IJAO
ISSN 0391-3988
Int J Artif Organs 2017; 40(8): 382-428
DOI: 10.5301/ijao.5000629
**ORAL PRESENTATIONS**

# Abstracts from the 44th ESAO and 7th IFAO Congress, 6-9 September 2017, Vienna, Austria

## Session: Liver Failure

### O1
### MARS EFFICIENCY ACCORDING TO TREATMENT MODALITIES: EXPERIENCE IN PATIENTS AFFECTED BY ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) AND COMPARISON WITH DATA REPORTED IN THE LITERATURE

*Marangoni R, Bellati G, Colombo A*
Department of Medicine, S. Anna Hospital, Como, Italy

**Background:** Data reported in the literature on the efficiency of MARS (Molecular Adsorbent Recirculating System) in ACLF treatment are often inconsistent. Moreover, no guidelines are available for MARS treatment, whose modalities can play an important role in the removal of liver metabolite.
**Aim:** To compare the effects of MARS treatment in 119 patients with those described in the literature.
**Methods:** 119 patients affected by ACLF secondary to different primary liver diseases have been treated with MARS according to the following protocol: 2-7 daily sessions according to the patient's need; 5 hours/session; 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. The obtained results have been compared with data from other studies on the effects of MARS treatment in patients affected by ACLF.
**Results:** Among 119 patients, the recovery of liver function and clinical improvement were reached in 96 with INR lower than 3; no improvement has been observed in patients with INR higher than 3. The evaluation of the published data has revealed that conflicting results reported in different studies on MARS efficacy are associated to the heterogeneity of clinical conditions of the treated patients, and specifically to different underlying liver diseases, degree of liver failure before treatment and MARS treatment modalities. Better results have been assessed in patients with liver failure without impairment of coagulation factors.
**Conclusions:** Our experience confirms that the efficacy of MARS treatment in ACLF is strictly related to clinical conditions before treatment. In particular, greater advantages have been obtained in ACLF patients who were not at the end stage of the disease that is with coagulation factors not altered yet. Treatment modalities are nevertheless important to achieve the higher exploitation of the method.

### O2
### MOLECULAR ADSORBENT RECIRCULATING SYSTEM (MARS) IN ACUTE LIVER INJURY AND GRAFT DYSFUNCTION: RESULTS FROM A CASE CONTROL STUDY

*Gerth H[1], Thölking G[1], Hüsing-Kabar A[2], Kabar I[2], Schmidt H[2], Pohlen M[3]*
[1]Department of Nephrology, University Hospital Münster, Münster, Germany
[2]Department of Hepatology, University Hospital Münster, Münster, Germany
[3]Department of Oncology, University Hospital Münster, Münster, Germany

**Background:** The primary therapeutic goal in treatment of liver injury is supporting liver regeneration on the one hand or bridging to liver transplantation (LT) on the other hand. Molecular adsorbent recirculating system (MARS) therapy has shown beneficial effect on specific symptoms of liver failure but a general survival advantage has not been shown yet.
**Aim:** We studied the effects of MARS therapy compared to standard medical treatment (SMT) in two separate patient cohorts, namely, in patients presented with an acute liver injury and in those with graft dysfunction (GD).
**Methods:** We report on our experience over a 6.5 year period with 73 patients treated with SMT or SMT and MARS (MARS group). 53 patients who suffered from acute liver injury in the native liver without a preexisting liver disease (SMT n = 31, MARS n = 22) and 20 patients showed a severe GD after LT (SMT n = 10, MARS n = 10).
**Results:** The whole cohort was characterized by predominantly hemodynamic and respiratory stable patients with a low HE-grade and a MELD-score of 20.57 (MARS) or 22.51 (SMT, p = 0.555), respectively. Within the MARS group, the median number of extracorporeal therapy sessions was four (range = 3-5 sessions). Independent of the underlying etiology, MARS improved the patients' bilirubin values for the short term compared to SMT alone. In patients with acute liver injury, this response sustained even after end of MARS therapy. Contrary, majority of patients with GD and initial response to MARS therapy worsened in hyperbilirubinemia. No differences in 28-day mortality were observed in acute liver injury (MARS 5.3% [95% CI: 0-15.3]; SMT 3.3% [95% CI: 0-9.8], p = 0.754) and GD (MARS 20.0% [95% CI: 0-44.7], SMT 11.1% [95% CI: 0-31.7], p = 0.478).
**Conclusions:** Although not improving 28-day mortality, MARS therapy increased short-term response in patients with acute liver injury as well as with GD. Especially in acute hepatic injury, use of MARS therapy resulted in a sustained stabilization of the liver function and improved liver regeneration. It might be hypothesized that short-term response to MARS predicts further course of disease.

### O3
### EFFECTS OF NORMOTHERMIC LIVER PERFUSION AFTER 1 HOUR OF WARM ISCHEMIA

*Fernandez-Lopez I[1], Rivera A[1], Sanchez del Arco R[1], Gutierrez-Gutierrez J[1], Banares J[2], Del Cañizo J[1,2]*
[1]Artificial Circulation Laboratory, Experimental Surgery, Hospital General Universitario Gregorio Marañon, Madrid, Spain
[2]Department of Surgery, Universidad Complutense de Madrid, Madrid, Spain

**Background:** In order to rise livers graft availability, uncontrolled donation after circulatory death have been proposed. Diverse studies have questioned the paradigm of cold storage, proposing normothermic perfusion as more efficient.
**Aim:** The aim is to determine the hemodynamics and biochemical alterations due to ischemia-reperfusion injury in livers subjected to warm ischemia.
**Methods:** 9 livers from Minipigs were perfused in normothermia for 6 hours. These one were divided into: non–ischemic group (control, n = 4) and ischemic group (t = 60 min of warm ischemia, n = 5). Hemodynamics parameters, biliary outcome and perfusion solution samples were collected and compared hourly. Tissue samples were harvested at the end of the surgery and at the end of perfusion; in the ischemic group another one was harvested at the end of warm ischemia time. Student t test was performed, considering p<0,05 as significant.
**Results:** The normothermic perfusions of the livers, submitted warm ischemia were hemodynamically stable. Total and Hepatic artery flow were higher in ischemic group, whereas Portal vein flow in control. Cytolytic parameters were raised in ischemic group, though the percent increase of ALT levels was higher in control. Oxygen consumption and biliary production were higher in ischemic group. After warm ischemia, pathologic samples shown microvesicular steatosis, that solved after perfusion. There were no differences in first and last samples between each group.
**Conclusions:** One hour of warm ischemic injury increases the organ flux after normothermic reperfusion mainly due to an increased artery flux. Ischemia increases the hourly bile production. Further studies must be made to elucidate if this results in a better graft function. The perfusion machine is able to revert the hepatocytic mitochondrial dysfunction, suggested by the microvesicular steatosis. Next molecular assays should be done.

**O4**

**LIVER FUNCTIONALITY MODEL DURING NORMOTHERMIC PERFUSION**

*Rivera A[1], Fernandez-Lopez I[1], Gutierrez-Gutierrez J[1], Sanchez del Arco R[1], Martinez J[2], Del Cañizo J[1,2]*

[1]Artificial Circulation Laboratory, Experimental Surgery, Hospital General Universitario Gregorio Marañon, Madrid, Spain

[2]Department of Surgery, Universidad Complutense de Madrid, Madrid, Spain

**Background:** Normothermic liver perfusion is a developing technic in graft storage field. Currently, most of the measured values during perfusions, such as ion levels or transaminases, have not been considered as potential markers of liver functionality. Otherwise, there are some parameters that have shown to be correlated with a better liver graft function after perfusion (biliary outcome, oxygen consumption, ATP levels) although many of them are difficult to obtain immediately.

**Aim:** The aim is to identify subrogate markers able to evaluate in real time hepatic function during perfusion.

**Methods:** Nine porcine livers were perfused in normothermic conditions for 6 hours using a machine developed in our laboratory. They were exposed to different ischemia times from 45 minutes to 90 minutes. We collected hemodynamical (pressure, flow, resistance), biochemical (ions, lactate, AST, ALT, glucose, ALP, LDH, hemoglobin), and function (biliary outcome, oxygen consumption) parameters. For statistical analysis multiple linear regression was performed, using biliary outcome and oxygen consumption as response variables. Explanatory variables for the best model were selected as coefficient of determination R2 closes to 1.

**Results:** Platelets (Pl), sodium (Na) and hemoglobin (Hb) showed to be adequate predictable variables for oxygen consumption per 100 grams (OC)(R = 0,785). Organ flux per gram (OF), calcium (Ca) and percent increase of AST levels (AST) showed to be adequate predictable variables for biliary outcome (BO) (R = 0,734). There were no collinearity between the explanatory variables. ALT, ALP and LDH showed linear relationship, they were excluded from the analysis.

**Conclusions:** Biochemical parameters such as calcium, sodium, AST, hemoglobin and platelets levels are feasible and immediate variables to assess liver functionality. Multifactiorial analysis and mathematical modeling are viable tools in real time evaluation of liver injury.

## Session - Biomaterials I: Hard Tissue Replacement

**O5**

**STRUCTURE AND PROPERTIES OF CARBON FIBER-REINFORCED HYDROXYAPATITE COMPOSITE MATRIX**

*Arkharova N[1], Klechkovskaya V[1], Krylov S[2], Avvakumov I[2], Voronzov A[2], Krylov N[2], Krasheninnikov M[3], Oganesan R[3]*

[1]Shubnikov Institute of Crystallography of FSRC "Crystallography and Photonics" of RAS, Moscow, Russian Federation

[2]BITECA, Moscow, Russian Federation

[3]Sechenov First Moscow State Medical University, Moscow, Russian Federation

**Background:** Carbon fiber -hydroxyapatite (CF-HAP) composites are promising materials for bone tissue engineering. The reinforcement of HAP with CF leads to improve physico-chemical and biological properties of the monolithic HAP.

**Aim:** The aim of this work is the development of highly porous carbon fiber- hydroxyapatite composite matrix with superior mechanical and biological properties. For this goal a novel method of CF-HAP preparation was proposed: carbon fibers (5-10%) were added to water solution during synthesis of HAP nanocrystals. The morphology, micro- and nanostructure, mechanical and biological properties of prepared CF-HAP composites were characterized.

**Methods:** Nano-HAP and nano-HAP partially substituted by iodine and selenium ions (Iris, Russia) were synthesized. Polysaccharides (PS) supplied from Kelco were used as modifying agents. The reinforcement of HAP was achieved by addition of carbon fiber (Grafit, Russia) to HAP-PS matrix. The morphology, structure and phase composition of CF-HAP composites were analyzed by SEM, FTIR, XRD and ED methods. Nanostructure and HAP orientation relative to carbon fibers were examined by TEM and HRTEM methods. The cytotoxicity of CF-HAP materials was evaluated by the standard methods using human mesenchymal cells (MSC).

**Results:** HA-CF composites with various content of the CF from 5 to 10% possess open micro-and nanoporous structure with porosity up to 80%. It was found that an increase in the CF content results in an increase of Young's modulus values. CF-HAP composites support mesenchymal cell viability.

**Conclusions:** The highly porous carbon fiber- hydroxyapatite (CF-HAP) composite matrixes with various CF content were synthesized. These materials with superior mechanical and biological properties could be promising bone substitute materials.

**O6**

**SUPRAMOLECULAR GELATIN NANO-COMPOSITES WITH ENHANCED SOL-GEL TRANSITION TEMPERATURE**

*Mohseni Moghaddam M, Shokrolahi P, Barzin J*

Biomaterials Department, Iran Polymer and Petrochemical Institute, Tehran, Islamic Republic of Iran

**Background:** Generally nature of the crosslinks in the networks of hydrogels such as gelatin, are classified to covalent and non-covalent. Hydrogen bonding is the most useful interactions in self- assembly. UPy (where UPy is a quadruple H-bonding motif) grafted Zn-substituted HAp was synthesized and as we have presented in ESAO2016, the effects of Zn substitution on structural properties of the HAp were investigated specifically.

**Aim:** The aim of this study was to develop novel supramolecular gelatin-based composites including modified gelatin with UPy motifs (GelUPy) and the combination of GelUPy with UPy grafted Zn-doped HAp particles to become acquainted in hard tissue regeneration.

**Methods:** Briefly GelUPy was synthesized in two steps. First, pyrimidinone was reacted with hexadiisocyanate (UPy precursor). Second, Gelatin and the UPy precursor were reacted to yield modified gelatin and also ZnHApUPy nanoparticles were synthesized for the same.

**Results:** In FTIR spectrum of GelUPy, a peak was appeared at 1659 cm-1 correlated with urea-C=O vibrations. Also, a characteristic peak was seen for the = C-H stretching vibration of the UPy motif at 3053 cm-1. Mechanical properties of the composites were investigated on the swollen disks. The acquired stress-strain curves showed an increasing stiffness for The swollen disks containing GelUPy, and ZnHApUPy showed the maximum value of compressive modulus of about 841 KPa, while the minimum amount was registered for those which containing GelUPy and ZnHAp (about 564 KPa). The sol-gel transition temperature (Tgel) changes of the Gelupy and the supramolecular disks was investigated through rheological measurements. Tgel at about 62°C was recorded for GelUPy indicating a significant increase compared to the native gelatin. Therefore, GelUPy and its composites with ZnHApUPy hold promise as tissue engineering materials.

**Conclusions:** We showed that GelUPy and UPy grafted Zn- HAp could be synthesized and combined to yield supramolecular nano-composites which can be considered as useful materials for application as bone tissue engineering scaffolds.

**O7**

**EXPERIMENTAL INVESTIGATION AND NUMERICAL ANALYSIS OF THE PMMA- BASED BIOCOMPATIBLE VERTEBRAL CEMENT FLOW**

*Obidowski D, Sobczak K, Witkowski D, Tyfa Z, Stajuda M, Reorowicz P, Palczynski T, Józwik K*

Institute of Turbomachinery, Lodz University of Technology, Lodz, Poland

**Background:** A significant progress in medicine is constantly increasing an average human lifespan. The aging of the organism usually leads to an inevitable degradation of bone tissues. As a result, there is an increase of the number of people suffering from the osteoporosis, hence, vertebroplasty and kyphoplasty procedures are getting more common. Surgeon must have a control over the whole process of the vertebra filling avoiding a contact with the surrounding tissues. Cements used during those procedures are non- Newtonian fluids and are characterized by a high and increasing-in-time dynamic viscosity. Thus, thorough examination of the cement flow distribution is mandatory.

**Aim:** The paramount objective of the following research was to establish the flow parameters of the PMMA- based bone cement flow on the test rig,

mimicking conditions representing the cement injection. Obtained results served as the basis for the numerical analysis of the cement flow, leading to creation of an algorithm that enables performing the virtual vertebroplasty.
**Methods:** Experimental tests have been performed with the use of the different channels (varied shapes, internal diameters, lengths). During tests, a pressure drop and velocity of the medium were acquired. On the basis of the experiments, cement properties were estimated for further use in the numerical simulations, carried out as a multiphase, unsteady flow, utilizing the time-dependent viscosity model.
**Results:** Authors designed and built an experimental setup allowing one to perform the virtual vertebroplasty. Results obtained on the test rig were used during the numerical analysis of the cement flow. Satisfactory numerical results were obtained, notwithstanding low Reynolds number and complex fluid model.
**Conclusions:** A conformity between experimental and numerical analysis was reached, what suggests the reliability of both techniques.
**Acknowledgements:** This project was financially-supported by The National Center for Research and Development in Poland (PBS3/B9/45/2015).

## O8
## TRANSFORMATION OF HYDROGEL SCAFFOLDS USING ULTRASHORT LASER PULSES FOR TISSUE ENGINEERING

*Savelyev M, Gerasimenko A, Ickitidze L, Podgaetsky V, Selishchev S*
Biomedical Systems, Moscow Institute of Electronic Technology (MIET), Moscow, Russian Federation

**Background:** Lasers generating pulses with high peak powers in the range of ultrashort pulse duration open up new opportunities for modern biomedical material science. With their help, it is possible to create materials and structures that possess bioresorbability and biostability for regenerative medicine and tissue engineering, when 3D cellular matrices are used to restore solid tissues.
**Aim:** To generate biodegradable cells scaffolds with laser radiation with ultrashort pulse at high peak power. In this case, the interaction of laser radiation with substance is fundamentally different from the effect of laser radiation of low power, due to the appearance of nonlinear effects leading to the transformation of the material.
**Methods:** Laser radiation with high-power (causes nonlinear effects) was used for the formation of 3-D structures. The threshold intensities of the rise of nonlinear effects and photoinduced transformation were determined from the results of the Z-scan and the method of fixed location of the sample. A hydrogel suitable for the formation of the scaffold was prepared from the 25% solution of bovine serum albumin in water with 0.001 g/L of high-purity carbon nanotubes.
**Results:** The optical characteristics of the hydrogel were obtained: linear absorption 1.3 1/cm, nonlinear absorption 350 cm/GW, values of the thresholds intensities of the nonlinear interaction 0.5 KW and photoinduced transformation of the sample as a function of the duration of the action of laser radiation in the pulsed mode. Scaffold was formed using the technique of structuring high-power laser radiation that causes nonlinear effects in the substance. The exposure time of ultrashort laser radiation varied from 20-60 seconds, depending on the laser radiation power from 0.085 to 0.015 MW.
**Conclusions:** Cells scaffolds were obtained from the hydrogel for using in the recovery of hard tissues. Increasing the peak power of laser radiation leads to a reduction in the time required to form the scaffold at a given point.

