs) with dimensions similar to those of the fibrilar components of natural ECM. An advantage of this method is that NFs can be further designed for their orientation and cell binding properties.
Material and methods: Here we report on the production of a novel type of hybrid, fibrinogen/poly-L, D-lactic acid (FBG/PLA) NFs that were recently developed in our Lab and their use to obtain a control over the differentiation potential of human MSCs to chondrogenic lineages. These NFs, combining the good cell recognition properties of native FBG with the excellent mechanical properties of PLA, were further arranged as random or aligned and combined with adipose tissue derived human MSCs to arrange constructs that provide culturing of cells at 2D and/or 3D (sandwich-like) environment.
Results: The well-developed focal adhesion complexes and actin cytoskeleton confirm the proper interaction of MSCs with NFs. When constructs were further cultured in complete chondrogenic medium for 50 days we obtained an alizarin red positive stained cartilage-like tissue. qPCR for Collagen 2, Collagen 10 and RUNX9 genes was used to quantify the efficacy of cells differentiation to chondrogenic lineage. Our results show that human MSCs produce more and better organized cartilage in 2D environment and the random NFs tend to override aligned in respect to collagen 2 genes activation.
Discussion: Collectively, our studies show that NFs organization (random vs. aligned) and dimensionality (2D vs. 3D) may provide a kay for controlling the differentiation of human MSC to chondrogenic lineage.

O106
BIOACTIVE MULTILAYERS IMPROVE OSTEOBLAST RESPONSE
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Introduction: A novel method called layer-by-layer (LbL) technique allows the build-up of multilayers on substrates by alternating depositing of polycations and polyanions like synthetic and biogenic polyelectrolytes (e.g. proteins or glycosaminoglycans). Surface properties and composition of multilayers can be used to control adhesion and function of cells on materials for a variety of medical applications like implants, catheters, tissue engineering scaffolds.
Material and methods: Biogenic polyelectrolyte (PE) pairs used in this study were poly-l-lysine (PLL)/fibrinogen (FBG) and avidin (AVI)/biotinylated chondroitin sulfate (BCS). Additionally a synthetic polyallylamine hydrochloride (PAAH)/polystyrene sulfonate (PSS) were used for multilayer formation. Water contact angle (WCA), surface plasmon resonance (SPR) and atomic force microscopy (AFM) were used to study layer growth and surface topography. The MG63 osteoblast cell line was applied to characterize biocompatibility and osteogenic activity of multilayers.
Results: Layer growth and surface properties were highly dependent on type of PE pair. Studies with MG63 cells showed that none of the multilayer sys-

tems had adverse effect on cell behavior. Additionally these layers promoted a significant increase in the activity of alkaline phosphatase-a marker of osteogenic activity with PAAH/PSS yielding highest values.
Discussion: The comparative study of biocompatibility of synthetic and biogenic polyelectrolyte multilayer systems revealed that both provide surface coatings of high biocompatibility with lack of toxic effects, promotion of cell growth and osteogenic differentiation. In conclusion of this study, multilayer systems made by LbL are useful for coating implants or tissue engineering scaffolds for repair of bone.

Oral Session - VAD's in Paediatric and Adult Congenital Heart Disease, O107-O109

O107
THE POTENTIAL OF VAD SUPPORT IN THE SYSTEMIC RIGHT VENTRICLE

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Introduction: Transposition of the great arteries (TGA) occurs in approximately 25 per 100000 live births. The standard treatment up to the late 1970's was an atrial switch procedure. These patients however continue to live with a systemic right ventricle that often fails in the course of their lifetime. The aim of this review is to report on the current experience with mechanical support for the failing systemic right ventricle.
Material and methods: We searched the literature as well as our own database for patients with a failing systemic right ventricle receiving a ventricular assist device (VAD).
Results: We identified 36 unique cases (32 and 4). The median patient age was 35 years (13 to 66 years). The mean duration of VAD support was 312 days (5 to 988 days). Twenty-two (61%) patients had a history of TGA after atrial switch and fourteen (39%) congenitally corrected TGA patients (ccTGA) were supported. All patients had end-stage systemic right ventricular failure and twelve patients (33%) had pulmonary hypertension (PHT). Eleven patients (31%) received a pulsatile-flow VAD and 25 patients (69%) a continuous-flow VAD. Thirteen patients (36%) were successfully bridged to heart transplantation after a median duration of mechanical support of 330 days (84 to 720 days). Six deaths occurred (17%) and sixteen patients (44%) were still on VAD support awaiting transplantation. One patient (3%) could be weaned from the device after 43 days of VAD support. Of the PHT patients, five patients (42%) could be bridged to transplantation. Five patients (42%) are still awaiting cardiac transplantation. Two died (16%) before a donor heart became available.
Discussion: VAD support is a valuable solution to support the failing systemic ventricle in TGA after atrial switch and ccTGA patients, even in patients with PHT. The use of VAD support in the systemic right ventricle will become increasingly important.