## O9
## OSTEO-BALLS WITH ORGANIC-INORGANIC CHIMERIC HYDROGEL MICROBEADS FOR RAPID BONE FORMATION

*Iwanaga S, Nakamura M*
Faculty of Engineering, University of Toyama, Toyama, Japan

**Background:** In bone tissue engineering, solid scaffolds such as hydroxyapatite (HA) or tricalcium phosphate (TCP) are frequently used for implantable artificial bone materials. On the other hand, soft mater such as collagen is also one of important constituents. Thus, mixture of collagen and HA is often used for bone tissue engineering. HA is useful for increasing tissue stiffness, however, it takes long time to fabricate bone tissues because remodeling speed of HA is slow.
**Aim:** In this paper, we tried to create soft-mater materials that enables to achieve rapid Ca crystallization. We focused on organic-inorganic chimeric hydrogel suitable for osteoblast calcification and applied this material to form osteo-balls, which can be unit parts for fabrication of 3D bone tissues.
**Methods:** To prepare chimeric hydrogel, methacrylated gelatin was modified with phosphate and silane. The modified gelatin was crosslinked by UV. Crosslinked gels were soaked into Hanks' balanced salt solution (HBSS) to replace DMSO. Then, chimeric hydrogel was soaked with simulated body fluid (SBF) for 3 days at 37°C. After soaking, gel was washed with HBSS and stained with alizarin red to confirm Ca crystallization.
**Results:** The surface of chimeric hydrogel was strongly stained with alizarin red. On the other hand, unmodified hydrogel was not stained even after soaking into SBF. Cells adhered onto microbead surfaces. After differentiation, cells were considerably stained by alizarin red. Osteo-balls were easily integrated by molding. After mold-culturing with differentiation medium, Ca crystallization of integrated 3D structure was also confirmed by alizarin red staining.
**Conclusions:** In this study, we fabricated 3D tissues using osteo-balls. Gelatin was modified with phosphate and silane, and rapid Ca crystallization was observed onto osteo-ball fabricated with the organic-inorganic chimeric hydrogel. Thus, it is indicated that unit parts for rabid bone formation would be easily fabricated with our method. We believe our material and fabrication technology would be helpful for rapid bone tissue engineering.

## O10
## BONE INGROWTH IN MACRO POROUS TRICALCIUM PHOSPHATE IMPLANTS PRODUCED BY LITHOGRAPHY-BASED CERAMIC MANUFACTURING (LCM)

*Bomze D[1], Schwentenwein M[1], Weber F[2], Homa J[1]*
[1]Lithoz GmBH, Vienna, Austria
[2]Center of Dental Medicine, University of Zurich, Zurich, Switzerland

**Background:** Tricalcium phosphate (TCP) is established as material for bone replacement and bone cements in medical applications because of its bioresorbability and the similarity to hydroxyl apatite, the inorganic phase in bone tissue. LCM is a 3D printing technique that structures ceramic slurries, which consist of ceramic particles dispersed in an organic binder matrix, in a layer-by-layer process using visible light. Thus it is possible to create even complex 3D structures virtually without any limitation in design. This technology has emerged as the state of the art method for the additive manufacturing of dense high- performance technical ceramics and bioresorbable ceramics.
**Aim:** The aim of this contribution was to analyse the geometrical reproducibility of LCM manufactured TCP scaffolds. Furthermore, a comparison between TCP and titanium as implant material concerning the ingrowth of native bone was conducted.
**Methods:** Ceramic slurry consisting of TCP particles in an organic binder system was structured by the LCM process to produce a green body. This green body was subsequently thermally post-processed in order to remove the temporary polymeric binder, resulting in the final ceramic part. These parts were subsequently analysed towards their pore dimensions and in an in-vivo study on New Zealand White Rabbits concerning their ability to enhance healing of artificial bone defects.
**Results:** It could be shown that the reproducibility of the LCM process for TCP scaffolds is about 20 µm and that porous scaffolds with pore sizes down to 200 µm can be produced well with this process. The tissue sections revealed that TCP performs equally compared to the state of the art material titanium in terms of defect bridging. The bony area of the defect sites could be improved in case of the TCP based implants compared to those filled with titanium implants.
**Conclusions:** LCM is a very promising technique for the production of bioresorbable ceramic scaffolds with high reproducibility. Furthermore it was demonstrated, that the 3D printed TCP implants led to faster bone ingrowth into defects compared to implants made of titanium.

## Symposium: Limb Prostheses

### O11
### DEVELOPMENT OF A MODULAR BIONIC PROTOTYPE ARM PROSTHESIS

*Kast C[1,2], Rosenauer B[1], Meissner H[1], Aramphianlert W[1,2], Krenn M[1,3], Hofer C[4], Aszmann O[2], Mayr W[1,3]*
[1]Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria
[2]Christian Doppler Laboratory for Restoration of Extremity Function, Division of Plastic and Reconstructive Surgery, Department of Medical University of Vienna, Vienna, Austria
[3]Institute of Electrodynamics, Microwave and Circuit Engineering, Vienna University of Technology, Vienna, Austria
[4]Otto Bock Healthcare Products GmbH, Vienna, Austria

**Background:** Current achievements for arm prostheses focus on critical factors for clinical use, such as weight, bulk, and controllability. Especially for transhumeral amputees, light but still robust devices are important.
**Aim:** Here, we present a new concept of a modular system, based on bionic design principles, that is adaptable to the specific level of amputation of an arm. Additionally, the prosthetic arm mimics the weight distribution of a human arm.
**Methods:** The design concept follows three basic rules. First, the actuators are driving the joints by wires, which allows placement of the driving components within the prosthetic shaft or on other comfortable body areas outside of the artificial arm. This ensures a relief of contact pressure on the stump and potential side effects. Second, the prosthesis is deployable for transradial and transhumeral amputees. Third, lightweight and silent operation. The construction materials are AlCu4Mg1, Titan Grade 5, and carbon fiber enforced epoxy. Theses materials have similar load capacities as stainless steel, but less weight. The developed cambelt gear and low noise servo motors with optimized control patterns keep movement associated noise levels as low as possible.
**Results:** The ranges of motion are 120° for the elbow joint and 270° for the wrist joint. The elbow joint can lift a weight of maximal 3.3 kg with a lever of 30 cm through the entire range of motion within two seconds.
**Conclusions:** The system provides a novel bionic design that allows usage not only for transradial but also transhumeral amputation. The proximal weight distribution and the used materials increase the wearing comfort in daily tasks and mimic to a high extend physiological conditions.

### O12
### A PRELIMINARY TEST OF ONLINE LEARNING FES CONTROL BY FEEDBACK ERROR LEARNING USING FUZZY CONTROLLER IN CONTROLLING KNEE EXTENSION MOVEMENT

*Watanabe T, Akaike N*
Graduate School of Biomedical Engineering, Tohoku University, Sendai, Japan

**Background:** Feedback control is required to restoring movements by FES. However, it has not been used practically. Some of possible reasons are considered to be in designing a feedback FES controller and its parameter determination, and nonlinear characteristics with large time delay in muscle response to electrical stimulation.
**Aim:** This study focused on realizing a hybrid controller consists of feedback and feedforward controllers for FES control, which can be effective to control the musculoskeletal system that has nonlinear characteristics and large time delay. Fuzzy controller is considered to be useful to realize a practical feedback FES controller. The aim of this study was to test feedback error learning (FEL) using fuzzy feedback controller for realizing feedforward FES controller in controlling knee extension movements that has large time delay.
**Methods:** The FEL using fuzzy FES controller was tested in controlling knee extension movement through computer simulation and an experimental control with a healthy subject. Artificial neural network (ANN) was trained by off-line and online learnings to develop the inverse dynamics model (IDM) of electrically stimulated musculoskeletal system that can be used as a feedforward controller. The knee joint was controlled by stimulation to a knee extensor muscle for sinusoidal angle pattern.
**Results:** The computer simulation test showed that the IDM was developed by ANN learning in both of off- line and online learnings. However, the IDM was not learned adequately in experimental control by the off- line learning. On the other hand, the ANN could learn the IDM though online learning showing that decrease of control error and stimulation output of the feedback controller and increase of stimulation output of the ANN.
**Conclusions:** The results suggested that online learning was effective for the FEL with a fuzzy controller in knee extension control. There was a possibility that large time delay in responses to electrical stimulation became a problem in learning of the ANN by the off-line learning.

### O13
### DEVELOPMENT PROCESS OF PROSTHETIC DEVICE FOR UPPER LIMB

*L. M. Okumura M[1], Canciglieri Junior O[1], M. Souza T[2], M. Botelho M[3]*
[1]Industrial and Systems Engineering Graduate Program, Pontifical Catholic University of Paraná, Paraná, Brazil
[2]Mechanical Engineering Graduate Program, "Julio de Mesquita Filho" São Paulo State University, São Paulo, Brazil
[3]Research Center of Assistive Technology, Pontifical Catholic University of Paraná, Paraná, Brazil

**Background:** Hand agenesia difficults finger grasp execution. Objects and utensils are firmed through finger grasp integrated to the movement of the upper limb, which stimulates muscles and strengthen the arm and forearm structure. The usage of the prosthetic device enables a child with hand agenesia to exercise the arm while realizing functional activities.
**Aim:** Elaborate the process of integrated development of a prosthetic device (PIDPD), which executes the functions of bidigital and pluridigital finger grasp.
**Methods:** The research elaborates PIDPD for upper limb through the Design for Assistive Technology, which investigates and defines the characteristics and specificity of the user with upper limb agenesia in order to realize a functional activity with the fingers. PIDPD was applied in a study case to confection a device with finger grasp function.
**Results:** PIDPD presents 3 multidisciplinary phases: pre-prosthetic, development of the device and pos- prosthetic. On the first phase many health professionals collaborated to diagnostic and identify physiologic structures of a girl with finger agenesia. On the second phase the involved user and family members to investigate the intended activities to be realized by using the prosthetic device. The user's requirements and necessities were aggregated to the device. In sequence, the components of the device were elaborated for manufacturing through 3D printing. The portions with holding function are easily connected and removed from the main piece. On the pos-prosthetic phase it was realized an evaluation and the patient's rehabilitation program.
**Conclusions:** PIDPD with multidisciplinary work promote security and effectiveness in the process. Rehabilitation program prepares the person with upper limb agenesia before the usage of the device. Realizing a functional activity contributes to a lower index of prosthetic device abandonment.

## Session - Heart and Pump: Modelling and Control

### O14
### VENOUS PHYSIOLOGY AND CAVOPULMONARY SUPPORT IN FONTAN PATIENTS

*Granegger M[1,2], Schweiger M[1], Schmid Daners M[2], Hübler M[1]*
[1]Cardiac Surgery, University Children's Hospital Zurich, Switzerland
[2]pd|z Product Development Group, ETH Zurich, Zurich, Switzerland

**Background:** Currently, no established treatment options for patients with a total cavopulmonary connection (TCPC) and cardiovascular failure are available. Mechanical circulatory support (MCS) in cavopulmonary position seems a promising approach in case of increased pulmonary vascular resistance (PVR).

**Aim:** In this study, the impact of MCS in cavopulmonary position on the venous physiology was investigated with the aim to identify the optimal MCS adjustment strategy.
**Methods:** By making use of Guyton's model of the venous physiology and a lumped parameter model of the cardiovascular system the relationship between mean circulatory filling pressure (MCFP), atrial pressure and resistance to venous return (VR) for this patient population was investigated. Further, the influence of aortopulmonary collaterals was derived. The impact of a physiologic controlled MCS in this condition was identified.
**Results:** In the numerical model, hemodynamics of Fontan patients (age 13.5 ± 2.2 years, n = 27) could be achieved within half a standard deviation of reported values. The MCFP was identified to occur close to the central veins and was 11 mmHg in excellent Fontan patients at a CO of 4 L/min. Under steady state conditions, pathologic PVRs (3 Wood Units) and collateral flow (0.4 L/min) in failing Fontan conditions require an adaptation of MCFP (>20 mmHg) to ensure the same CO. Properly controlled MCS restores the location of occurrence and the value of MCFP to physiologic ranges.
**Conclusions:** With MCS in cavopulmonary position a physiologic VR mechanism even in failing Fontan patients can be achieved. However, adaptation and control of such devices based on the physiologic need of the patient seems mandatory.

## O15
## EXERCISE PHYSIOLOGY WITH A VAD: STUDY OF LEFT VENTRICULAR ENERGETICS WITH A COMPUTATIONAL MODEL

*Fresiello L[1,2], Rademakers F[3], Claus P[4], Ferrari G[5], Graefe R[6], Di Molfetta A[7], Meyns B[1]*
[1]Department of Cardiac Surgery, KU Leuven, Leuven, Belgium
[2]Institute of Clinical Physiology, CNR, Pisa, Italy
[3]Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium
[4]Department of Cardiovascular Diseases, KU Leuven, Leuven, Belgium
[5]IBBE, Polish Academy of Sciences, Warsaw, Poland
[6]ReinVAD, GmbH, Aachen, Germany
[7]Department of Pediatric Cardiology, Pediatric Hospital Bambino Gesù, Rome, Italy

**Background:** Physical exercise is associated with an increase in cardiac output. In patients with a ventricular assist device (VAD), the left ventricle starts to eject as a response to the higher oxygen demand from the tissues.
**Aim:** In this work we analyzed how the left ventricular work evolves from rest to exercise.
**Methods:** The study was conducted using a computational cardiorespiratory simulator adapted to reproduce exercise physiology. The simulator was set to reproduce a heart failure condition with a VAD (implemented according to the pressure-flow characteristics of a Heartmate II pump). At first we simulated a rest condition with a VAD speed of 9500 rpm (REST), then exercise (cycling at 80 watts) with a VAD speed of 9500 rpm (EXE1) and 12000 rpm (EXE2). Left ventricular pressure-volume areas (PVA) were calculated and expressed as myocardial oxygen consumption (MVO2) using the formula of Suga H, Am J Physiol.1979.
**Results:** At REST VAD flow (VADF) is 4.3 l/min, left ventricular flow (LVF) 0 l/min, mean systemic arterial pressure (PAS) 88 mmHg and heart rate (HR) 78 bpm. At EXE1 VADF is 5.2 l/min, LVF 2.1 l/min, PAS 84 mmHg and HR 115 bpm. At EXE2 VADF is 8.0 l/min, LVF 0 l/min, PAS 96 mmHg and HR 114 bpm. The PVA and MVO2 are: 6300 mmHg·ml/beat and 8.9 $mlO_2$/min at REST, 8512 mmHg·ml/beat and 16.6 $mlO_2$/min at EXE1 and 7568 mmHg·ml/beat and 15.0 $mlO_2$/min at EXE2.
**Conclusions:** Physical activity requires a highly energetic expense for the heart that translates into an increase in oxygen consumption. The current VADs, optimized at rest condition, are not capable to adapt to exercise, so the left ventricle has to contribute itself to increase cardiac output. A VAD speed modulation could permit to better unload the ventricle and partially reduce its workload.

## O16
## IN VITRO EVALUATION OF STARLING-LIKE CONTROL BASED ON ESTIMATED LEFT VENTRICULAR STROKE WORK

*Wu E[1,2], Pauls J[1,2], Stevens M[3,4], Tansley G[1,5], Fraser J[1,2], Gregory S[1,2,5]*
[1]ICETLAB, Critical Care Research Group, Brisbane, Australia
[2]School of Medicine, The University of Queensland, Brisbane, Australia
[3]Graduate School of Biomedical Engineering, University of New South Wales, Sidney, Australia
[4]Central Clinical School, Sydney Medical University, Sidney, Australia
[5]School of Engineering, Griffith University, Brisbane, Australia

**Background:** Constant speed rotary blood pumps (RBPs) lack a flow balancing mechanism, which may cause left ventricular (LV) suction, reduced unloading and limited exercise capacity. A controller that measures LV stroke work (LVSW) and adjusts RBP hydraulic work, matching a healthy heart's Starling curve, may prevent these complications. However, current implantable sensors that measure LVSW are not clinically accepted and instead, estimates using RBP signals may be a suitable alternative.
**Aim:** We aimed to evaluate a Starling-like controller using an estimate of LVSW based on RBP signals.
**Methods:** To relate RBP signals to LVSW, data was generated in a mock loop using a HeartWare HVAD in a range of cardiovascular conditions. A regression model related RBP signals to LVSW on a training set, which was then assessed on a validation set and applied to a Starling-like estimated stroke work controller (ESWC). The ESWC functioned by combining RBP hydraulic work and estimated LVSW, to match a healthy heart's Starling curve for a given preload. The ESWC was evaluated with changes in systemic (SVR) and pulmonary vascular resistance (PVR) and an exercise condition and compared against a measured stroke work controller (MSWC) and constant speed (CS).
**Results:** A 6-term estimate of LVSW, using RBP flow and power, showed strong correlation in training and validation sets (r2: 0.91 & 0.93). During control evaluation, CS resulted in LV suction as PVR increased to 500 dyne.s.cm-5, whilst both controllers prevented this. In exercise, both controllers resulted in greater cardiac output (9.0 L/min) and LVSW unloading (0.38 J) compared to CS (8.3 L/min & 0.63 J).
**Conclusions:** The ESWC, using RBP flow and power to estimate LVSW, prevented LV suction, increased LV unloading and exercise capacity by adjusting RBP hydraulic work to mimic the Starling mechanism.

## O17
## STROKE VOLUME ESTIMATION AND EXTREME MEMBRANE POSITIONS DETECTION IN PULSATILE VENTRICULAR ASSIST DEVICE

*Siewnicka A, Janiszowski K, Fajdek B, Wnuk P*
Institute of Automatic Control and Robotics, Warsaw University of Technology, Warsaw, Poland

**Background:** Most of the popular control systems of pulsatile ventricular assist devices (VADs) are not adaptive. Automation of its control requires knowledge about the stroke volume and detection of extreme membrane position. No adequate measuring systems are presently used.
**Aim:** The aim of presented work was to develop algorithms for stroke volume estimation and extreme membrane position detection. The method was supposed to be based on the standard signals accessible in the device control unit.
**Methods:** On the base of the model of the flow in the device blood chamber, the algorithm of stroke volume estimation was proposed. As the flow integration results in multiplication of transducers errors, the proposed method compensates its impact and eliminates the drift. The diagnostic algorithm of complete filling and ejection detects the corresponding loss of flow occurring before the change of the unit driving phase.
**Results:** Developed algorithms were tested on the research stand consisting of the VAD connected with the hybrid cardiovascular simulator. The studies were carried out for different sets of device operation parameters and various simulated states of the cardiovascular system. The stroke volume estimation error was about 10% in relation to the ultrasonic measurement. The membrane extreme position detection algorithm was working errorless in all investigated cases.
**Conclusions:** The proposed algorithms estimate the stroke volume and detect extreme membrane position basing on the modeled value of the VAD blood flow and using only the standard signals delivered from the control

unit of assist device. The application of these methods will improve control parameters selection and may lead to the development of adaptive control systems for pulsatile VADs.