O108
SURGICAL STRATEGIES FOR THE TREATMENT OF RIGHT VENTRICULAR FAILURE AFTER LVAD IMPLANTATION: A SIMULATION STUDY

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Introduction: Right ventricular failure (RVF) is one of the major complications in LVAD patients. Beyond the drugs therapy, the most reliable option is the RVAD implantation. However, BIVAD patients are associated with a poor prognosis and the management of two devices could increase the incidence of complications. Alternative approaches were experimented: the creation of an atrial septal defect (ASD), a cavo-aortic shunt (CAS) and a cavo-pulmonary connection (CPC). This work aims at using a lumped parameter model (LPM) to compare the ASD, CPC, CAS, RVAD effects in LVAD+RVF patients.
Material and methods: Data of five LVAD patients were retrospectively collected to simulate patients baseline. The effects of continuous flow LVAD implantation complicated by RVF was simulated for each patient. Finally, the ASD, CPC, CAS and RVAD treatments were simulated for each LVAD+RVF patient.
Results: LPM can well reproduce patients baseline and the haemodynamic effects of the surgical strategies according to literature data. With the different surgical treatment, an unloading of the right ventricle and an increment of left ventricular preload were observed with an overall improvement of the haemodynamics (total cardiac output (CO) increment: ASD 15%, CPC 10%, CAS 70% RVAD 20%; right ventricular external work (RVEW) decrement: ASD 19%, CPC 46%, CAS 76%, RVAD 32%; LVEW increment: ASD 12%, CPC 28%, RVAD 64%; Pulmonary to systemic flow ratio (Qp/Qs) decrement: ASD 40%, CAS 80%).
Discussion: The creation of a calibrated ASD or the RVAD implantation seems to be the more safety and reliable options. However, the RVAD seems to increase more the LVEW. Finally, CAS seems to create a non favourable Qp/Qs, while CPC could unload the RV, without a significant increment of CO. Simulation could support clinicians in therapy personalization.

O109
AXIAL-PUMP-ASSISTED TOTAL CAVOPULMONARY CONNECTION WITH AN INNOVATIVE TOPOLOGY

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Introduction: Up to 40% of patients with total cavopulmonary connection (TCPC) experience late failure with systemic venous hypertension and liver dysfunction. This study provides a CFD characterization of a novel treatment by mechanically assisted TCPC, in a modified geometry (already studied in animal experiments).
Material and methods: 3D TCPC models were created by means of computer-aided design (CAD) software: 1) a model with an axial pump, similar to the child version of Jarvik Child 2000 pump, positioned in the extracardiac conduit, between the two caval veins' district and the pulmonary arteries' district; 2) a second model without the pump allowed us to to compare results of the former model with those relative to the unassisted circulation. A mesh with 1,000,000 elementary volume elements for the 2.1 cm^3 internal volume of the pump was used for the CFD simulations. Pressure and flow fields characterizing the TCPC were evaluated. The Viscous-RNG-k-model was chosen, in order to consider the turbulent flow inside the pump. The rpm values were set independently from the flow rate, in order to investigate the most advantageous rotational speed at each flow rate.
Results: The simulations showed that the pump generates a pressure loss across the device from a minimum of -90 mmHg to a maximum of 132 mmHg, in the range of operating conditions tested. Particular care must be taken for ruling out the case of high negative pressure upstream of the pump, which may generate collapse of the venous compartment.
Discussion: The assisted TCPC can generate a pressure distribution which could prove itself beneficial for a patient with failing Fontan circulation, thanks to the appropriate selection of surgical connection and operating parameters as confirmed by *in vivo* study on animals performed by using this geometry.

Oral Session - Cardiovascular CFD, O110-O115

O110
INJECTION MOULDING PROCESS: CFD EVALUATION ON THE ORIENTATION OF POLYMERIC CHAINS FOR MANUFACTURING HEART VALVES

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Introduction: Polymeric Heart Valve (PHV) prostheses aim at combining the hemodynamic advantages of biological valves with the durability of mechanical valves. Styrene Block Polymers (SBPs) appear to be the best materials for this application, because of their excellent biocompatibility, chemical stability and fatigue resistance. SBPs can be processed by injection moulding, allowing controlling the alignment of the polystyrene micro-chains. Aim of this work is to simulate the injection moulding process to analyse polymer chains orientation within the PHV leaflets and optimise manufacturing.
Material and methods: Small Angle X-ray Scattering Analysis was performed on a thin membrane made of poly-(Styrene-Isoprene-Butadiene-Styrene) with 19% styrene (SI/BS19) manufactured by injection moulding, to visualise the polymer chains orientation in the material. Based on these data a total of

six numerical models (Fluent®14.0, ANSYS Inc., Canonsburg, PA, USA) of the PHV mould differing in the polymer injection inlets and outlets were developed. A hexahedral mesh, including approximately 1,000,000 cells was used. The Carreau Model was used to describe SI/BS19 rheology. Data from the computational analysis were used to calculate the directions along which the polymer chains were aligned.
Results: SI/BS19 chains orientation along the leaflets is mainly perpendicular to the flow direction of the polymer. Polymer chains orientation along the leaflets does not change significantly when different locations of the injectors are considered. Also different polymer mass flow rates exerts negligible effects on the polymer chains orientation.
Discussion: The numerical model allowed a reliable simulation of the injection moulding process showing that a different location of the injectors do not affect polymer chains orientation as well as different mass flow rates of the polymer. These results allow the optimisation of the moulding process in terms of minimisation of the manufacturing time duration.

O111
PATIENT-SPECIFIC COMPUTER MODELS AS A TRANSLATIONAL TOOL TO TAILOR CATHETER CARDIOVASCULAR INTERVENTIONS
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Introduction: In this study, we explore the potential use of a patient-specific modelling framework for predicting clinical outcomes of cardiovascular interventions for the treatment of complex congenital heart diseases.
Material and methods: A small cohort of patients (n = 10) who were referred to our Centre for percutaneous pulmonary valve implantation (PPVI) and aortic coarctation stenting, and presenting complex anatomical features, was considered in this study. Clinical image data acquired for conventional assessment were post-processed to set up the 3D patient-specific implantation site, thus modelling realistic anatomy, physiology and boundary conditions. According to the clinical indication, various cardiovascular devices including balloons, stents and valves were virtually implanted in each patient-specific model. Finite element (FE) and computational fluid dynamics (CFD) analyses were used prospectively to simulate device implantation and investigate hemodynamic changes. Clinical outcomes from the real procedures, when already performed, were compared with the predictions of the computational analysis.
Results: Simulations allowed assessment of intervention feasibility and device selection for each individual case. Potential post-operative scenarios were highlighted by the measure of contact areas between device and implantation site, and vessel wall stress distributions. Computational fluid-dynamic analyses in the coarctation patients were helpful to assess flow split after intervention using different stenting approaches. Clinical procedures were carried out in accordance with the computational predictions in all cases except one PPVI. The computational framework process was completed within a week with no requirements for additional clinical data or increase in direct costs.
Discussion: Translation of patient-specific cardiovascular models towards their clinical use is promising to support interventional planning of complex cases. Simulations can predict outcomes of interventions reliably, rapidly, and at low costs. In addition, these tools can provide information about the performance of existing devices and potentially support the development of new ones.