**O18**
**CARDIAC CONTRACTILITY INDEX DERIVED FROM PUMP FLOW DURING EXTERNAL ROTARY BLOOD PUMP SUPPORT: AN IN VITRO STUDY**

*Naiyanetr P, Khienwad T*
Department of Biomedical Engineering, Faculty of Engineering, Mahidol University, Bangkok, Thailand

**Background:** Cardiac contractility index is a key success of bridge-to-recovery and destination therapy during rotary blood pump (RBP) support. The IQ index that derived from pump flow has proposed for internal RBP support.
**Aim:** This study investigate the effect of tubing length and the stroke volume (SV) during external RBP support using physiological mock circulatory loop (MCL).
**Methods:** The IQ index is defined as a slope of a linear regression between the maximum derivative of the pump flow (dQ/dtmax) and its peak-to-peak value of pump flow (QP2P) at the same cycle. For in vitro study, Mahidol-centrifugal blood pump and physiological MCL was used. For length study, the length of inlet and outlet tubes was varied at 130, 50, and 10 cm and 130, 50 and 50 cm, respectively. For stroke volume study, the SV was varied from 30 to 80 ml (+10 ml each step). For all studies, the RBP was varied from 2000 to 3500 rpm (+50 rpm each step).
**Results:** For length study, IQ index was 2.0041, 1.9825, and 1.9734 s-1 at 260, 100, and 60 cm of tubing length, respectively. The linear regression between dQ/dtmax and QP2P was shown by r2 (0.9954 0.9967 and 0.9976, respectively). For stroke volume study, IQ index was 1.79, 1.97, 1.96, 1.97, 1.97, and 1.97 s-1 at 30, 40, 50, 60, 70, and 80 ml, respectively. The effect of tubing length on the value of IQ index was only shown at SV = 30 ml (IQ index: 1.94, 1.79 and 1.79 s-1 at 260, 100, and 60 cm of tubing length respectively).
**Conclusions:** The IQ index that is the cardiac contractility index derived from pump flow can be used to assessment of cardiac function at difference tubing length and SV during external rotary blood pump support. Therefore, IQ index can be used for continuous monitoring of cardiac contractility in patient with internal and external RBP support.

**O19**
**ECG-SYNCHRONIZED ROTATIONAL SPEED CHANGE SYSTEM HAS PREVENTIVE EFFECT ON RIGHT HEART FAILURE DURING CONTINUOUS-FLOW LEFT VENTRICULAR ASSIST DEVICE SUPPORT**

*Akiyama D[1,2], Nishimura T[3], Iizuka K[1], Mizuno T[1], Tsukiya T[1], Takewa Y[1], Ono M[2], Tatsumi E[1]*
[1]Department of Artificial Organs, National Cerebral and Cardiovascular Center, Research Institute, Osaka, Japan
[2]Department of Cardiothoracic Surgery, University of Tokyo Hospital, Tokyo, Japan
[3]Department of Cardiovascular Surgery, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

**Background:** Right heart failure (RHF) is a serious complication during continuous-flow left ventricular assist device (CF-LVAD) support. One mechanism of RHF is continuous septal shift due to continuous left ventricular (LV) unloading. We have previously developed Novel Heart Load Control System (NHLCS) which changes the rotational speed (RS) of CF-LVAD (EVAHEART) synchronously to cardiac cycle, utilizing the ECG signal. NHLCS could control LV load (i.e. pressure and volume) while maintaining systemic flow. So, we hypothesized NHLCS could prevent RHF, through the septum by controlling LV load.
**Aim:** To prove NHLCS could improve right ventricular function, compared to constant RS mode by P-V loop analysis of both ventricles.
**Methods:** In six adult goats (BW 44.9 ± 5.4 kg), EVAHEART was implanted. Heart failure was induced by drip infusion of beta blocker, esmolol. We monitored flows of asc. Aorta, PA trunk, and pump outlet, pressures of four heart chambers and great vessels. Millar conductance catheters were introduced to both ventricles for P-V loop analysis. EVAHEART was driven in constant RS mode, and NHLCS counterpulse mode (raising RS during diastolic phase), and these indices, especially, pressure, volume, and stroke work expressed by area of P-V loop, of both ventricles were analyzed. Whole analysis was carried out under full bypass condition while maintaining same systemic flow between two modes.
**Results:** As compared to constant RS mode, counterpulse mode significantly increased LV maximal pressure, increased LV stroke work, and decreased LV end-diastolic volume. And this mode increased RV end-diastolic volume (142 ± 11 vs 148 ± 14 ml) and RV stroke work (283 ± 174 vs 376 ± 190 ml·mmHg).
**Conclusions:** This result implies NHLCS could become a promising option for preventing RHF in CF-LVAD patients.

## Session: Materials in Apheresis and Dialysis

**O20**
**BLOOD-BIOMATERIAL INTERACTIONS IN EXTRACORPOREAL CIRCULATION**

*Campbell Ritchie A*
Department of Mechanical, Materials and Manufacturing Engineering, University of Nottingham, Nottingham, UK

**Background:** Therapeutic benefits of extracorporeal procedures must be balanced against the effects of exposing the formed elements of the blood to non-biological materials. Coagulation can be prevented using a systemic anticoagulant, although this will have consequences after the procedure, and effects on the immune system, particularly activation of the white blood cells via the complement system's alternate pathway. Willem Kolff stated that the ultimate goal of an extracorporeal therapy should be to restore happiness, rather than just prolonging life.
**Aim:** In this presentation, I will review the events occurring after blood is exposed to the biomaterials of the extracorporeal circuit, and outline the improvements made in recent years in reducing the side-effects of extracorporeal circulation.
**Methods:** In recent years, citrate has superseded heparin as a systemic anticoagulant in renal replacement therapies due to its ability to be removed by dialysis and non-activation of the complement system. Better biomaterials and patient care have improved the quality of life for patients undergoing regular extracorporeal procedures. Challenges still remain in more invasive procedures such as extracorporeal membrane oxygenation (ECMO), where a larger proportion of the blood volume is exposed to the material.
**Results:** Extracorporeal circulation can result in activation of the complement system and activation of the coagulation cascade. ECMO, with the attendant effects of major surgery and release of tissue factors into the blood, presents the greatest challenge of all, and in this case, post-operative management is also critical to the outcome. Correct specification of biomaterials can minimise the negative effects while maximising the therapeutic benefits of the treatment.
**Conclusions:** Researchers and Clinicians should be aware of the possible side effects of extracorporeal therapies, and development of new devices should focus on improving the biomaterials used in making the devices, better methods for coagulation control, and improvement management of comorbidities in chronic conditions.

**O21**
**MIXED MATRIX MEMBRANES FOR OUTSIDE-IN DIALYSIS**

*ter Beek O, Pavlenko D, Stamatialis D*
Department of Biomaterials Science and Technology, MIRA Institute, University of Twente, Enschede, The Netherlands

**Background:** Inefficient toxin removal is one of hemodialysis' major bottlenecks. Conventional dialyzers are not able to sufficiently remove protein-bound toxins (PBT) and it takes time to remove middle and charged molecules, because the intracellular compartment's volume is bigger than that of plasma. As a result, accumulation of these toxins can lead to renal failure progression and higher mortality rates. Mixed matrix membranes (MMM) and outside-in dialysis can significantly increase toxin removal; MMM use adsorption and dialysis to remove PBT (1) and outside-in dialysis uses reversed dialysis configuration where dialysate flows through fibers' lumen and blood flows through dialyzer's inter-fiber space (2). This avoids fiber clogging and

subsequent shortened filter life and is therefore more suitable for prolonged dialysis to increase toxin removal.
**Aim:** Here, we present the development of new generation MMM suitable for outside-in dialysis.
**Methods:** Dual layer, outside-in hollow fibers MMM were obtained by dry-wet spinning. Activated carbon particles (AC) were embedded in a polymer inner layer and direct sorbent-blood contact was avoided by a particle-free outer layer which acts as hemocompatible and selective barrier. Membranes were characterized by scanning electron microscopy and water permeance experiments. Furthermore, long-term performance and toxin removal were studied using cross-flow experiments with model creatinine solution and human plasma spiked with indoxyl sulfate. Inside-out MMM and commercial Fresenius F8HPS were used for comparison.
**Results:** New outside-in MMM have high porosity with highly interconnected pores. The pore morphology is rather sponge-like on the outer layer and AC are well dispersed in the MMM inner layer. Membranes have ultrafiltration coefficient of 7 mL/h·mmHg and achieve creatinine clearance similar to F8HPS fibers. Investigation of PBT removal and long-term membrane performance are currently in progress.
**Conclusions:** New outside-in MMM suggest great potential for development of membranes suitable for prolonged dialysis with improved toxin removal. LSH Impuls Kidney Port project 1. Pavlenko, et al, Sci Rep, 6(2016),1-9; 2. Dukhin, et al, J Membr Sci, 464(2014),173-178.

## O22
## MIXED MATRIX MEMBRANES FOR THE REMOVAL OF ENDOTOXINS DURING HEMODIALYSIS

*Geremia I, Pavlenko D, Stamatialis D*
Department of Biomaterials Science and Technology, University of Twente, Enschede, The Netherlands

**Background:** Despite technical advances in water purification and microbiological quality control of the dialysate, many clinical centers still do not meet the microbiological requirements for this latter. The long exposure to the dialysate (18000-30000 liters/patient/year) increases the risk for the blood to be in contact with pyrogens (1). The hemodialysis membrane is the final barrier to prevent endotoxins to access the blood and to cause pyrogenic reactions which can lead to progressive inflammatory diseases. Adsorption is considered the safest and most promising strategy for the removal of endotoxins from the dialysate to avoid their back-transport to the blood.
**Aim:** Dual mixed matrix membranes (MMM), which combine dialysis and adsorption in a single step, have shown that they can remove a broad range of uremic toxins, including creatinine and protein-bound toxins (2). In this work we investigate whether the MMM can also be used for the removal of endotoxins from the dialysate.
**Methods:** MMM, composed by activated carbon particles (AC) embedded into polyethersulfone and polyvinylpirrolidone blend (2), were investigated for endotoxin adsorption. Static and dynamic adsorption experiments in dialysate were performed. Purified lipopolysaccharide originating from Escherichia coli 0111:B4 was used as endotoxin model. The endotoxin content was determined by the quantitative Limulus amebocyte lysate assay.
**Results:** The MMM, due to the high adsorption capacity of AC, can remove 70000 EU/g of membrane after four hours' experiment. The adsorption data were compared with PES/PVP fibers and with commercial hemodialyzers showing an increased removal of endotoxins with MMM.
**Conclusions:** The MMMS here described exhibit a clear ability in removing endotoxins from the dialysate. They act like a final safety barrier to avoid endotoxins to be back-transported to the blood.
**Acknowledgements:** This work is financially supported by EU Marie Curie ITN-TheLink (grant agreement no. 642890). References: 1. Henrie, M. et al., Artificial Organs, 32, 701-710, 2008; 2. Pavlenko, D. et al., Sci. Rep., 6, 1-9, 2016.

## O23
## INTEGRALLY SKINNED ASYMMETRIC CELLULOSE ACETATE-SILICA MEMBRANES FOR EXTRACORPOREAL BLOOD ULTRAFILTRATION

*Faria M, Moreira C, de Pinho M*
Department of Chemical Engineering, Instituto Superior Técnico, University of Lisbon, Lisbon, Portugal

**Background:** Fluid volume management is one of the most important problems of contemporary End Stage Renal Disease (ESRD) and decompensated Congestive Heart Failure (CHF). Blood ultrafiltration (UF) is capable of the physical removal of fluid, cytokines and other toxins by convection.
**Aim:** This study reports the synthesis and characterization of high flux integrally skinned asymmetric Cellulose Acetate-Silica (CA-Si) membranes for extracorporeal blood ultrafiltration.
**Methods:** The CA-Si hybrid membranes were synthesized via the coupling of the phase inversion and the sol-gel techniques. The tetraethoxysilane (TEOS) is used as a precursor of the sol-gel reactions in acidic conditions and at room temperature. Casting solutions containing 5%, 11%, 18% and 25% (w/w) silica rendered, CA-Si5, CA-Si11, CA-Si18 and CA-Si25 membranes. The membranes were characterized by Scanning Electron Microscopy (SEM), Zeta potential, ATR-FTIR and RMN. Permeation experiments were carried out to yield Hydraulic Permeability (Lp), Molecular Weight Cut-Off (MWCO) and rejection coefficients to a set of reference solutes. In-vitro hemocompatibility was evaluated in terms of hemolysis index, thrombosis degree and platelet adhesion and activation according to the ISO 10993-4:2002 standard using pooled sheep blood anticoagulated with acid citrate dextrose (ACD) at a blood/ACD ratio of 9:1.
**Results:** The CA-Si11, CA-Si18 and CA-Si25 membranes have hydraulic permeabilities of 81 kg/(hm2bar), 59 kg/(hm2bar) and 57 kg/(hm2bar), respectively. This represents an increase in hydraulic permeability compared to the CA membrane (32 kg/(hm2bar)). The corresponding MWCOs of the CA-Si hybrid membranes are 96 kDa, 111 kDa and 79 kDa. The MWCO of the pristine CA membrane is 31 kDa.
**Conclusions:** All of the CA-Si hybrid membranes can be selected for water removal with simultaneous total rejection of albumin and total permeation of urea. The efficiency of water removal and selective permeation to middle size molecules can be assessed.

## O24
## INTERPRETING PORE SIZE VALUES IN MEMBRANES FOR RENAL REPLACEMENT THERAPY

*Boschetti-de-Fierro A[1], Storr M[1], Beck W[2], Krause B[1]*
[1]Research and Development, Baxter International Inc., Hechingen, Germany
[2]Therapeutic Area, Baxter International Inc., Hechingen, Germany

**Background:** The pore size in membranes is usually determined in vitro, either as an effective or average size of the pore size distribution. Certain considerations are required in order to infer whether one given molecule would pass through the membrane.
**Aim:** We aim to offer a guide to interpret pore sizes, based on experimental results published [Boschetti-de- Fierro et al., Sci Rep. 5:18448].
**Methods:** The effective pore size is derived from the cut-off of the membrane, which is usually defined as the molecular weight of those molecules with retention of 90%. The average pore size, on the other hand, is calculated from the log-normal distribution of pore sizes. In the practice, both values are often calculated from in vitro sieving profiles of neutral molecules. Membranes can be characterized in their pristine state, or after blood contact to account for the formation of a protein layer over the membrane.
**Results:** For a given membrane, one could report four different values of pore size. For example, for Theranova (Baxter International Inc.), the effective pore radius is 5.0 ± 0.1 nm before blood contact and 3.0 ± 0.1 nm after, while the average pore radius is 4.1 ± 0.2 nm before blood contact and 2.5 ± 0.1 nm after.
**Conclusions:** In order to compare different membranes, the effective pore size before blood contact is used, since that measurement is simple and usually available for most membranes. In order to know whether a given substance passes through the membrane, the effective pore size after blood contact should be considered. This value should be compared to the hydrodynamic radius of the substance and not to its molecular weight since chain

flexibility and aggregation state influence the actual molecule size. Average pore size values can be used to compare different membranes. However, the real value of the log-normal distribution relies on the variance (values not shown). It describes the width of the distribution, which is a direct indication of the selectivity of the membrane.

**O25**

**BIOCOMPATIBLE COMPARISON IN POLYSULFONE MEMBRANES BETWEEN POLYVINYLPYRROLIDONE AND HYDROPHILIC POLYMER COATING FOR HEMODIALYSIS**

*Togo K[1,2], Yamamoto M[2], Imai M[2], Yamashita A[2]*
[1]Department of Health Medical, Faculty of Health and Medical Science, Teikyo Heisei University, Tokyo, Japan
[2]Department of Chemical Science and Technology, Faculty of Bioscience and Applied Chemistry, Hosei University, Tokyo, Japan

**Background:** Currently, polysulfone membranes (PS) have been widely used for hemodialysis because the permeability is higher than membranes of other materials. Many PS contain a hydrophilizing agent such as polyvinylpyrrolidone (PVP) to improve biocompatibility. Meanwhile, recently, numerous manufactures produce hemodialyzeres of PS using a variety of polymers for the same reason.
**Aim:** The purpose of this study was to compare biocompatibility in PS between PVP and hydrophilic polymer coating.
**Methods:** We compared the biocompatibility of the following dialyzers: RENAK PS-1.0 (RENAK, Kawasumi laboratories) was a diameter of hollow fiber of 185 µm, and was PS with a PVP. NV-10S (NV, Toray Medical) was a diameter of hollow fiber of 200 µm, and was PS with a hydrophilic polymer. Each dialyzer and circuit was set. First, test blood was collected from healthy volunteer. Then, the test blood was filled each circuit. Next, blood pump was initiated. The blood flow rate was 200 mL/min. Then, we measured the platelet counts and platelet surface markers (CD41 and CD42b) at 30 min, 2 h and 4 h after the initiation of blood circulation. Furthermore, the membrane inner surfaces were analysed by Scanning Electron Microscope.
**Results:** Though the platelet counts of initiation was 271,000 ± 35,000/µL, the average platelet counts were 60,000 ± 9,000/µL and 35,000 ± 11,000/µL with RENAK and NV at 4 h, respectively. The average expression of CD41 and CD42b decreased by 34.0 ± 30.7% and 16.6 ± 15.1% with NV, respectively, whereas they decreased by only 59.2 ± 45.7% and 38.6 ± 31.0% with RENAK, respectively. The adhesion of the platelets was found in NV, but not in RENAK.
**Conclusions:** The blood compatibility of RENAK was better than that NV. This is because the diameter of hollow fiber of RENAK was less than that of NV, it was inferred that high shear stress contributed to this more than any other factors.

**O26**

**ASSESSMENT OF BLOOD TRAUMA DUE TO HEMATOCRIT VARIATIONS IN DIALYZERS**

*Mouzakis F, Poorkhalil A, Kashefi A, Mottaghy K*
ECC Lab, Institute of Physiology, RWTH Aachen University, Aachen, Germany

**Background:** Contemporary therapies for ESRD patients comprise a wide range of Hemodialysis modalities, most of which rely heavily on dialyzers and hemofilters. Ongoing research on the mass transfer phenomena occurring in such devices sheds increasingly more light upon their effect on the efficacy of Hemodialysis treatments.
**Aim:** This study attempts to evaluate the extent of blood trauma generated by the frequent implementation of capillary membranes during hemodialysis therapy sessions, by means of mathematical modeling and in vitro investigations.
**Methods:** An analytical model has been developed that simulates the convectional processes in a dialyzer. In addition, diverse experimental methods have been employed in order to validate the mathematical model, including a customized hemodialysis circuit featuring multiple sampling possibilities, and a Couette flow system reproducing the effect of shear stress in capillary membranes.
**Results:** Experimental data are fed into the model, which retrospectively predicts the course of Hematocrit along the fibers, contingent on filtration/backfiltration. Correspondingly, the findings of our in vitro investigations with the hemodialysis circuit corroborate the model's predictions. Based on the attained hematocrit and shear rate levels, the hemolysis rate occurring in the dialyzer is estimated, and subsequently blood trauma is determined in the form of a Damage Index.
**Conclusions:** Validation of the model's predictions with experimental data, yields a very good agreement, which confirms the model's accuracy, as well as the precision of the various experimental methods implemented. The mathematical model developed for the needs of this study could serve as a tool for the optimization of hemodialysis treatments through parameter fine-tuning, in furtherance of reducing patient strain. Furthermore, standardization of blood trauma assessment techniques could lead to improved hemodialysis treatments through optimization of the convectional processes in the dialyzer modules.

## Symposium: New Aspects of Albumin (Albunet)

**O27**

**THE EUROPEAN ALBUNET: MISSION AND VISIONS**

*Baurmeister U, Vienken J*
Albunet, Wupperthal, Germany

**Background:** Albumin represents the most frequent protein found in the serum of mammals. Main functions of albumin are related to the maintenance of oncotic pressure and its capacity to reversibly bind toxic compounds and pharmaceutical drugs. However, binding constants must be considered not to be constant, they merely depend on various physiological bystander effects, such as the presence of bivalent cations, diseases, such as kidney- or liver disease and related treatment modalities.
**Aim:** The EUROPEAN ALBUNET has been established to investigate modifications of the albumin molecule and it´s in vitro and in vivo clinical consequences.
**Results:** Vision: The goal of ALBUNET is to establish a cooperative research platform in order to deepen and spread the knowledge about albumin in basic and clinical science communities. The first public appearance of ALBUNET was at the Annual Congress of the European Society of Artificial Organs in Warsaw in 2016. ALBUNET is seeking collaboration of other European medical networks such as EUTOX.org and SEPNET.de, as well as scientists from the European Society for Artificial Organs.

**O28**

**ANALYSIS OF ALBUMIN FUNCTION BY INVESTIGATING CONFORMATIONAL MOBILITY**

*Schnurr K, Waterstradt K*
Advanced Molecular Diagnostics, MedInnovation GmbH, Berlin, Germany

**Background:** Albumin is the major plasma protein, it is a very flexible molecule with seven known binding sites for long chain fatty acids, which differ in their binding affinity. It´s well known physiological functions beside others are the maintenance of osmotic pressure and the transport function for fatty acids and other hydrophobic substances, trace elements and also medical drugs. Binding of these molecules can affect the ability of conformational mobility of human serum albumin. In addition, the detoxification is an important function of serum albumin and pathophysiological changes can influence this functionality. This albumin function correlates to dangerous illnesses, such as sepsis or liver failure. Serum albumin removes metabolites and toxins by transport to the liver, to help the organism to detoxify and regenerate.
**Methods:** The Albumin-functionality-test based on EPR spectroscopy can detect these modified binding and functional characteristics of serum albumin. The used radical supporting spin probe binds analogous other natural albumin ligands variably strong in different albumin binding sites and thus serves as indirect marker for the serum albumin functionality.
**Results:** Due to a comparison of three different mixtures of albumin and a spin labeled fatty acid the Albumin-functionality-test simulate binding, transport and release conditions in vitro. Thus an "effective" albumin concentration

could be determined, which quantifies the amount of functional albumin in the patient in comparison to healthy population.
**Conclusions:** Following results of various investigations, the Albumin-functionality-test can be applied for: 1. the monitoring of disease progression, 2. the prognosis of sepsis and liver diseases, 3. for the examination of liver dialysis treatment modalities and their efficiency, and 4. for the quality control of commercially available albumin solutions.

### O29
### NON-INVASIVE MONITORING OF BILIRUBIN DECREASE IN EXTRACORPOREAL LIVER SUPPORT PATIENTS

*Preussiger M[1], Tyczynski B[2], Kribben A[2], Jost U[3]*
[1]MBR Optical Systems, Wuppertal, Germany
[2]University Clinic, University Duisburg-Essen, Germany
[3]HepaNet GmbH, Germany

**Background:** Hepatic diseases are wide spread and complicated to be handled due to secondary complications. Extracorporeal liver support therapies (ELST) are used to bridge the time to transplantation or to support liver function recovery. Since bilirubin is one of the prominent toxins to be removed, its actual status during ELST is a standard indicator for therapy efficiency. Reduction of bilirubin is variable and e.g. dependent on albumin concentration. To enable treatment regulation, a device for point-of-care measurement of the bilirubin gradient is required.
**Methods:** A non-invasive device for measuring the transcutaneous bilirubin (TcB) concentra¬tion in blood circulation with visible reflection spectroscopy was tested (bilispect?, MBR Optical Systems GmbH, Wuppertal). Measurements during treatments with the fractionated plasma separation and adsorption system (Prometheus?, FPSA) assessed the function and reliability of the device and evaluated the decrease in bilirubin concentrations compared to serum bilirubin levels (SBR). SBR samples were taken at the beginning of the therapy and after every 2 hours; TcB readings every hour.
**Results:** Correlation of calculated TcB-concentrations to SBR was good ($r = 0.97$, $p<0.002$, $r = 0.99$, $p<0.001$). The fitted SBR decrease per hour showed patient-variable values. Both exponential and polynomial decrease 2nd order were observed with a percentage decrease of 28% or 49% of the start concentration (25.1 mg/dl, 18.5 mg/dl).
**Conclusions:** The developed non-invasive device enables the measurement of bilirubin concentrations comparable to SBR. It is a promising method to regulate therapy time of ELST with online-monitoring as well as to analyze the rebound effect after therapy. As a result, the reduction of blood sampling in patients and related costs can be expected.

### O30
### EXTRACORPOREAL LIVER SUPPORT: APPROACHING THE PATIENT WITH LIVER FAILURE

*Tyczynski B[1], Kribben A[1], Saner F[2]*
[1]Department of Nephrology, University Hospital Essen, Essen, Germany
[2]Department of General, Visceral and Transplantation Surgery, University Hospital Essen, Essen, Germany

**Background:** The number of patients with chronic liver disease is growing. Mortality ranges between 40 and 60% after acute decompensation. In patients with acute liver failure mortality peeks up to 50-80%. Around 33% of the patients are dying before transplantation. Aim of a liver assist device is the bridging of time to recompensation or to transplantation.
**Methods:** Liver assist devices can be divided in artificial- and bio-artificial liver assist devices. They have to remove water soluble toxins and protein bound toxins. The bio-artificial liver assist device consists of an artificial liver assist device in combination with living liver cells. Artificial liver support devices are amongst others: Plasma exchange, albumin dialysis, hemodialysis/hemofiltration, plasma adsorption, hemoperfusion, and combination systems like MARS™, Prometheus™ or HepaWash™.
**Results:** Despite first encouraging results with the use of liver assist devices in small studies, the biggest trial with the MARS™-system (RELIEF, 2013, n = 186) failed to show improved survival. The second big study on acute on chronic liver failure patients with the Prometheus™-system, also failed the primary endpoint to show an overall improved survival. However a predefined subgroup analysis of patients with HRS 1 and/or MELD above 30 showed a better 90 day survival under treatment (HELIOS, 2012, n = 145). In 2016 a multicenter trial was published evaluating the effect of high volume plasma exchange (HVP) in 182 patients with acute liver failure. The authors reported on a significantly improved survival in non- transplant patients with acute liver failure under HVP-treatment.
**Conclusions:** Until now the only definitive treatment of end-stage-liver disease remains liver transplantation, but it is substantially limited due to organ shortage. The treatment of patients with liver failure remains a major challenge for the involved physician. Liver assist devices are available, but robust data regarding survival benefit are lacking.

### O31
### OPAL VS MARS: A CASE CONTROL STUDY OF 2 EXTRACORPOREAL ALBUMIN DIALYSIS TECHNIQUES

*Wilms C[1], Maschmeier M[1], Gerth H[2], Pohlen M[3], Thölking G[2], Pavenstädt H[1], Koch R[4], Schmidt H[1]*
[1]Department of Transplantation Medicine, University Hospital Münster, Münster, Germany

**Background:** Extracorporeal albumin dialysis (ECAD) is used in liver failure patients to enable liver recovery and bridge to transplantation. Molecular adsorbent recirculating system (MARS) has demonstrated beneficial effects on symptoms of liver disease and proved to be safe. Open albumin dialysis (OPAL) uses a different type of adsorber allowing for better clearance due to processed albumin. We compared OPAL and MARS in liver failure patients with respect to treatment related patient conditions, liver function and safety.
**Methods:** In a case controlled study, 28 liver failure patients received at least 3 ECAD treatments. 14 patients were treated with MARS and matched to 14 patients treated with OPAL. Indication for ECAD was progressive icterus with liver failure (bilirubin >12 mg/dl) without evidence of extrahepatic origin. To eliminate confounding, individual case-control patient matching was performed. Both MELD-Score and platelet number were selected matching variables with a maximum of 10% difference. Outcome analysis included clinical and lab-parameters recorded before & after each treatment as well as dialysis related side effects and adverse events.
**Results:** In addition to improved or stable laboratory parameters (reduced bilirubin-values MARS-group -18,1% and OPAL-group -20% to baseline; stable liver function & renal fct-parameters), short-term mortality (up to day 21) was 0% both in the MARS and the OPAL group. Following ECAD treatments thrombocyte values decreased (MARS -31% and OPAL -27% to baseline), but did not differ significantly between the groups. During all ECAD-procedures patients in both groups were hemodynamically stable. In the MARS- group, we observed 3 adverse events not related to the dialysis procedure. In the OPAL-group the number of adverse events was 4, one was related to the procedure (catheter-infection).
**Conclusions:** The study shows for the first time that both procedures are effective and that the OPAL system can be applied safely.

## Symposium: ICCAC-ESAO International VAD Coordinators

### O32
### DO LVAD PATIENTS NEED A SPECIFIC DIET TO CONTROL WEIGHT?

*Vandersmissen K[1], Driesen J[1], Vandenbossche K[1], Droogne W[2], Jacobs S[1], Fresiello L[1], Rega F[1], Gerits K[1], Meyns B[1]*
[1]Department of Cardiac Surgery, UZ Leuven, Leuven, Belgium
[2]Department of Cardiology, UZ Leuven, Leuven, Belgium

**Background:** Some patients gain significant weight after LVAD implantation. Besides potential development of obesity, weight gain can lead to specific wound care problems at the cable exit site.
**Aim:** We sought to analyze if weight gain is structural after LVAD implantation and if consequently preventive measures concerning their diet should be implemented.

**Methods:** We retrospectively analyzed 84 consecutive LVAD patients discharged from hospital, from December 2007 to January 2016. We considered the body mass index (BMI) at the moment of VAD implantation as the baseline BMI. Evolution of body weight and body mass index was followed over a period of 2 years. No specific diet prescriptions were given. We distinguished patients receiving the LVAD after a period of chronic heart failure (n = 57, 68%) and patients suffering from acute heart failure (n = 27, 32%).
**Results:** Baseline BMI of both groups is not significantly different (p = 0.58): 24.9 ± 4.3 for patients with chronic heart failure and 24.5 ± 3.1 for patients with acute heart failure. The BMI of the patients with acute heart failure remained unchanged throughout the observation period. Patients suffering from chronic heart failure did gain weight. At 12 months after LVAD implantation, they had an increase in BMI (BMI = 25.2 ± 3.4), which sustained up to 24 months (BMI = 26.1 ± 4.2). Figure 1 shows percent BMI change over time through 24 months of LVAD support for the 2 groups. There was a statistical significant change over time in BMI for patients suffering from chronic heart failure at 18 months (p = 0.04).
**Conclusions:** Patients with chronic heart failure had an increase in BMI after LVAD implantation and these changes persisted through 24 months. However, their BMI remained clinically acceptable and can be explained as a result of their improved general condition. The BMI of the patients with acute heart failure remained unchanged. So we conclude that weight gain after LVAD implantation is not structural.

## Symposium: Citrate Anticoagulation

### O33
### INFLUENCE OF CITRATE CONCENTRATION ON PLATELET ACTIVATION DURING LIPID APHERESIS

*Weiss R[1], Semak V[1], Fischer M[1,2], Weber V[1,2]*
[1]Christian Doppler Laboratory for Innovative Therapy Approaches in Sepsis, Danube University Krems, Krems, Austria
[2]Center for Biomedical Technology, Danube University Krems, Krems, Austria

**Background:** Contact of whole blood with adsorbent polymers requires blood compatible surfaces to minimize activation of blood cells and initiation of coagulation, cell adhesion, and release of extracellular vesicles (EVs).
**Aim:** We assessed the influence of citrate anticoagulation on cellular activation and adhesion during low density lipoprotein (LDL) apheresis and aimed to develop blood compatible matrices with zwitterionic coatings to reduce cell and protein adsorption.
**Methods:** Blood was drawn from healthy volunteer donors and anticoagulated with citrate (2.8, 5.6 and 13 mM final concentration). Aliquots of 50 mL were recirculated over columns (3.5 × 1.8 cm) containing polyacrylate-based adsorbents for LDL apheresis (DALI), at a flow rate of 1.2 ml/min for 4 h. Samples were taken every hour, and blood cells in the flow-through were quantified using a blood cell counter. EVs were determined with a Gallios Flow Cytometer (Beckman Coulter) after calibration with polystyrene beads (0.1, 0.3, 0.5 and 0.9 μm). Lactadherin staining was used to identify phosphatidylserine-exposing EVs. The following markers were used to differentiate cell-derived EVs: CD14+ (monocytes); CD41+ (platelets); CD235a+ (red blood cells). Platelet activation was monitored by expression of p-selectin, platelet factor-4 (PF4), and PAC-1 (activated GPIIb/IIIa).
**Results:** Platelet activation markers were significantly elevated for citrate concentrations below 5.6 mM, which was accompanied by significantly higher adhesion of platelets and white blood cells to the adsorbents. Likewise, the release of EVs was dependent on citrate concentration with higher numbers of EVs at lower citrate concentration. Novel sulfobetaine zwitterionic copolymers with photolabile anchoring moieties were synthesized and covalently deposited on the surface of the adsorbent upon irradiation with UV light.
**Conclusions:** Our data show that the use of a citrate concentration of 5.6 mM in whole blood ensures a minimal level of cellular activation.

### O34
### CITRATE CLEARANCE OF CURRENT DIALYSERS: AN IN VITRO STUDY

*Hartmann J, Unterberger M, Strobl K*
Center for Biomedical Technology, Danube University Krems, Krems, Austria

**Background:** Although citrate anticoagulation is increasingly used in extracorporeal therapies, there is still a lack of studies regarding the clearance rates of current dialysers. In order to avoid citrate accumulation followed by acid-base imbalance of the patient, a systematic assessment of the clearance of commonly used filter types and sizes is necessary.
**Aim:** The aim of this in vitro study was the characterization of different high-flux polysulfone hollow fibre filters for chronic as well as for acute dialysis regarding their clearance for citrate. Furthermore, the citrate to urea clearance ratio at different plasma (QP) and dialysate (QD) flow rates was assessed.
**Methods:** The experiments were carried out in an in vitro setup using the Fresenius Medical Care 4008 H and the multiFiltrate dialysis machines. Citrated FFP (1.5 L) was spiked with urea and recirculated for 30 minutes. The plasma and dialysate flow rates were chosen according to the most commonly used flow rates for treatment stated in the individual filters data sheet. The characterized filters were AV 400S Ultraflux, FX 1000 HDF, FX 1000 HDF Cordiax, FX 100 Cordiax, FX 80 Cordiax and the FX 60 (FMC, Germany). Urea and citrate concentrations were measured after 5, 10, 15, 20 and 25 min at the filter inlet (ci) and the filter outlet (co). The clearance (C) was calculated with the formula C = QP*(ci-co)/ci. All experiments were carried out in triplicates.
**Results:** For filters used in chronic dialysis, the relative citrate clearance is higher than 80% of the plasma flow when a QP to QD flow ratio of 1:2.5 or lower is applied. For increasing flow ratios, the relative clearance decreases to 60% at a ratio of 1:1. The citrate to urea clearance ratio was in the range of 0.80-0.95 for treatment conditions used in chronic dialysis and below 0.70 for typical conditions of acute dialysis.
**Conclusions:** A reasonable setting of the blood to dialysate flow proportion not only helps to improve patient safety, but also optimizes the cost-benefit ratio for extracorporeal therapies.

## Session: Tissue Engineering and Regenerative Medicine I

## O36
## TISSUE-ENGINEERED HEART VALVE CAN CHANGE HISTOLOGICAL CHARACTER AFTER IMPLANTATION

*Takewa Y[1], Nakayama Y[2], Sumikura H[1], Akiyama D[1], Katagiri N[1], Takeshita D[1], Tatsumi E[1]*

[1]Department of Artificial Organs, National Cerebral and Cardiovascular Center, Osaka, Japan

[2]Division of Medical Engineering and Materials, National Cerebral and Cardiovascular Center, Osaka, Japan

**Background:** A novel autologous-tissue heart valve (biovalve) was developed with a unique in-body tissue engineering. This valve is expected to be a viable bioprosthesis keeping better biocompatibility and durability.
**Aim:** We investigated the time-course histological change of implanted biovalves in large animal experiments.
**Methods:** Many kinds and sizes of biovalves can be made by designing basic plastic molds with 3D printer easily and quickly. In this study, a valve with a metallic stent for transcatheter implantation was selected.
We embedded the mold with a stent in the subcutaneous space of an adult goat for 1-2 months. After extracting the mold with the tissue en bloc and removing the mold only, stent biovalve with beautiful tri- leaflets was constituted from autologous connective tissues and fibroblasts. Eight stent biovalves were implanted in the goats' pulmonary artery (PA) in situ with transcatheter apical approach technique.
**Results:** Six out of 8 goats were successfully implanted the stent biovalve in the PA position. Angiography showed smooth movement of the leaflets. The stent biovalves were extracted at several durations (1-6 months and as long as possible) to observe the tissue transition. The maximum duration reached to 19 months. The leaflets of the biovalve kept their shape and elasticity, and neither calcification nor thrombi were observed even after 19 months. Histological examination of the biovalves showed the autologous cells covering the laminar surface of the valve leaflets as the endothelium even 1 month later. The autologous cells have also spread inside the leaflets gradually in 19 months and finally constructed characteristic tissues like native leaflets.
**Conclusions:** Implanted biovalves can adapt their histological character to the environment. They have a potential to be used for viable bioprosthesis and to keep better function and biocompatibility longer than current valve substitutes.