O112
IN-SILICO AND *IN-VITRO* TESTS OF A NOVEL MODULAR HEART VALVE PROSTHESIS FOR THE PULMONARY POSITION
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Introduction: A transcatheter modular pulmonary heart valve prosthesis was developed for the percutaneous treatment of patients with insufficient pulmonary valves, conduits etc. which have a larger anatomy and cannot be treated with the commercially available devices on the market (Medtronic Melody and Edwards Pulmonic). The modular device consists of the valve bearing basic element (BE) and an anchoring element (AE). Latter can be connected on top or bottom to the BE and adapt to the deformed anatomy. Here, the flexibility and the adaptation of the device are tested in-silico.
Material and methods: A 35 mm OD nitinol BE and a 40 mm OD AE were iteratively developed by means of an anatomy analysis of the pulmonary artery (PA), CAD tools and finite element analysis (FEA). The AE was designed with small curved struts in axial direction for a better flexibility during insertion via catheter through the right ventricle. A FEA model was implemented in Abaqus (Simulia, USA) to test the flexibility in axial direction of the BE and the complete device (both elements connected together) during insertion procedure. The simulation contains 3 steps: (1) crimping of the device, (2) insertion via catheter through the curved pathway, (3) deployment. A second FEA model mimics the deployment into a PA to test the adaptation. The simulation contains 3 steps: (1) crimping of the device, (2) deployment in the PA, (3) pressure on the leaflets.
Results: Both elements were designed as short as possible to fit into a PA. The flexibility in axial direction of the AE, tested in-silico seems to be sufficient for insertion via catheter through the curved pathway. The device adapts well to the anatomy of the PA.
Discussion: The developed transcatheter modular pulmonary heart valve prosthesis showed good in-silico results. *In-vitro* tests are ongoing to validate the simulations and to further develop the prosthesis.

O113
OVERSIZING PULMONARY CONDUITS IN CHILDREN: HEMODYNAMIC CONSEQUENCES
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Introduction: Implanting the largest valved conduit possible-oversizing-for reconstruction of absent right ventricle to pulmonary artery connection in certain types of congenital heart defects was suggested as a compensating measure for somatic outgrowth of the patient. One effect that has not been investigated yet is the hemodynamic consequence of implanting a larger sized conduit in a child pulmonary artery.
Material and methods: To determine the impact of conduit oversizing on the hemodynamics, calculated wall shear stresses (WSS) of image-based Computational Fluid Dynamic (CFD) simulations were used as indicator. Three different sizes of valved conduits (20 mm, 22 mm and 24 mm), including the largest possible conduit size, virtually implanted in a child sized healthy pulmonary artery and the corresponding adult sized model were investigated. The size of the child model was chosen to correspond to the age and body surface of a child who's body growth has become more stable, so oversizing would exert its hemodynamic effects for a longer period of time.
Results: The child and adult models show a decrease of the mean WSS (approx. 26%) in the whole domain with an increase of the conduit size. When looking at the mean WSS at the anastomosis, for the child model the WSS is significantly increased (approx. 40%) when oversizing (Z-score + 3.21). In contrast, the stresses are decreased for the adult model (34%) when using the largest conduit (Z-score + 0.25).
Discussion: Based on the results of this study, it must be considered that choosing a prosthesis size which will lead to high WSS and associated intimal reaction can defeat the benefit of having a nominally larger orifice area directly after implantation. A 40% increase of WSS is significant and could explain clinically observed problems of implanting certain types of conduits with well described outcomes of supravalvular/distal anastomotic stenosis.

O114
CFD ANALYSIS OF PRE- AND POST-INTERVENTIONAL HEMODYNAMICS IN BAV PATIENTS UNDERGOING VALVE AND/OR AORTIC SURGERY
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Introduction: Aortic regurgitation and dilatation are two comorbidities commonly seen in bicuspid aortic valve (BAV) patients. Both pathologies

frequently require intervention. Aortic regurgitation is typically treated by aortic valve replacement to avoid congestive heart failure, while aortic dilatation is commonly treated by vascular graft implantation to prevent aortic dissection or rupture. To avoid adverse outcomes, treatment is often without alternative. Nevertheless, comparing pre- and post-interventional state in these patients can help understand the effects of valve and aortic surgery on aortic hemodynamics.
Material and methods: Pre- and post-interventional MRI data was obtained from 6 patients exhibiting BAV and at least one associated comorbidity (dilatation and/or regurgitation), who underwent valve and/or aortic surgery. Interventions included valve-sparing aortic root replacement, Ross-Konno procedure and composite aortic valve graft replacement. Aortic geometries were reconstructed from conventional MRI data and peak-systolic steady-state CFD simulation was subsequently performed on these geometries. 4D flow MRI data was used to obtain patient-specific inlet velocity profiles.
Results: Replacement of the dilated ascending aorta led to increased wall shear stress in two patients, likely due to the reduced vessel diameter after surgery. Few relevant differences beyond wall shear stress were seen between pre- and post-interventional flow fields, when flow rates were kept identical. When accounting for the post-interventional reduction in systolic flow rate seen in the regurgitation patients, aortic hemodynamic in this group improved compared to the pre-interventional state.
Discussion: Reductions in aortic diameter due to treatment of dilatation may lead to locally increased wall shear stress. The pathological relevance of this finding remains to be evaluated. Furthermore treatment of aortic regurgitation may lead to improved aortic hemodynamics through reduction of peak systolic flow rate.