## O37
## RECONSTRUCTING THE BLOOD VASCULATURE WITHIN DECELLULARIZED LIVER FOR GENERATING A FUNCTIONAL HUMANIZED ORGAN

*Hussein K[1-4], Woo H[1,4,5]*

[1]Stem Cell Institute, Kangwon National University, Chuncheon, Gangwon, Republic of Korea

[2]Research Institute for Veterinary Science, College of Veterinary Medicine, Seoul National University, Seoul, Republic of Korea

[3]Adult Stem Cell Research Center, College of Veterinary Medicine, Seoul National University, Seoul, Republic of Korea

[4]College of Veterinary Medicine, Kangwon National University, Chuncheon, Gangwon, Republic of Korea

[5]Harvard Stem Cell Institute, Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, USA

**Background:** Whole organ decellularization is a cell removal process that creates a natural extracellular matrix for use in transplantation. A lack of an intact endothelial layer in the vascular network of decellularized organs results in blood clotting even with anti-coagulation treatment.
**Aim:** We hypothesized that a heparin-gelatin mixture (HG) can act as an antithrombotic coating reagent and induce attachment and migration of endothelial cells (ECs) on vascular wall surfaces within decellularized livers, with subsequent parenchymal cell function enhancement.
**Methods:** Portal vein (PV) perfusion was performed for right lateral lobe decellularization of porcine livers. We tested if HG-precoating of isolated decellularized PV could increase EC attachment and migration. Additionally, we coated PV and hepatic artery walls in decellularized liver with HG, and then repopulated it with ECs and maintained it under vascular flow in a bioreactor for 10 days. Re-endothelialized scaffolds were perfused with porcine blood for thrombogenicity evaluation. We then co-cultured hepatocellular carcinoma (HepG2) cells and ECs to evaluate the effect of endothelialization on parenchymal cells. Finally, we transplanted these scaffolds heterotopically in pigs.
**Results:** HG improved ECs' ability to migrate and adhere to vessel discs. ECs efficiently covered the vascular compartments within decellularized scaffolds and maintained function and proliferation after HG- precoating. No thrombosis was observed after 24 h blood perfusion in HG-precoated scaffolds, indicating a fully endothelialized vascular tree. HepG2 cells displayed a higher function in scaffolds endothelialized after HG-precoating compared to uncoated scaffolds in vitro and after in vivo transplantation.
**Conclusions:** Our results are promising to the pursuit of generating a fully functional human-sized tissue engineered liver scaffold with non-thrombogenic, patent vessels that can be used as liver assist-systems or for in vivo transplantation.

## O38
## EFFECT OF POROSITY IN FREEZE-DRIED DECELLULARIZED PORCINE PULMONARY HEART VALVES ON PROTEINS AND BIOMECHANICAL PROPERTIES

*Vásquez-Rivera A[1], Oldenhof H[2], Haverich A[3], Korossis S[3,4], Hilfiker A[3,5], Wolkers W[1]*

[1]Institute of Multiphase Processes, Leibniz Universität Hannover, Hannover, Germany

[2]Unit for Reproductive Medicine, University of Veterinary Medicine Hannover, Hannover, Germany

[3]Department of Cardiothoracic, Transplantation and Vascular Surgery, Hannover, Germany

[4]Lower Saxony Centre for Biomedical Engineering Implant Research and Development, Hannover Medical School, Hannover, Germany

[5]Leibniz Research Laboratories for Biotechnology and Artificial Organs, Hannover Medical School, Hannover, Germany

**Background:** Freeze-dried of decellularized heart valves facilitates easy storage and transport for clinical use. Ice crystal damage is one of the main damaging events during freeze-drying, resulting in pores in the tissue after rehydration. Sucrose can be used to reduce the adverse effects of freeze-drying, via glass formation and reduction of ice crystal formation.
**Aim:** To quantify pore formation in freeze-dried porcine pulmonary heart valve scaffolds, and to identify the effects of pores on the overall protein secondary structure, protein stability and biomechanical properties.
**Methods:** H&E staining was used to visualize structures in tissue sections. Quantification of porosity was determined via image analysis using ImageJ software. DSC was used to study ice crystal formation and protein denaturation temperatures. FTIR was used to study the overall protein secondary structure. Biomechanical properties were evaluated using a uniaxial tensile tester.
**Results:** Valves that were freeze-dried without protectants displayed a significant increase in porosity compared to controls. Pore formation changed biomechanical characteristics of tissues. Heat stability and overall secondary structure of proteins were not affected by pore formation. Exposure to a 40% (w/v) sucrose solution appeared to be sufficient to avoid pore formation.
**Conclusions:** Pores in freeze-dried heart valves alter biomechanical characteristics, whereas tissue proteins are not affected in terms of overall protein secondary structure and heat stability. A 40% (w/v) sucrose solution is needed to avoid pore formation in freeze-dried heart valves and to preserve biomechanical characteristics.

**O39**

**MID-TERM OUTCOME OF CARDIAC REGENERATIVE THERAPY WITH AUTOLOGOUS MYOBLAST CELL SHEET TRANSPLANTATION FOR ISCHEMIC CARDIOMYOPATHY**

*Domae K, Miyagawa S, Yoshikawa Y, Hata H, Saito S, Kashiyama N, Toda K, Sawa Y*
Department of Cardiovascular Surgery, Osaka University, Osaka, Japan

**Background:** Transplantation of autologous myoblast cells into the heart has been shown to yield functional recovery of the failing heart via "paracrine effects" that enhance the native regenerative process. We have introduced skeletal myoblast cell (SMBc) sheet methods for treating severe heart failure (HF), in which scaffold-free cell-sheets are attached on the epicardial surface to maximize the paracrine effects.
**Aim:** The aim of this study is to evaluate the mid-term outcome and therapeutic efficacy of SMBc sheet transplantation for treating severe HF due to ischemic cardiomyopathy.
**Methods:** This study enrolled 15 patients (mean age, 53 ± 15 years) with chronic advanced HF despite optimum treatments. Scaffold-free cell-sheets containing SMBc (average: 5.4 ± 3.0 × 108 cells) was transplanted over the left ventricular (LV) free wall via the left thoracotomy without concomitant procedures. Average follow-up was 4.0 ± 1.7 years.
**Results:** All patients discharged from the hospital without procedure-related complications and lethal arrhythmias. NYHA functional class was significantly decreased (2.9 ± 0.5 to 1.9 ± 0.3 $p<0.05$) and 6-minute walk distance was increased (405 ± 111 to 489 ± 158 m $p<0.05$) at 1 year, while these values maintained until the latest follow-up. Echocardiographically, LV systolic and diastolic diameters significantly decreased and ejection fraction significantly increased. In addition, pulmonary vascular resistance (PVR) significantly decreased (2.6 ± 1.6 to 2.0 ± 0.7 WU $p<0.05$). Incidence of requiring in-hospital treatment for HF was significantly decreased after SMBc sheet treatment (0.84 to 0.15 event/year $p<0.01$). Three-year freedom from MACE was 100% and three-year freedom from all-cause death was 90.9%.
**Conclusions:** Mid-term outcome of SMBc sheet transplantation for ischemic cardiomyopathy was acceptable for safety, improvement of their quality of life and functional recovery, including reduced PVR.

## Symposium: Cardiac Valves

**O40**

**IN VITRO CALCIFICATION AND MECHANICAL LOADING ON HEART VALVES: DEVELOPMENT OF NEW AND IMPROVED MODEL OF IN VIVO PROCESSES**

*D'Alessandro C[1,5], Koutsoukos P[2,3,5], Korossis S[4,5], Mavrilas D[1,5]*
[1]Mechanical and Aeronautical Department, University of Patras, Patras, Greece
[2]Department of Chemical Engineering, University of Patras, Patras, Greece
[3]Department of Chemical Engineering, FORTH-Institute, Heraklion, Greece
[4]Cardiothoracic, Transplantation and Vascular Surgery Department, Hannover Medical School, Hannover, Germany
[5]TECAS Project, Germany

**Background:** Current biological heart valve prostheses are limited in their life span due to the deposition of calcium phosphate crystals that formed into the tissue structure and consequently stiffen the leaflet material, causing stenosis or insufficiency.
**Aim:** In the present work a novel in vitro model is presented, allowing fast and accurate assessment and comparison of the calcification potential of different biomaterials used in heart valve replacements including the effect of mechanical loading.
**Methods:** Based on previous works done with constant supersaturation systems (CSR), a mock circulatory loop was adapted to a CSR to simulate physiological flow conditions for the evaluation of glutaraldehyde fixed (GAV) and decellularized (DCV) porcine aortic valves. By monitoring the pH of the solution (7.40 ± 0.01, @37C) while maintaining constant composition conditions an estimation of the calcification rate is possible. The morphological and chemical identification of the deposits was done by SEM-EDS. The solution's composition in calcium and phosphate ions was also assessed.
**Results:** The preliminary study of DCVs in the circulatory loop showed accelerated pH drop of whole aortic roots in comparison with GAVs undergoing mild flow conditions, indicating an increased calcification rate concordant with the deposits found by SEM-EDS. More in depth analysis of the images obtained by SEM- EDS showed an elevated amount of deposits on the heart valve leaflet's aortic side compared to the ventricular side.
**Conclusions:** A novel model for in vitro screening of the calcification potential of valvular scaffolds was developed. The model developed was able to simulate physiological pressures and flow conditions. The experimental model proved to be a powerful tool for the investigation of the effect of mechanical loading in the calcification of valvular scaffolds.

**O41**

**FUNCTIONAL MITRAL REGURGITATION MODEL IN AN EX-VIVO PLATFORM**

*Jaworek M[1,2], Lucherini F[1,2], Romagnoni C[2,3], Gelpi G[2,3], Contino M[2,3], Romitelli P[4], Antona C[2,3], Fiore G[1,2], Vismara R[1,2]*
[1]Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milan, Italy
[2]ForcardioLab, Fondazione per la Ricerca in Cardiochirurgia ONLUS, Milan, Italy
[3]Cardiovascular Department, 'Luigi Sacco' General Hospital, Milan, Italy
[4]Abbott Vascular International, Brussels, Belgium

**Background:** Mitral valve diseases are the most common valvular pathologies. One of them, functional mitral regurgitation (FMR), has complex mechanism involving dilation of the mitral annulus and displacement of the papillary muscles. Currently, the treatment strategies are being redefined due to the advancements in percutaneous techniques and high level of recurrence following the mitral annuloplasty.
**Aim:** To develop an experimental method to simulate FMR in an ex-vivo platform which could be of use in the new FMR treatments evaluation and as a realistic clinicians training platform.
**Methods:** A passive beating heart platform comprising a cyclically pressurized porcine heart was employed. The mitral annulus and papillary muscles were mechanically dilated and displaced using ad hoc designed 3D printed devices. The effects on hemodynamics and valve morphology (echocardiography) were evaluated experimentally in 10 swine heart samples.
**Results:** FMR inducement caused overall hemodynamic alterations (cardiac output drop of 33 ± 11%, increased systolic atrial pressure of 18 ± 7% in respect to the baseline). Mitral apparatus reshaping was evidenced by increased antero-posterior distance, tenting area and coaptation height (all with $p<0.05$ vs. baseline) resembling the most common dysfunction associated with FMR, type IIIb, featuring the restricted leaflet motion.
**Conclusions:** Reliable and well-controllable model of FMR was obtained. A realistic setting of the full heart anatomy and pulsatile flow conditions was provided allowing for a direct visual inspection via fiberscope and echocardiographic assessment. It can be employed in the preclinical research, medical education and clinicians' training. This work was supported by the European Commission within the H2020 Framework through the MSCA-ITN-ETN (project number 642458).

**O42**

**IN-VIVO EVALUATION OF CONVES A NOVEL DEVICE FOR A SUTURELESS AORTIC GRAFT ANASTOMOSIS**

*Dual S[1], Muller A[1], Brinkmann O[1], Boës S[1], Sündermann S[2], Falk V[2], Meboldt M[1], Schmid Daners M[1]*
[1]pd|z Product Development Group Zurich, ETH Zurich, Zurich, Switzerland
[2]Deutsches Herzzentrum Berlin, Berlin, Germany

**Background:** Suturing of the graft anastomosis to the aorta during left ventricular assist device implantation is effortful and time-consuming.
**Aim:** To simplify and shorten this procedure, we developed ConVes - a sutureless device to construct an aortic anastomosis even under minimal access conditions. The aim of this study is to test the anastomosis procedure with the novel device in vivo.

**Methods:** Three aortic anastomoses were constructed by a cardiac surgeon on the beating heart of two healthy pigs without cross-clamping of the aorta under minimal access conditions. With an encased balloon catheter, the novel device deploys a membrane covered stent with a flange inside the aortic wall. The procedure consists of the following steps: 1) puncture of the aorta 2) insertion of the catheter 3) flange unfolding 4) expansion of the stent by inflation and deflation of the balloon 5) retrieval of the device. Mechanical stoppers guide correct stent placement. We studied time for completion, blood loss, handling (subjective) and the hemodynamic characteristics of the device.
**Results:** All anastomoses were successfully constructed in less than eight minutes. The surgeon could access the aorta and correctly position the device. The blood inflow angle was between 30° and 45° and the implantable stent was fully unfolded inside the aorta. The total blood loss during the surgical interventions was 600-1400 mL, while most of the loss occurred during the retrieval of the device.
**Conclusions:** ConVes allows aortic anastomosis under minimal access conditions. The novel device enables a 2.5 times faster anastomosis procedure than a standard suture. The anastomosis was leak-free and the required inflow angle was achieved. Possible aortic tissue trauma arising from the stent expansion might be a limitation of the concept and will be examined. Our study is limited to few samples and the use of healthy porcine aortas. With further improvement ConVes has the potential to facilitate the implantation of a ventricular assist device.

### O43
### DEVELOPMENT OF AN INNOVATIVE DESIGN FOR A LARGE-SIZE PERCUTANEOUS PULMONARY VALVE PROSTHESIS

*Gruenwald A, Egron S, Kaufmann T, Steinseifer U*
Department of Cardiovascular Engineering, RWTH Aachen, Aachen, Germany

**Background:** Out of 1000 newborns 8 are born with a congenital heart disease. The most common defects are found in the right ventricular outflow tract and the following pulmonary valve. Pulmonary regurgitation (PR) is the most common long-term effect in these patients. Treatment of PR is often difficult and usually requires open-heart surgery. Percutaneous pulmonary valve prostheses (PPVP) have gained more importance recently as a minimally-invasive alternative. However, it is estimated that only 15% of the PR patients can be treated with the most commonly used PPVP.
**Aim:** This work aims to a) define requirements for a novel PPVP based on patient groups and intervention conditions and b) develop a novel PPVP design suitable for a wide range of patients based on these requirements.
**Methods:** Requirements for the new PPVP were identified based on literature and clinical input. It is important to understand what factors limit the use of currently available prostheses. Elasticity, anchoring, adaptability, repositioning and minimal average diameter (35 mm) for the new PPVP were identified as crucial factors. Based on this analysis a new PPVP stent design was iteratively developed using a combination of CAD (design) and FEM (simulation).
**Results:** The new stent design for the PPVP presents a diameter of 40 mm and an innovative structure, consisting of differently oriented diamonds. Therefore, it can be used for much larger anatomies compared to the most widely used PPVP (Medtronic Melody® with a diameter of 22 mm). In the central section, the diamonds are smaller compared to the upper and lower section. This structural division allows the stent to fulfill various functions. In the center a sufficient radial force is generated and the outer parts allow good positioning and anchoring.
**Conclusions:** The stent design has been elaborated and shows promising result. It fulfills and even exceeds the analyzed requirements. It is to be expected that a prosthesis based on this design could reduce the number of often young patients who require an invasive surgical procedure.

## Session: Experimental Models for Cardiovascular Devices

### O44
### MOCK CIRCULATION FOR VENTRICULAR ASSIST DEVICES

*Affeld K[1], Oeckel R[1], Lommel M[1], Kaufmann F[2], Kertzscher U[1]*
[1]Laboratory for Biofluid Mechanics, Charité - Universitätsmedizin Berlin, Berlin, Germany
[2]DHZB - German Heart Center Berlin, Berlin, Germany

**Background:** Patient supported with ventricular assist devices (VAD) usually have a remaining cardiac function. VADs nowadays are continuous flow rotary blood pumps. The generated flow is a function of the pressure difference (pressure head) between outflow (arterial pressure) and inflow (intra-ventricular pressure) and depending on the chosen rotational speed. Flow and pressure head represent the operating point on the characteristic HQ-curve of each speed setting. If the flow according to this operational point exceeds the venous return to the left ventricle, the ventricle will collapse and negative pressures (i.e. suction) will occur at the inflow of the pump.
**Aim:** Objective of the research is the development of a mock circulation, which permits to model this interaction.
**Methods:** The mock circulation models only the arterial system of the human circulation. The main elements are: left atrium, left ventricle, aorta, arterial compliance and arterial resistance. To the left ventricle a cardiac assist device can be attached, in this case an HVAD is used. Simulated contractions of the left ventricle can be activated in two modes: manual and automatic. The manual mode is intended for the training of VAD coordinators or cardiologists, which set the speed of the cardiac assist device according to the physiologic situation. The automatic mode is intended for measuring the performance of the cardiac assist device under defined conditions. The artificial ventricle can be controlled in its parameters pulse rate, stroke volume, atrial pressure and arterial resistance.
**Results:** As criteria for the proper function of the mock circulation, the aortic pressure over time curve is taken: the resulting curve is very similar to the physiological pressure curves in various settings of left ventricular unloading.
**Conclusions:** A mock circulation has been developed, which models the interaction of a partially active left ventricle and a cardiac assist device accurately.

### O45
### IN VITRO FLOW INVESTIGATION IN THE AORTA WITH TWO DIFFERENT COMPLIANCES USING STEREO PIV

*Mueller I, Buesen M, Jentsch S, Steinseifer U*
Department of Cardiovascular Engineering, Institute of Applied Medical Engineering, Aachen, Germany

**Background:** The aorta with its compliance plays a major role in hemodynamics as it saves a portion of ejected blood during systole to release it later in diastole, thus guaranteeing a continuous positive blood flow. The aortic compliance decreases with increasing age, which is related to several cardiovascular diseases. Changes in flow patterns and pressure curves, due to varying aortic compliances, are difficult to investigate in vivo.
**Aim:** The aim of the present work was the investigation of the 3D flow field in the aorta with stereo PIV in dependence on two different compliances.
**Methods:** An experimental setup with an anatomically correct silicone phantom of the aortic arch was connected to a physiological mock circulation loop. The aorta was surrounded by a fluid filled box and compliance values were adjusted with an attached air chamber. Stereo particle image velocimetry (PIV) measurements were carried out in 44 planes covering the whole ascending aorta and the aortic arch for two different compliances.
**Results:** The two adjusted compliances were set to 2.53 $mm^2 \times mmHg^{-1}$ and 5.51 $mm^2 \times mmHg^{-1}$. For the first time the flow field inside an elastic aorta was investigated and was found to be in good comparison to literature data. At the distal end of the aortic arch, flow separation occurred at the curvature during early systole. At a low compliance, the flow separation point occurred

further upstream und the recirculation region is bigger. During diastole a clockwise rotating helical flow appears in the ascending aorta. The helical pitch is smaller with a higher compliance and at the same time more coils appear.
**Conclusions:** With the experimental setup effects of compliance changes could be investigated in vitro in a standardized manner. This setup also enables the investigation of cannulation methods in a flexible aorta and serves as a validation tool for CFD simulations.

**O46**
**OPTIMISATION OF NUMERICAL HAEMOLYSIS MODEL TO ENABLE ACCURATE PREDICTION OF HAEMOLYSIS PERFORMANCE IN VENTRICULAR ASSIST DEVICES**
*Yousef H[1], Molteni A[2], Rolland S[1], Low K[1], Sienz J[1]*
[1]ASTUTE 2020 (Advanced Sustainable Manufacturing Technologies), Swansea University, Swansea, UK
[2]Calon Cardio-Technology Ltd, Swansea, UK

**Background:** Haemolysis is recognised as clinically relevant adverse effect of Ventricular Assist Devices (VADs). A numerical model capable of providing accurate estimates of haemolysis is an essential tool in the design iteration process to reduce blood damage.
**Aim:** The current work introduces particles tracks recirculation analysis to better represent laboratory haemolysis experiments and to improve the numerical haemolysis predictions in VADs.
**Methods:** Originally, haemolysis was calculated using a power law function of shear stress and exposure time along particles tracks passing once through VAD, 'Single Pass'. To match simulation residence time to experiment time three approaches were implemented. The first is 'Scaled Single Pass' (SSP) and it is a linear scaling of 'Single Pass' residence times. The second is 'Same Track Recirculation' (STR) which recirculates particles over their original tracks. The third is 'Random Track Recirculation' which recirculates particle over randomly selected tracks. The above analyses were carried out on centrifugal and axial pumps, among which HVAD and HeartMate-II. The pumps were divided into 2 groups: calibration and validation. Seven different calibration and validation combinations were used in the fitting process which produced 7 different sets of model coefficients. The fitted results using different methods were compared against 'Single Pass' results.
**Results:** Implementing track recirculation analysis improved model prediction by up to 60% with SSP and STR performing the best and both yielding similar coefficients. SSP was the most efficient implementation because it involved a simple scaling-up calculation step. It predicts all centrifugal pumps haemolysis within 40% (calibration and validation), and the axial pump below 70%.
**Conclusions:** The absolute haemolysis estimate has been significantly improved compared to the 'Single Pass' numerical model by accounting for recirculation. More experiments are planned to improve numerical predictions.

**O47**
**THE ANASTOMOSIS ANGLE OF OUTFLOW GRAFT TO AORTA INFLUENCES ON HEMODYNAMICS OF AORTIC VALVE REGURGITATION IN LEFT VENTRICULAR ASSIST DEVICE SUPPORT**
*Iizuka K[1,2], Nishinaka T[2], Sumikura H[1], Mizuno T[1], Tsukiya T[1], Takewa Y[1], Yamazaki K[2], Tatsumi E[1]*
[1]Department of Artificial Organs, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan
[2]Department of Cardiovascular Surgery, Tokyo Women's Medical University, Tokyo, Japan

**Background:** Aortic valve regurgitation (AR) is a worrisome problem in left ventricular assist device (LVAD) support, which can cause LVAD-LV recirculation. Many studies indicated that anastomosis design of outflow graft could influence on occurrence of AR. In our previous study, we demonstrated that the angle of outflow graft to the aorta (O-A angle) had an impact on progression of AR in LVAD patients.
**Aim:** How the O-A angle influence on hemodynamics in presence of AR was investigated in acute animal experiments.
**Methods:** Five calves underwent a continuous-flow LVAD (EVAHEART) implantation through median sternotomy. An outflow graft was sutured to the ascending aorta. A custom-made O-A angle regulating supporter was placed on the anastomosis site. Cardiac dysfunction was induced by continuous infusion of a beta blockade. The AR model was established by placing a vena cava filter in aortic valve. Hemodynamics and cardiac oxygen metabolism (pulmonary artery flow; PAF, pump flow; PF, Coronary artery flow; CoF, and oxygen extraction rate; O2ER) were evaluated at three different O-A angle (45, 90, 135 degrees) and three degrees of AR (none, mild, severe).
**Results:** PF didn't change in any setting. PAF maintained at any O-A angle in none AR and in mild AR, however it decreased at larger O-A angle in severe AR, indicating that LVAD-LV recirculation increased at larger O-A angle in severe AR. CoF didn't change in none AR, while it decreased at larger O-A angle in mild AR and in severe AR. The magnitude of CoF decrease was greater in severe AR than in mild AR. O2ER maintained at any O-A angle in none AR and in mild AR, but it increased at larger O-A angle in severe AR.
**Conclusions:** Large O-A angle, creating more counter flow against native heart outflow, can increase the LVAD-LV recirculation in presence of severe AR, and can worsen cardiac oxygen metabolism.

**O48**
**CARDIAC FLOW PATTERNS DURING MECHANICAL CIRCULATORY SUPPORT AS A POSSIBLE LINK TO STROKE DEVELOPMENT**
*Aigner P[1,2], Moscato F[1,2], Schima H[1-3]*
[1]Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria
[2]Ludwig Boltzmann Cluster for Cardiovascular Research, Vienna, Austria
[3]Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria

**Background:** Mechanical Circulatory Support (MCS) developed over the last years towards a reliable treatment alternative to cardiac transplantation in end stage heart failure. However adverse events and thrombotic events pose a risk for the development of stroke. These complications are probably related to flow stagnation areas and consequently thrombus formation within the left ventricle.
**Aim:** The aim of this work is to identify areas of low washout, flow stagnation and possible thrombus development in cardiac models.
**Methods:** Different cardiac models made from silicone were built to mimic patient specific geometries and various support situations (pump flow: 0, 3, 4, 5 l/min, Stroke volume: 0-70 ml) reaching from an unsupported healthy heart via different pulsatile situations through to an akinetic heart were simulated. Flow patterns were measured with Particle Image Velocimetry for a total cardiac output of 5 l/min and mean arterial pressure of 90 mmHg.
**Results:** Flow patterns within the cardiac simulator were strongly dependent on the different support situations. One large rotational pattern was observed in the unsupported heart. With increasing MCS speed this patterns dissolved and completely disappeared in the akinetic hearts. Areas with little washout and low velocities for long periods were identified close to the MCS inflow cannula and next to the left ventricular outflow tract and trend to be larger in bigger ventricles.
**Conclusions:** Effects of mechanical circulatory system largely alter natural cardiac flow patterns. Higher pump speeds and flow rates completely dissolve the physiologic rotational flow pattern during diastole and might cause flow stagnation and thrombus formation. Areas with low washout were identified close to the pump cannula and in highly supported and akinetic hearts close to the left ventricular outflow tract.

**O49**
**NITRIC OXIDE ADMINISTRATION TO THE GAS INFLOW OF OXYGENATOR IMPROVES CEREBRAL PERFUSION AND NEUROPROTECTION DURING ECMO**
*Ahmed N[1], Linardi D[2], San Biagio L[2], Tessari M[2], Bombieri S[2], Faggian G[2], Rungatscher A[2]*
[1]Biomedical Sciences Department, King Edward Medical University, Lahore, Pakistan
[2]Division of Cardiac Surgery, Surgery Department, University of Verona, Verona, Italy

**Background:** The hemolytic product free-hemoglobin (fHb) reduces nitric oxide (NO) bioavailability during extracorporeal membrane oxygenation (ECMO) and may be a possible factor in the pathogenesis of impaired cerebral blood flow (CBF).

**Aim:** This study was conducted to investigate whether NO administration in the ECMO circuit can improve CBF and offer neuroprotection during ECMO support.
**Methods:** Venoarterial ECMO was instituted for 60 minutes in male Sprage-Dawley adult rats. They were randomised to receive 20 ppm NO to the gas inflow of the ECMO oxygenator or standard conduct of ECMO.
**Results:** NO caused a moderate decrease of arterial blood pressure and cerebral perfusion pressure. Conversely, CBF measured by laser-Doppler flowmetry increased significantly in NO treated animals. The rate of injured neurons in the hippocampal CA1-field was significantly reduced in NO treated animals (12.1 ± 3%) compared to controls (18.5 ± 5%), as well as the number of Caspase-3 positive neurons.
**Conclusions:** Administration of NO can attenuate cerebral perfusion impairment during ECMO and reduce neuronal damage in spite of a moderate hypotensive side effect. This may reflect the reversal of NO consumption due to fHb. In the clinical setting, delivery of NO to the oxygenator gas flow during ECMO could ameliorate neurologic outcome.

## Session: Challenges for Dialysis Devices

### O50
### HAEMODIALYSER CLOTTING: THE INNER COUNTS

*Vanommeslaeghe F, Van Biesen W, Dierick M, Van Hoorebeke L, Dhondt A, Eloot S*
Department of Nephrology, Ghent University, Ghent, Belgium

**Background:** Coagulation in the haemodialysis (HD) circuit decreases treatment efficiency and can result in substantial blood loss. Some health care facilities follow machine parameters such as venous pressure, transmembrane pressure (TMP) and online clearance monitoring (OCM) to detect coagulation during treatment. An accepted method to quantify the extent of coagulation in dialysers is lacking.
**Aim:** We used a micro-CT scanning technique as gold standard to evaluate accuracy of machine parameters and visual scoring to reflect coagulation in the dialyser.
**Methods:** Outpatient HD patients (n = 20) were treated with haemodiafiltration for 245 ± 20 min with a FX600 dialyser on a 5008 dialysis machine (both Fresenius, Germany) using their usual LMWH dose. Every 30 min, blood, dialysate, ultrafiltration and substitution flows, blood inlet and blood outlet pressure, TMP, blood volume monitoring and OCM, all as indicated by the machine, were registered. After dialysis, haemodialyser, venous chamber and line were colour scored and clot sizes were registered. 24 h positive pressure ventilation was applied to the dialyser and dry mass was measured. The 20 used and 3 non-used dialysers were scanned (resolution 25 µm) in HECTOR (High-Energy CT scanner Optimised for Research). After image reconstruction, the open, non-coagulated fibers were counted in a representative cross-section at the dialyser outlet (ImageJ, Fiji).
**Results:** In non-used vs used FX600 dialysers, 10748 ± 2 vs 8930 ± 2465 [range 534-10692] open fibers were counted. The number of non-coagulated fibers correlated with the visual scoring of the dialyser (R = -0.637; P = 0.003) and venous chamber (R = -0.584; P = 0.007), and the post-dialysis dialyser dry mass (R = -0.786; P<0.001), but not with any of the measured machine parameters.
**Conclusions:** Micro-CT scanning is a feasible and reliable tool for quantitative evaluation of coagulation in used dialysers, and can be considered as gold standard. At present, there seems to be no valid parameter for coagulation in the filter during the HD session. The described technique can contribute to the development of indicators of clotting during dialysis.

### O51
### IMPACT OF INITIAL DIALYSIS MODALITY ON THE SURVIVAL OF PATIENTS WITH ESRD: A PROPENSITY-MATCHED STUDY

*Yao X, Zhang P, Zhang L, Shao X, Lei W, Chen J*
Kidney Disease Center, 1st Affialiated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

**Background:** Published studies comparing outcomes of Peritoneal dialysis (PD) and hemodialysis (HD) among ESRD patients have reported conflicting results, few large-scale study has so far investigated the effect of initial dialysis modalities on mortality in Chinese populations.
**Aim:** This study aimed to compare survival between incident PD and propensity score- matched HD patients in China.
**Methods:** The data were from Zhejiang Dialysis Quality and Management Center Database between 2010 and 2014, which including 225 blood purification centers and 93 peritoneal dialysis centers in Zhejiang Province of China. All patients were followed up until death or the end of 2015. Patients with dialysis vintage less than 90 days and under 18 years old were excluded. PD patients were matched in a 1:1 fashion with HD patients. Then survival analysis was performed using the Kaplan–Meier method, Log-Rank test and Cox proportional hazard regression model.
**Results:** A total of 22379 patients were enrolled (17029 (76.1%) HD patients), followed for a median of 29 months (3~72 months). We matched 5030 patient pairs with similar propensity scores, and no significant difference was observed between the baseline characteristics of two groups. Kaplan-Meier survival curve revealed that overall mortality rate in HD patients was significantly higher than that in PD patients (P<0.001), after adjusting by age, gender, causes of ESRD and comorbid conditions, Cox proportional hazard model showed that HD (vs. PD) was associated with an increased risk for morality (HR:1.239,95% CI: 1.130-1.358). In subgroup analysis indicated that PD patients below 65 years old and nondiabetic had a lower mortality ratio than HD patients.
**Conclusions:** ESRD patients who initiated dialysis with PD yielded superior survival rates compared to HD. Subgroup analysis revealed that most subgroups, such as nondiabetic patients below 65 years old, favoring PD. Increased use of PD as initial dialysis modality in ESRD patients could be encouraged in Chinese populations.

### O52
### MASS-SPECTROMETRY BASED PLASMA PROTEOMICS TO FIND THE UNDERLYING MOLECULAR DETERMINANTS OF HYPERTENSION

*Gajjala P, Jankowski V, Jankowski J*
Institute for Molecular Cardiovascular Research, University Hospital, RWTH Aachen University, Aachen, Germany

**Background:** Despite advancements in lowering blood pressure, the best approach to lower it remains controversial due to the lack of information on its molecular basis.
**Aim:** We, therefore, performed plasma proteomics of plasma from hypertensive patients to identify molecular determinants detectable in hypertensives but not in normotensives vice versa.
**Methods:** Plasma samples from hypertensive (n = 118) and normotensive subjects (n = 85) from the "InGenious Hypercare" cohort were used for this study. We performed liquid chromatography online coupled to electrospray ionisation quadrupole ion trap mass spectrometry for analysis of the plasma samples after sample preparation. Using biostatistical methods hypertension specific plasma peptides were identified and a model was developed using least absolute shrinkage and selection operator logistic regression. The underlying peptides were identified and sequenced offline using matrix-assisted laser desorption ionisation orbitrap mass spectrometry.
**Results:** By comparison of the molecular composition of the plasma samples, 27 molecular determinants were identified differently expressed in hypertensives from normotensives. 70% of the molecular determinants selected were found to occur less likely in hypertensive patients. In cross-validation, the overall R-square was 0.434 and the area under the ROC curve was 0.891 with 95% confidence interval 0.8482 to 0.9349, P<0.0001. The mean value of the cross-validated proteomic score of normotensive and hypertensive patients was found to be -2.007 ± 0.3568 and 3.383 ± 0.2643, P<0.0001 respectively.
**Conclusions:** The status of hypertension and normotension was successfully classified based on molecular determinants identified in plasma. The identified molecular determinants may be the starting point for further studies to clarify the molecular causes of hypertension.

**O53**

**BLOOD FOAM IN THE AIR TRAP DURING HAEMODIALYSIS**

*Jonsson P[1,2], Lindmark L[2], Karlsson L[1], Hedlund A[1], Lundberg L[1], Axelsson J[2], Stegmayr B[1]*
[1]Public Health and Clinical Medicine, Umea University, Umea, Sweden
[2]Radiation Science, Radiation Physics, Umea University, Umea, Sweden

**Background:** During clinical haemodialysis (HD) the staff noted formation of large amounts of visible foam in blood lines using Gambro Artis dialysis device. No alarm was activated.
**Aim:** We urgently started to investigate the possible reason for such foam formation.
**Methods:** Extent of foam was graded 0-10 (none-extensive). Two blinded persons evaluated photos taken of air traps in use. 37 patients performed consecutive HD with Fresenius (FX; CorDiax used for high flux HD: FX80 and FX100, FX1000) and Baxter dialyzers (PF210H). Dialyses devices were Gambro Artis (GA) and Fresenius 5008 (F5008). The extracorporeal circuit of GA was primed by dialysate automatically using software 8.15006 (Baxter). The priming volume was 1500 ml, extended up to 4250, due to visible foam in GA, upon manufacturers recommendations. For investigation we also used GAMPT ultrasound device and CT-scan methods.
**Results:** Priming up to 4250 ml did not eliminate visible foam. Micro bubble measurement during HD revealed the air to derive from the dialyzers. When using PF210H, and priming volume of 1500 ml, significantly less foam than for FX was present in GA ($p<0.01$). PF210H and GA had the similar outcome as FX and F5008. The extent of foam correlated with the size of the FX-dialyzer surface ($p = 0.002$). The autopriming program was updated into version 8.21 by the manufacturer (Baxter). The extent of foam in the air trap using FX dialyzers now was reduced and there was no longer any difference between FX- and PF dialyzers. Sometimes still foam could be visible in the air trap during HD with both devices.
**Conclusions:** This study urgently calls for attention of blood foam developed in the venous air trap when using GA devices and priming software 8.15006 in combination with Fresenius dialyzers. An updated automatic priming software (version 8.21) of Artis should be requested to reduced the extent of foam for the Fresenius dialyzers. The FX vs PF210H dialyzers have different priming techniques that still are not optimal. Further development is needed.