O115
NUMERICAL INVESTIGATION OF HEMODYNAMICS AFTER VALVE REPLACEMENT IN BICUSPID AORTIC VALVE PATIENTS

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Introduction: Bicuspid aortic valve (BAV), one of the most common congenital heart diseases, is associated with several sequelae such as: aortic dilation, aneurysm formation and regurgitation. Additionally, BAV occurs in approximately two thirds of patients suffering coarctation of the aorta. BAV treatment usually consists of replacement of the aortic valve with biological or mechanical valves. Since this procedure poses a high risk of bleeding and thrombosis, it is only performed if a significant valve stenosis or aortic regurgitation is present. Therefore, a tool to predict aortic hemodynamics after valve replacement might improve treatment outcome and life expectancy of BAV patients.
Material and methods: Cardiac MRI, including conventional structural data, as well as 4D flow data, from six patients was acquired. Three-dimensional aortic geometries of these patients were segmented including the aortic root and valve area. Biological and mechanical valve geometries were inserted virtually into these aortic geometries at the valve area. Peak systolic velocity vector fields in front of the inserted valve geometries were extracted from the 4D flow MRI data and applied as boundary condition of a steady state CFD Simulation.
Results: Virtual valve replacement using mechanical valves led toa decreased helicity and smaller secondary flow structures within the ascending aorta. Consequently, replacement using a biological valve resulted in approximate two-fold increase of degree of secondary flow. Other parameters, such as surface averaged wall shear stress, pressure drop and turbulence were also increased using biological valves.
Discussion: Using virtual valve treatment, we were able to show striking differences in aortic hemodynamics after insertion of biological and mechanical valves. The meaning of these differences is yet unclear and needs further investigation and validation. Numerical Investigation of hemodynamic change after virtual valve replacement might be a helpful tool for patient-specific treatment planning and thus could lead to an enhanced life expectancy.

Oral Session - Haemocompatibility, O116-O121

O116
HAEMOCOMPATIBILITY OF DEXTRAN COATED ACTIVATED CARBON MATERIALS

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Introduction: The surface properties of a biomaterial play a crucial role in their functionality, when used in an extracorporeal application. Activated carbon (AC) material during contact with blood can induce a range of biological responses such as; protein adsorption, thrombus formation, and inflammation resulting in unwanted clinical side effects. Our aim was to utilize pharmaceutical quality dextran, a biocompatible molecule to coat an adsorbent AC and study the coating influence on material porosity and haemocompatibility.
Material and methods: The granulated AC (HSGD) was obtained by pyrolysis of nitrogen containing synthetic resins with subsequent activation by IEPOR (Ukraine). A range of 5-30% dextran coated AC beads were prepared and characterised by low temperature nitrogen porosimetry to establish the effect of coating on their porosity. A comprehensive haemocompatibility study using healthy donor blood was carried out according to European standard (EN ISO 10993 part 4) including; coagulation, haematology, platelet and complement system analysis.
Results: The majority of surface area and pore volume of HSGD is represented by “small” (mean diameter 3.2 nm) and “large” mesopores (mean diameter 48 nm). Surface area and pore volume of both sizes of mesopore are reduced in direct relation to the percent dextran coating. The batch studies of AC incubation with blood demonstrate that coating improves haemocompatibility by reducing: AC fine formation, fibrinogen adsorption, haemolysis, complement activation and albumin adsorption. Uncoated as well as dextran coated AC in these experiments did not appreciably activate blood cells or the coagulation system.
Discussion: These findings suggest that the AC material HSGD, particularly with a dextran coating, is a suitable adsorbent material for blood contacting extracorporeal applications.