**O54**

**DIFFERENTIATION AND HETEROGENEITY OF BIOMATERIAL-INDUCED MULTINUCLEATED GIANT CELLS: CONNECTION BETWEEN INFLAMMATION AND TISSUE REGENERATION**

*Barbeck M[1], Unger R[2], Booms P[3], Kirkpatrick C[3], Ghanaati S[3]*
[1]Berlin-Brandenburg Center for Regenerative Therapies, Charité-Universitätsmedizin Berlin, Berlin, Germany
[2]Institute of Pathology, Repair-Lab, University Medical Center of the Johannes Gutenberg University, Mainz, Germany
[3]FORM-Lab, Department for Oral, Cranio-Maxillofacial and Facial Plastic Surgery, Medical Center of the Goethe University Frankfurt, Frankfurt, Germany

**Background:** Biomaterial-associated multinucleated giant cells (BMGCs) have been found within the implantation beds of many different biomaterials. However, their exact differentiation and their involvement in the inflammatory and healing events of the foreign body response still remain mostly unclear. Various findings suggest that these cells belong to the cell line of the foreign body giant cells (FBGCs), which are of "inflammatory origin", and they may provide a phenotypic heterogeneity equivalent to that of macrophages.
**Aim:** To substantiate our hypothesis of the differentiation and of the phenotypic and functional relationship between macrophages and BMGCs, antibodies for the detection of giant cell-specific antibodies as well as for detection of different pro- and anti-inflammatory macrophage subpopulations were applied.
**Methods:** In a first study tissue samples from a clinical study were used to analyze the origin of BMGCs in the implant beds of a synthetic and a xenogeneic bone substitute by the application of immunohistochemical methods. Two antibodies against integrin molecules specific for osteoclasts (β-3 integrin) or FBGCs (β-2 integrin) were used. In a second study immunohistochemical and histomorphometrical techniques were applied to analyze the heterogeneity of BMGCs.
**Results:** The results indicate that the BMGCs are FBGCs and express both pro- and anti-inflammatory molecules to the same extent, which substantiates the heterogeneity of FBGCs comparable to that of macrophages.
**Conclusions:** These data give new insight into the tissue reaction to biomaterials. Based on this new knowledge further research concerning the proteomic profile of FBGCs especially with respect to the different physicochemical properties of biomaterials is necessary.

**O55**

**CYTOKINE PROFILES IN SEPSIS PATIENTS**

*Eichhorn T[1], Linsberger I[1], Lauková L[2], König F[3], Hörmann C[4], Weber V[1]*
[1]Christian Doppler Laboratory for Innovative Therapy Approaches in Sepsis, Danube University Krems, Krems, Austria
[2]Institute of Molecular Biomedicine, Comenius University, Bratislava, Slovakia
[3]Institute for Medical Statistics, Medical University Vienna, Vienna, Austria
[4]University Hospital St. Pölten, St. Pölten, Austria

**Background:** Sepsis results from a complex and highly variable host response to invading pathogens, making the selection of patient populations who might profit from distinct interventions challenging.
**Aim:** We studied cytokine profiles in patients with acute renal failure in the course of sepsis and assessed differences in cytokine depletion in continuous veno-venous hemodialysis (CVVHD) with the high cut-off (HCO) hemofilter EMiC2 and the standard filter AV1000S (both from Fresenius Medical Care).
**Methods:** We measured cytokine profiles and cytokine depletion in a single-center, randomized, controlled clinical trial including 30 patients. CVVHD was performed with the multiFiltrate Acute Therapy System and Ci-Ca anticoagulation. Plasma was collected at baseline and after 1, 24, 48 h, and characterized using a 27-plex inflammation bead array. In addition, albumin, extracellular DNA, histones, HMGB-1, CRP, LBP, sCD14, and endocan were quantified. IL-6, IL-8, IL-10, TNF-α, and albumin were also measured in the effluent.
**Results:** The study population revealed large variations in plasma cytokine concentrations (e.g. IL-6, 26-40600 pg/ml). SAPS and TISS scores did not correlate with biomarker levels. Correlations were shown for extracellular DNA, HMGB-1, and histones. LBP significantly correlated with sCD14 and CRP. Patients treated with the HCO filter showed a significantly higher percentage of IL-6 and IL-8 in the effluent relative to plasma levels. The filters did not differ with respect to albumin removal. No differences in biomarker levels were found after 48 h for HCO vs. standard filter.
**Conclusions:** CVVHD-HCO achieved increased removal of IL-6 and IL-8, but did not result in decreased cytokine concentrations after 48 h. The broad range of plasma cytokine levels underlines the need for efficient systems to move toward personalized adjunctive sepsis treatments.

**O56**

**THE RISK OF CATHETER-RELATED BLOODSTREAM INFECTION WITH TEMPORARY FEMORAL HEMODIALYSIS CATHETERS**

*Gerasimovska V, Gerasimovska-Kitanovska B, Sikole A*
University Clinic of Nephrology, Skopje, Macedonia

**Background:** Central venous catheters used for HD are a common cause of catheter—related bloodstream infection (CRBI). Staphylococci account for most infections, but enterococcal infections are increasingly observed.
**Aim:** Current guidelines recommend that femoral venous access should be avoided to reduce CRBI.
**Methods:** In a retrospective study we looked at the outcome of a group of 650 patients (pts) receiving chronic haemodialysis treatment via a 821 temporary femoral catheters (FC) during the 3-years period. Each catheter was followed individually until it was removed or until the end of the study, and catheters with CRBI caused by different microbiological organisms were analysed. Blood cultures from peripheral blood and catheter were performed and catheter tips were microbiologicaly analysed too. Antibiotic therapy was used always when we have suspicion of CRBI.
**Results:** During this study 129 removed FC has positive blood cultures for gram-positive cocci and gram- negative bacteria. FC were removed when no longer required (permanent VA was performed), or significant complications

occurred - 31 were removed under suspicion for CRBI. Cumulative duration of FC were 5997 days (average 44 days).S.aures was isolated in 50 FC -38,7% (15 were MRSA strains), and CoNS was isolated in 54 FC-41,9% (11 methicilin resistant strains), Enterococcus was isolated in 16 FC- 12,4%. Forty one pts have clinical signs of infection- chills and high temperature during the HD. Infective rate was 0,83 episodes/1000 catheter days. Usually used systemics antibiotics were Vancomycin, Cefotaxim and Ciprofloxacin. We analysed risk factors for catheter survival in this group with Cox regression model adjusted for age, sex and comorbidity and we found that they are risk factors: age (<51/>51) (p = 0,0007) sex (p = 0,002905) and diabetes mellitus (p = 0,008).
**Conclusions:** Factors affecting whether or not a FC should be removed in the face od CRBI include clinical response to treatment, presence of metastatic complications, and infecting agent.

## Symposium: Challenges in Vascular Tissue Engineering

### O57
### S-NITROSO HUMAN SERUM ALBUMIN RELEASING POLY(E-CAPROLACTONE) SMALL DIAMETER VASCULAR GRAFT

*Enayati M[1,2], Schneider K[1,2], Hallström S[3], Almeria C[2], Grasl C[2,4], Kaun C[5], Messner B[6], Schima H[2,4,6],Podesser B[1,2], Bergmeister H[1,2]*
[1]Department of Biomedical Research, Medical University of Vienna, Vienna, Austria
[2]Ludwig Boltzmann Cluster for Cardiovascular Research, Vienna, Austria
[3]Institute of Physiological Chemistry, Medical University of Graz, Graz, Austria
[4]Center of Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria
[5]Department of Medicine II, Medical University of Vienna, Vienna, Austria
[6]Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria

**Background:** Despite intensive research, an efficient small diameter graft is still unavailable. Nitric oxide (NO), plays a crucial role in maintaining patency of the vascular system by regulating platelet activation and neointimal hyperplasia.
**Aim:** This study aimed to fabricate electrospun s-nitroso human serum albumin (s-NO-HAS) loaded poly(ε-caprolactone) (PCL) vascular grafts to increase the patency rate of synthetic small diameter vascular graft. Non-loaded Grafts served as controls.
**Methods:** The effects of NO-grafts on endothelialization and smooth muscle cell proliferation were assessed via XTT assay using primary HUVECs and human SMCs. The role of NO on expression of adhesion molecules (ICAM-1, VCAM-1) and tissue factor (TF) were studied in HUVECS. Furthermore, the role of NO on expression of pro- and anti-inflammatory cytokines (IL1α, TNFα, IL10) and M1/M2 macrophage markers (CCR7, CD80, CD163) in human macrophages were studied via PCR. Grafts have been further implanted into the infrarenal aorta of rats (n = 7) up to 3 months.
**Results:** Conduits composed of 8% PCL showed the highest NO encapsulation effect. NO loaded grafts significantly enhanced endothelialization while preventing smooth muscle cell proliferation. NO attenuated the expression of ICAM-1, VCAM-1 and TF. Furthermore, it up-regulated anti-inflammatory cytokines (IL10) and M2 macrophage marker (CD163). After a short up-regulation phase of pro-inflammatory genes (CD80, IL1α, TNFα), these genes were down-regulated significantly.. All grafts were patent after 3 months implantation.
**Conclusions:** NO encapsulated grafts supported the proliferation of endothelial cells while inhibiting SMC proliferation in-vitro. They regulated the inflammation and prevented the focal adhesion and accumulation of leukoctyes via the inhition of ICAM-1 and VCAM-1 expression in endothelial cells. Endothelialization was promoted in NO loaded grafts in-vivo.

### O58
### NEOINTIMA INDUCING PROCESS ON SMALL-DIAMETER DECELLULARIZED VASCULAR GRAFT MODIFIED WITH THE BIOACTIVE PEPTIDE

*Mahara A, Munisso M, Yamaoka T*
Department of Biomedical Engineering, National Cerebral and Cardiovascular Center, Osaka, Japan

**Background:** Although small-diameter vascular graft with less than 4 mm of inner diameter is required in clinical site, synthetic grafts occlude rapidly when transplanted in patient body. In our previous work, we reported a good patency of small-diameter acellular vascular graft modified with bioactive peptide in minipig model. When the graft was transplanted as femoral-femoral bypass, neointima formed on the graft surface by the action of immobilized bioactive-peptide. However, it is not revealed that how the peptide-modification contribute to the neointima formation and patency in vivo.
**Aim:** In this study, we investigated the neointima inducing process on the acellular graft.
**Methods:** Decellularized ostrich carotid artery was used as the graft material. Luminal surface was modified with bioactive-peptide of which sequence was previously reported. The acellular graft was connected to the cardiopulmonary system, and the surface was observed by SEM after contacting with the heparinized-blood flow. After transplantation into minipig for 1, 3, and 7 days, neointima formation was evaluated by immunostaining and FACS analysis.
**Results:** After contacting with the blood for one hour, microthrombosis formed on unmodified graft surface. In contrast, the thrombosis was not observed on peptide-modified surface. After one day transplantation, CD34 and Flk-1 positive cells were accumulated on the luminal surface at the place far from the native blood vessel, and the CD31 and CD105 markers were confirmed after 3 and 7 days transplantation. The expression of Flk-1 and CD34 was not indicated at the luminal surface after 3 month transplantation.
**Conclusions:** Modified peptide has anti-thrombosis property against heparinized blood. The graft surface captured the circulating endothelial progenitor cells during 24 hours under blood flow condition, and the intima layer maturated in 3 month in vivo.

### O59
### DECELLULARIZED SMALL DIAMETER VASCULAR GRAFTS FROM THE HUMAN PLACENTA: ASSESSMENT OF THE FUNCTIONAL PERFORMANCE IN A RAT MODEL

*Schneider K[1,2], Enayati M[1,2], Pils A[1,2], Grasl C[2,3], Walter I[4], Teuschl A[5], Redl H[6], Wojta J[2,7], Messner B[8], Bergmeister H[1,2]*
[1]Department for Biomedical Research, Medical University Vienna, Vienna, Austria
[2]Ludwig Boltzmann Cluster for Cardiovascular Research, Vienna, Austria
[3]Center for Medical Physics and Biomedical Engineering, Medical University Vienna, Vienna, Austria
[4]Department of Pathobiology, University of Veterinary Medicine, Vienna, Austria
[5]Department of Biochemical Engineering, University of Applied Sciences Technikum Wien, Vienna, Austria
[6]Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria
[7]Surgical Research Laboratories, Medical University Vienna, Vienna, Austria
[8]Division of Internal Medicine II, Medical University Vienna, Vienna, Austria

**Background:** Decellularized matrix grafts are a promising approach to replace diseased small-diameter vascular segments because of their appropriate biomechanical properties and their potential to promote host cell migration and differentiation. Recently, we designed vascular grafts from the human placenta using two different decellularization protocols. Both materials types revealed excellent biocompatibility in- vitro and as subcutaneous implants.
**Aim:** In this study, we aimed to investigate the in-vivo functionality of these matrix grafts as aortic conduits in a rat model.
**Methods:** Matrix grafts, fabricated from human placental vessels were decellularized either by Triton X-100 or SDS and cross-linked with heparin. After characterization (biomechanical properties, quantification of DNA and extracellular matrix proteins, prostheses were implanted for 1 month into the aorta of Sprague- Dawley rats (n = 14). At retrieval specimens were analyzed by MRI angiography, electromyography and histology.

**Results:** Both groups showed high patency rates (100%) and no signs of thrombus formation, aneurysms or rupture. Both graft types revealed tissue specific cell migration and functional remodeling. Although a xenogenic implantation setting was used, minimal host inflammatory response was seen.
**Conclusions:** Decellularization of vessels from the human placenta is an efficient approach to fabricate small diameter vascular substitutes with excellent in-vivo performance.

**O60**
**APPLICATION OF THE XENOGENEIC DECELLULARIZED TUBE MATRIX PRODUCED BY IN VIVO TISSUE ENGINEERING TO THE 'OFF-THE-SHELF' SMALL- CALIBER VASCULAR GRAFT**
*Yamanami M[1], Kawasaki T[2], Kami D[2], Watanabe T[1], Kanda K[1], Gojo S[2], Yaku H[1]*
[1]Department of Cardiovascular Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan
[2]Department of Regenerative Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan

**Background:** We have developed in vivo tissue-engineered autologous small-caliber vascular grafts 'Biotubes', which withstood systemic blood pressure and exhibited excellent performances as small caliber vascular prostheses in animal models. However, as it takes 4 weeks to prepare Biotubes, they cannot be applied in emergent situations. Also, to respond to various types of surgery, it is ideal that grafts are readily available in advance.
**Aim:** The aim of this study is to develop the novel off-the-shelf small-caliber vascular grafts by decellularizing the in vivo tissue-engineered xenogeneic tubular materials.
**Methods:** Silicone rod molds (diameter: 2 mm, length: 10 cm) placed into subcutaneous pouches of beagle dogs for 4 weeks were harvested with their surrounded connective tissues. Tubular connective tissues were obtained after pulling out the impregnated molds. Subsequently, they were decellularized by perfusing with sodium dodecyl sulfate (SDS) and Triton-X. They were stored as off-the-shelf grafts in phosphate-buffered saline (PBS) at 4 degree for 1 week. The decellularized grafts derived from beagle dogs were xenogeneicly transplanted to the abdominal aorta of the rats (n = 3).
**Results:** No signs of abnormal inflammation or immunological problems due to the xenogeneic material were observed. Echocardiography revealed all grafts were patent at 1 month after implantation. Histological evaluation revealed that grafts formed neointima on the luminal surface and graft walls had cell infiltration. Little obvious accumulation of CD68+ macrophages in the graft wall was observed.
**Conclusions:** Xenogeneic decellularized tubular tissues functioned as small caliber vascular grafts as well as autologous biotubes. This technology enabled the easy fabrication of grafts from xenogeneic animals in advance and storage for a significant period, which satisfy the condition for off-the-shelf grafts.

## Symposium: Numerical Modelling in Hemodialysis

**O61**
**TOWARDS LONGITUDINAL ANALYSIS OF ARTERIOVENOUS FISTULA FOR HEMODIALYSIS USING CONTRAST-FREE MAGNETIC RESONANCE ANGIOGRAPHY**
*Bozzetto M[1], Brambilla P[2], Ene-Iordache B[1], Sironi S[2], Remuzzi G[1,3], Remuzzi A[1,4]*
[1]Department of Bioengineering, IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy
[2]Department of Imaging, ASST "Papa Giovanni XXIII", Bergamo, Italy
[3]Unit of Nephrology and Dialysis, ASST "Papa Giovanni XXIII", Bergamo, Italy
[4]Department of Management, Information and Production Engineering, University of Bergamo, Bergamo, Italy

**Background:** Autologous arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis, but it has high rate of early failure due to vascular stenosis. A growing body of evidence suggests a key role of hemodynamics in stenosis formation. To investigate the relationship between disturbed flow and AVF failure, longitudinal studies with repeated evaluations of hemodynamics and vascular changes are needed. These studies require reliable and non-invasive investigations to obtain patient-specific AVF models for computational fluid dynamics (CFD). To avoid the use of gadolinium, for risk of inducing nephrotoxic fibrosis in ESRD patients, novel protocols for contrast-free MR angiography are needed.
**Aim:** The aim of our study was to explore the feasibility of a novel protocol for contrast-free MR angiography to investigate AVF structural changes and flow field by CFD.
**Methods:** We acquired contrast-free MR in a 39-year male with radiocephalic side-to-end AVF. We performed 3D fast spin echo T1-weighted imaging (CUBE T1) on 1.5T scanner, with following parameters: 15 ms echo time; 24 ms echo-train length; 2 mm slice thickness; 0.55 × 0.55 × 2.0 mm voxel size. MR acquisition was performed 6 months after AVF creation and repeated 4 months later.
**Results:** Contrast-free CUBE T1 yielded high-resolution images within 5-10 minutes. Images were suitable for segmentation of AVF lumen and reconstruction of patient-specific 3D models that allowed high- resolution CFD analysis. Repeated acquisitions allowed evaluating changes in local hemodynamics and corresponding vessel structural changes between sequential acquisitions.
**Conclusions:** This novel contrast-free MRI strategy represents a feasible approach that can be used for prospective clinical investigations on the role of hemodynamics in AVF failure.