O117
THE FINE LINE IN TUNING HAEMO- AND BIO-COMPATIBILITY VIA SURFACE MODIFICATION: CASE STUDY OF GELATIN-PET SYSTEMS

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Introduction: More than half of the population suffers from cardiovascular diseases and the demand of synthetic grafts dramatically increased over the years. General requirements for synthetic grafts include the presence of a non-thrombogenic surface, host compatibility and sufficient mechanical strength. Poly(ethylene terephthalate), PET, fulfils the first requirements due to its excellent mechanical properties and inertness, respectively. Its major drawback is the poor surface properties that directly influence biological performances (eg. haemo-and bio-compatibility). Over the years, an impressive number of articles reported surface modification of PET. Most included cell tests or haemocompatibility screenings, but very few discussed both. In the present study, we show the importance of performing a complete screening of these materials. The influence of several parameters, such as substrate surface properties (eg. wettability, changed by plasma treatments) and surface modification protocols are thus herein reported. Most important, their effect over *in vitro* performance is presented.
Material and methods: Gelatin-modified PET were characterized in depth using SCA, AFM and XPS, combined with radiolabelling. Whole blood to assess preliminary haemocompatibility and HUVEC cells to investigate preliminary cell-biomaterial interactions were applied on all investigated samples.
Results: Synergetic effect of plasma treatment and variations of the applied surface modification protocol presented an unexpected poor haemocompatibility and ambiguous HUVEC adhesion results, while the influence of each parameter independently showed acceptable *in vitro* results.

Discussion: A multi-parameter study on surface modification of PET with gelatin was performed and successfully proved the major impact that a subtle change in protocol has over *in vitro* performances.
Acknowledgement: The authors would like to thank UGent (project GOA, BOF10/GOA/005) and FWO for the financial support.

O118
CONTROLLED RELEASE OF HYDROPHILIC PHARMACEUTICAL AGENTS FROM COAXIALLY ELECTROSPUN FIBERS
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Introduction: Coaxial electrospinning is a novel technique to prepare polymeric core-shell fibers, enabling the direct encapsulation of drugs in the core. Electrospun fibers have received scientific attention due to their unique properties including high surface-area-to-volume ratio and structural similarity to the extracellular matrix (ECM). Aim of this work was to create polymeric fibrous carriers and investigate their structural, morphological and physical properties, as well as, the release kinetics of the encapsulated drug.
Material and methods: Bovine serum albumin (BSA) and polycaprolactone (PCL) were separately dissolved in 2,2,2-trifluoroethanol (TFE) at concentrations of 15 mg/ml and 150 mg/ml, respectively. A blend solution with both substances was prepared to serve as a control. The morphological properties of the fibers were assessed with scanning electron microscopy (SEM). Cyclic uniaxial mechanical tests were performed by a tensile testing system (LM1 Test bench, BOSE). 15 × 10 mm strips were tested at 0-30% strain, 1 Hz and dry conditions. The hydrophilicity of the fibers was studied using a contact angle assay. The cumulative release of BSA was assessed by UV-vis spectrometry and the release mechanism was investigated.
Results: The coaxially spun fibers had a smooth, "spaghetti-like" shape with an average diameter of 0.96 ± 0.21 µm and a contact angle of 99.14 ± 7.58°, being more hydrophobic and thinner in contrast to the control sample. Young's modulus was significantly higher in the coaxial samples (59.78 ± 2.02 MPa coaxial vs 52.18 ± 1.16 MPa control). The total amount of BSA released during the first 24 hours was 42.23%, in contrast to 49.3% for the control, while Fickian diffusion was the release mechanism for both cases.
Discussion: Thinner, more hydrophobic fibers with higher tensile strength were created with the coaxial approach, providing a more sustained release of BSA as potential candidates for drug delivery applications.

O119
AN ELECTRO-ACTUATABLE HYDROGEL VASCULAR OCCLUSION DEVICE: AN *IN-VITRO* AND *IN-VIVO* EVALUATION
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Introduction: Because of favourable characteristics there is a growing interest for the use of hydrogels in biomedical applications. Moreover they can be activated by various stimuli, for example electrical fields. This study evaluates an electro-responsive hydrogel for intravascular applications.
Material and methods: Pluronic methacrylic acid hydrogel was tested *in-vitro* for its haemolytic and cytotoxic effects, and for its swelling and occlusion capacity. Minimal invasive implantation in the carotid artery of sheep was used to evaluate its long-term biological effects, through biochemical, macroscopic, radiographic, and microscopic evaluation.
Results: *In-vitro* evaluation showed no haemolytic or cytotoxic effects. Occlusion could be obtained within a short period of time. *In-vivo* evaluation showed a persistent occlusion of the artery at time of autopsy with no systemic effects and mild effects on the arterial wall.
Discussion: An endovascular delivered electro-responsive hydrogel can cause a long-term arterial occlusion. This material can be used as an endovascular occlusion device. More important it might be a base for future development of hydrogels for intravascular applications (e.g. intra-vascular drug delivery, aneurysm sac occlusion).

O120
QUANTIFICATION OF ADHERENT PLATELETS ON BIOMATERIALS. COMPARISON OF COLORIMETRIC AND MICROSCOPIC ASSESSMENT
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Introduction: Platelet adhesion to artificial surfaces is one of the most important indicators for the thrombogenicity of implant materials and assessed by different colorimetric- or microscopy-based techniques. Here, we study how colorimetric assay data correlate with the image-based quantification of adherent platelets by comparing two colorimetric assays (lactate dehydrogenase (LDH) and acid phosphatase (ACP)) with a microscopic approach.
Material and methods: An *in vitro* static thrombogenicity test was applied to study human platelet adhesion on: medical-grade polytetrafluoroethylene (PTFE), medical-grade silicone and cell culture-grade polyethylene terephthalate (PET). For the image-based determination of platelet densities, adherent platelets were fixed and fluorescently labelled. These densities were applied as reference values for the comparisons with results from the colorimetric assay. Correlation between different platelet concentrations and ACP as well as LDH absorbance measurements were analysed to estimate accuracy and association of both parameters. ACP and LDH release from resting and ADP-stimulated platelets was studied to estimate how platelet activation influences colorimetric assay results.
Results: Densities of adherent platelets ranged between 15,490 ± 3,370 platelets·mm^{-2} (PTFE) and 440 ± 110 platelets·mm^{-2} (silicone) and 5,080 ± 1,670 platelets·mm^{-2} (PET) and differed significantly between all polymers ($p<0.05$). Correlation coefficients between microscopic and colorimetric determination of platelet densities ranged between $r = 0.89$ (LDH, $p<0.0001$) and $r = 0.91$ (ACP, $p<0.0001$). Comparisons of both colorimetric assays revealed a correlation of $r = 0.9246$ ($p<0.0001$). ACP absorbance measurements of platelet standards corresponded well to an ideal linear regression while LDH data deviated from expected values. LDH release after platelet activation was significantly higher compared to ACP.
Discussion: Acceptable correlations of both colorimetric assays and the image-based assessment of adherent platelets were achieved at low platelet concentrations. For thrombogenicity studies applying physiological platelet concentrations, the ACP assay appears more suitable due to better linearity of the standards, less variability and lower susceptibility on platelet activation.

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FLOW SCALE AFFECTED THE SHEAR-INDUCED BLOOD TRAUMA
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Introduction: As suggested by many researchers, it is clear that the shear stress and its exposure time are main trigger to the blood trauma leading to the hemolysis according to the blood pump usage. Additionally, the recent study by Dr. Maruyama et al suggested that the surface roughness would be also a key parameter for the shear induced blood trauma (Maruyama et al J Artif Organs 2005). If their suggestion is truth, we supposed that the flow scale should also effect on the hemolysis. We made a hypothesis that the surface roughness to flow scale ratio should have a great impact upon the shear-induced hemolysis. Therefore the purpose of this study is to examine the feasibility of our hypothesis.
Material and methods: We developed the constant shear flow generator with the three kinds of inner cylinder's diameter for the adjustment of flow scale 1.00, 1.25, and 1.50 mm. The several levels of surface roughness between 0.3 and 0.9 were given to the surface of the inner cylinder. The porcine blood bought from the Slaughter house was exposed to the constant shear stress of 8.5 Pa using the shear generator under the several combination among the surface roughness and flow scale and exposure time. And then, the plasma free hemoglobin level of each condition was assessed by the light absorbance measurement.
Results: As we supposed, the hemolysis level increased with the decrease of flow scale under the similar surface roughness levels near 0.35. In addition, it was shown that the hemolysis level increased with the surface roughness to flow scale ratio.
Discussion: The result validated our hypothesis. We clearly showed that the flow scale gave an impact upon the hemolysis level, and the ratio of surface roughness scale to the flow scale would be very important for the hemolysis level.