**O62**
**AN EXPERIMENTAL SETUP TO STUDY THE OCCURRENCE OF PERIVASCULAR VIBRATIONS IN ARTERIOVENOUS VASCULAR ACCESS**
*Krueger U, Scholz H*
Department of Vascular Surgery, Queen Elisabeth Hospital, Berlin, Germany

**Background:** An arteriovenous fistula (AVF) requires relatively high blood flow rates to guarantee adequate hemodialysis and prevent thrombosis. The high flow rate leads to flow disturbances, which are severe enough to produce perivascular vibrations (PV). A palpable "thrill" is traditionally associated with the creation of a sufficient AVF. Nevertheless, the cause of this phenomenon remains unclear.
**Aim:** Nevertheless, the cause of this phenomenon remains unclear. So an experimental setup was developed to get answers.
**Methods:** An arteriovenous fistula was simulated by silicon tubes, connectors, and a latex balloon to simulate a sudden change of the diameter and a strongly complaint vein. We used a non-pulsatile perfusion with distilled water. The non-pulsatile perfusion was performed with distilled water using a centrifugal Bio- Pump (BioMedicus, Inc. USA). A micro-semiconductor pressure transducer with a cutoff frequency of 4 kHz was inserted into the balloon for local pressure measurements and subsequent frequency analysis.
Additionally, the fistula was investigated by Computation Flow Dynamics with a high time resolution (time steps 1 millisecond) using the same boundary conditions.
**Results:** On the balloon surface, PV were already palpable at laminar flow rates. The local pressure curve recorded in the model showed small fluctuating components superimposed to the mean pressure. The frequency analysis of the pressure fluctuations revealed the highest magnitudes up to 75 Hz at Re 1500 and up to 300 Hz at Re 4000. The CFD results show velocity fluctuations depending on the shape of the anastomosis.
**Conclusions:** The jump in diameter between the y-connector and the balloon causes a turbulent jet leading to local pressure fluctuations at laminar flow rates, which could be responsible for PV. Otherwise, it is known that wall regions with noticeable PV correlate strongly with intimal hyperplasia (Mark Fillinger, JVS, 1990). The PV can be reduced by alteration of the anastomotic design.

**O63**

**NUMERICAL HEMODYNAMIC SIMULATIONS FOR MONITORING OF VASCULAR PATIENTS**

*Carroll J[1], Colley E[1], Barber T[1], Thomas S[2,3]*
[1]School of Mechanical and Manufacturing Engineering, University of New South Wales, Sydney, Australia
[2]School of Medicine, University of New South Wales, Sydney, Australia
[3]Department of Vascular Surgery, Prince of Wales Hospital, Randwick, Australia

**Background:** Researchers have used computational fluid dynamics (CFD) to link pathologies of the vascular system with flow behaviours to identify at risk regions as well as potentially predict future disease onset. Patients with arteriovenous fistulas (AVF) required for hemodialysis have a very high incidence of vascular disease, due to the abnormal flows which develop due to the surgically created vascular bypass configuration.
**Aim:** We sought to create patient-specific simulations for a large and diverse range of patients, capturing both healthy and diseased AVF vasculatures. Results of the simulations were analyzed to gain insight into blood flow behaviours alongside various patient outcomes.
**Methods:** A 3D imaging system was developed linking b-mode ultrasound imaging with 3D motion tracking to spatially align frames to form a 3D volume with the image data. The AVF geometry was then segmented from this volume. Doppler flow measurements were taken during the scanning to form boundary conditions for the simulations. Models were then constructed to simulate blood flow throughout the pulse cycle for each scan. Flow results were compared between patients with both healthy and diseased vasculature, as well as before and after surgical interventions.
**Results:** Post processing of the CFD results identified regions of disturbed flow using various temporal metrics of wall shear stress defined in literature. We examined the various distributions of these metrics across the vascular surfaces to compare with clinical outcomes. In contrasting data from healthy vasculatures with diseased, we found higher occurrence of these regions. As well, in diseased cases we found a reduction in these regions after corrective surgical stenting procedures.
**Conclusions:** Patient monitoring using realistic CFD simulations of vasculature allowed for identification of regions of disturbed flow, the severity of which we found to correspond with vessel health and performance.

**O64**

**MODELLING OF CARDIOVASCULAR ALTERATIONS DURING CKD PROGRESSION**

*Casagrande G, Possenti L, Costantino M*
Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Milan, Italy

**Background:** Kidney and cardiovascular disease are strongly related. Dialysis therapy, involving rapid volume changes, induces a cardiovascular stress. In addition, due to the presence of the arteriovenous fistula (AVF), the mean cardiac output is often higher and its partition over the districts is strongly affected.
**Aim:** Aim of the study was to use a lumped parameter model of the arterial circulation to study cardiovascular alterations in a uremic patient, accounting for different degree of chronic kidney diseases (CKD) and for the possible presence of AVF.
**Methods:** A lumped parameter model of arterial and capillary circulation made of 63 arterial blocks and 30 peripheral districts was used. It includes four different peripheral controls (myogenic, metabolic, endothelial controls and the mechanical effect of peripheral filtration). The parameters to be modified to properly model the uremic condition has been determined and simulations of different CKD degree conditions have been ran to study alterations in peripheral pressures and filtration. The existent model was also modified to account for the possible presence of different kind of arteriovenous fistula, whose effect in terms of cardiac flow rate distribution among vascular districts was evaluated and compared with physiological conditions.
**Results:** CKD progression can be modeled modifying the renal artery resistance and the renal perfusion index. The model allows mapping pressure and flowing rate distribution along the arterial network. When AVF is present, a lower kidney flow rate and a higher perfusion in the arm with fistula was found, with an enhancement from 3% to 8% of the cardiac output. Other districts were, instead, affected by lower changes in flow rate distribution.
**Conclusions:** A proper calibration of the peripherally controlled lumped parameters model allows correctly describing CKD progress in uremic patients. Moreover, the inclusion of AVF permits to quantify the different partition of flow rate among the body districts and the differences in the peripheral controls action.

**O65**

**BAYESIAN IDENTIFICATION OF PATIENT-SPECIFIC PARAMETERS IN A DIALYSIS KINETIC MODEL**

*Bianchi C[1], Lanzarone E[2], Casagrande G[1], Costantino M[1]*
[1]CMIC, Politecnico di Milano, Milan, Italy
[2]IMATI, CNR, Pavia, Italy

**Background:** The several haemodialysis comorbidities point out the need for treatment customization. Many compartmental models, referred to average uremic patients, describe solute kinetics during HD. Some literature models consider patient-specific parameters, estimated through constrained nonlinear optimization algorithms, to predict the single patient response to the treatment, in order to prevent intra- dialysis complications and better manage the therapy prescription.
**Aim:** A Bayesian estimation approach was used, due to its versatility, to obtain a more robust estimation of the patient-specific parameters of similar models.
**Methods:** A parametric multi-compartment kinetic model, based on multiple-solute fluid and mass balance equations in which 3 patient-specific parameters act, was used. Parameters account for dialyzer filtration performance, relative capillary wall permeability and mass transfer efficiency across cell membrane. The likelihood function is a discretized version of the model and the posterior densities of model parameters are obtained through Markov Chain Monte Carlo simulation. First, the proposed approach was validated on a test instance replicating a HD session, in which the Bayesian method is applied using a complete and a reduced set of simulated observations of the state variables. Then, the method was validated using real clinical data acquired during 3 dialysis sessions. Real and estimated plasmatic concentrations and plasmatic volume were compared.
**Results:** Results of the computational validation show a good reproducibility of the test dataset, with negligible differences between simulated and estimated trends, both using a complete or reduced dataset. The application to real data shows an error always less of 10% with limited SD.
**Conclusions:** The Bayesian approach allows including the clinical prior knowledge on the parameters and directly evaluating the uncertainty associated with the estimates. The estimated values can be considered more stable and closer to the physics of the problem, avoiding the false positives results coming from different algorithms.

**O66**

**CARDIOVASCULAR RESPONSE TO HAEMODIALYSIS-A NEW INTEGRATED MATHEMATICAL MODEL**

*Pstras L[1], Waniewski J[1], Wojcik-Zaluska A[2], Zaluska W[3]*
[1]Nalecz Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, Warsaw, Poland
[2]Department of Physical Therapy and Rehabilitation, Medical University of Lublin, Lublin, Poland
[3]Department of Nephrology, Medical University of Lublin, Lublin, Poland

**Background:** During haemodialysis (HD), a few litres of fluid (water and solutes) are removed from the body over a relatively short period of time (typically three to five hours). As the fluid is removed directly from the blood, efficient vascular refilling is crucial for the proper function of the cardiovascular system. Up to 30% of dialyzed patients have, however, difficulties in responding to the reduction in blood volume, thus experiencing the highly problematic intradialytic hypotension.
**Aim:** To develop a comprehensive mathematical model of haemodynamic response to HD integrating cardiovascular dynamics with the whole body water and solute kinetics for a detailed analysis of the dialysis- induced transport processes and cardiovascular adaption to blood volume reduction.
**Methods:** A new compartmental model was developed to simulate the two-phase blood flow across the circulatory system and the dialyzer circuit, combined with the transport of water, ions and small molecules across the

capillary, cellular and dialyzer membranes. The model includes the flow of lymph, the transcapillary protein leakage and the dynamic blood pressure regulation through baroreflex control of heart rate, heart contractility, systemic resistance and venous capacity.
**Results:** The new model accurately describes the changes induced in the body by HD as validated on clinical data from the Lublin Medical University in Poland. Haemodynamic changes during HD are induced not only by the dialysis treatment itself, but also reflect the prior drawing of some of the patient's blood to fill the extracorporeal circuit, when the priming fluid is not infused to the patient. Tracking haematocrit or haemoglobin variations is not equivalent for the purpose of assessing the relative blood volume changes during HD.
**Conclusions:** The model enables a comprehensive simulation of cardiovascular response to HD including volume and osmolarity changes of all fluid compartments, thus providing a useful tool for analyzing the interactions between the cardiovascular system and reflex regulatory mechanisms in response to blood volume reduction.

## Session: Heart Regeneration and Transplantation

### O67
### CHARACTERIZATION OF MIRNA EXPRESSION IN CARDIAC ISOGRAFT VASCULOPATHY USING A HETEROTOPIC ABDOMINAL MOUSE HEART TRANSPLANTATION MODEL

*Schaefer A[1], Kiss A[1], Skalicky S[2], Hackl M[2], Kain R[3], Oszwald A[3], Podesser B[1]*
[1]Ludwig Boltzmann Cluster for Cardiovascular Research, Center for Biomedical Research, Medical University of Vienna, Vienna, Austria
[2]TAmiRNA GmbH, Vienna, Austria
[3]Clinical Institute of Pathology, Medical University of Vienna, Vienna, Austria

**Background:** Cardiac allograft vasculopathy (CAV) is limiting long term survival after cardiac transplantation. There is evidence that endothelial injury and dysfunction resulting from prolonged preservation and subsequent ischemia-reperfusion (IR)-injury play a role in the development of CAV.
**Aim:** Altered expression of endothelial transcription factor GATA-2 and its target endothelial enriched miR-126, and miR-92a are considered to be involved in vascular injury. The aim of our study is to clarify their role in the pathogenesis of CAV.
**Methods:** Isogenic transplantations were performed in male C57BL/6 mice aged 8-9 weeks. Donor hearts were harvested, stored in HTK-N solution for 12 h and heterotopically transplanted into the abdomen of the recipient. Two months after transplantation, left ventricle myocardial tissue samples from native and transplanted hearts were harvested. The expression of GATA-2, miR-126 and miR-92a was evaluated by RT-qPCR.
**Results:** Six transplantations were conducted successfully and vital grafts were harvested 2 months after transplantation. Mir-92a was upregulated in transplanted hearts compared to native hearts (-3.8 ± 0.2 vs. -4.1 ± 0.08; normalized expression to U6 snRNA). In contrast, the expression of miR-126 (0.4 ± 0.1 vs. 1.5 ± 0.08; normalized expression to U6 snRNA, P<0.01) and GATA-2 (-7.1 ± 0.2 vs. -5.1 ± 0.1; normalized expression to ACTB; P<0.01) was significantly decreased in transplanted hearts. Expression of mir-126 and GATA-2 positively correlated (r2 = 0.65, P<0.001, slope 1.5 ± 0.2).
**Conclusions:** Our results demonstrate for the first time that IR-injury markedly decreases the expression of endothelial transcription factor GATA-2 and its target miR-126 in transplanted hearts. Thus, modulation of GATA-2 and miR-126 signalling might represent a disease mechanism and provide a therapeutic target in CAV.

### O68
### REMOTE ISCHEMIC POSTCONDITIONING IMPROVES POST-ISCHEMIC CARDIAC FUNCTION: THE ROLE OF NEUREGULIN-1

*Pilz P, Lang M, Fonseca Goncalves I, Inci M, Hamza O, Kiss A, Podesser B*
Center for Biomedical Research, Ludwig Boltzmann Cluster for Cardiovascular Research, Medical University of Vienna, Vienna, Austria

**Background:** Acute myocardial infarction (MI) and heart failure are the major contributors to mortality and morbidity worldwide. Remote ischemic conditioning (RIC), defined as repeated episodes of non-lethal, transient ischemia/reperfusion (IR) insult in distal organs, protects the heart against subsequent IR injury, however the mechanism is not fully understood. Impairment of Neuregulin-1 (NRG-1)/ErbB2, ErbB3 and ErbB4 signalling pathway plays crucial role of post ischemic left ventricle (LV) dysfunction.
**Aim:** The aim of the study was to 1) investigate the effect of remote conditioning on post-ischemic cardiac function and 2) whether this associated with changes of NRG-1 expression.
**Methods:** Adult male anaesthetized OFA-1 rats were subjected to a permanent left coronary artery occlusion and allocated to (1) Sham operated (SOP, without occlusion; n = 3); (2) MI (n = 7) and (3) MI + RIC (n = 7; 3 cycles of 5 minutes of hindlimb ischemia and 5 minutes of reperfusion per day, for 5 days, started 3 days after MI induction). Functional parameters of the heart such as cardiac output (CO) and external heart work (EHW) and LV pump function were evaluated on an isolated erythrocyte-perfused working heart model. NRG-1 expression was assessed by ELISA.
**Results:** MI resulted in a significant increase of left ventricle/body weight ratio in comparison to sham operated group (P<0.05). This was in line with the reduction in CO and EHW (P<0.01, respectively) and with a clear reduction in plasma concentration of NRG-1. In contrast, RIC markedly improved post-infarcted cardiac function compared to IR group (CO and EHW, P<0.05, respectively) in association with the increase of plasma NRG-1 concentration. There was a trend of impairment of cardiac pump function in IR group in comparison to SOP, which was improved by RIC again.
**Conclusions:** We demonstrated that the improvement of post-infarcted cardiac function initiated by RIC is associated and correlated with the levels of NRG-1. These findings might represent a novel cardioprotective mechanism of RIC, mediated via the upregulation of NRG-1, as well as a potential therapeutic approach to attenuate adverse LV remodeling following MI.

### O69
### A MORPHO-BIOMECHANICAL PERSPECTIVE ON HEART REMODELING AFTER MI

*Rusu M[1], Curaj A[1,2], Wu Z[1,2], Jankowski J[1,3], Schuh A[3], Liehn E[1,4,5]*
[1]Institute for Molecular Cardiovascular Research (IMCAR), RWTH University Hospital, Aachen, Germany
[2]Institute for Experimental Molecular Imaging, RWTH University Hospital, Aachen, Germany
[3]Department of Experimental Vascular Pathology, Cardiovascular Research Institute, Maastricht, The Netherlands
[4]University Hospital, RWTH Aachen, Department of Cardiology, Pulmonology, Angiology and Intensive Care, Germany
[5]Human Genetic Laboratory, University of Medicine and Pharmacy, Craiova, Romania

**Background:** Healing after myocardial infarction (MI) results in a heterogeneous heart muscle contraction. The prediction of morpho-biomechanical characteristics of heart remodeling after MI is far for being understood. Border zone is one of the key mediator between remote and scar, which may finally predict the heart survival or failure.
**Aim:** To which extend the morpho-biomechanics of border zone sustain and monitor the restoring function of heart within the healing period of 28 days was the triggered question of this study.
**Methods:** Heart mouse tissues were sampled at different post- myocardial infarction periods. The morphological characteristics of border were investigated by liquid-atomic force microscopy, while Derjagin, Muller, Toropov model was used to quantify the Young's modulus.
**Results:** Two distinct morphological signatures developed at the border zone. In the remote close to border, collagen fibers follow the compact alignment of cardiomyocytes, while in the scar close to border, dense myofibrils aligned anisotropically. Large voids are present in the scar, which extend further into remote. The distinct morphological patterns seem to follow the progressive accumulation of collagen at border (54.7 ± 11.45% vs. control 0.3 ± 0.1%). While both scar and remote are less compliant at 7 days post-MI (Eremote = 27.3 ± 5.8 MPa, Escar = 30.5 ± 3.1 MPa vs. Econtrol 6.8 ± 2.7 MPa), 28 days post-MI the scar and remote close to border recover their compliance.
**Conclusions:** Studies conducted at the border zone anticipated that morphology and biomechanics, next to collagen synthesis and its structural organization are the key players to dictate the heart survival or rupture.

**O70**

**THE OCS HEART SYSTEM FOR EX-VIVO PERFUSION OF THE DONOR HEART: A STEP TOWARD FUTURE?**

*Botta I[1], Cannata A[1], Merlanti B[1], Campolo J[2], Gagliardone M[1], Frigerio M[1], Trivella M[2], Russo C[1]*
[1]Cardio-Thoraco-Vascular Department, Niguarda Hospital, Milan, Italy
[2]Institute of Clinical Physiology, CNR, Pisa, Italy

**Background:** The standard technique for donor heart preservation consists in cold static storage (CSS). The "Organ Care System (OCS)- Heart"-TransMedics (TM) is the only clinical platform for ex-vivo perfusion of human donor hearts. The system preserves the heart in a warm beating state.
**Aim:** To evaluate results of HTX performed with this innovative system.
**Methods:** From 2015 to 2017, 7 patients received a donor heart preserved with the OCS-Heart system. Mean recipient and donor age was 46 and 39 years. Ischemic, cardiopulmonary (CPB) bypass time and day-0/day-1 CK-MB levels (TM group) were compared with those of 95 patients transplanted with the CSS from 2009 and 2012 (ST group). The OCS was used for expected long ischemic times or for adverse donor (cardiac arrest) or recipient (infected LVAD, ECMO and unusual anatomy) features.
**Results:** Technical complications did not occur. Mean out of the body perfusion time was 296 minutes. Mean ischemic and CPB time was 124 and 249 (TM group) vs 187 and 202 in the ST group (P = 0.01 and 0.70). The OCS allowed to spare 159 minutes of estimated ischemia. D0/D1 CK-MB was 115 and 36 vs 125 and 47 ng/ml in the ST group (P = 0.9 and 0.5). ICU stay was 20 days. Two patients died for hemorragic shock (LVAD recipient, 1 day after HTX) and for multiorgan failure (58 days). One patient developed a severe right failure, treated by mechanical assistence, weaned after 8 days. Five recipients are alive at a mean FU of 12 months.
**Conclusions:** Heart transplantation using donor hearts preserved with the "OCS Heart" is technically safe. It allows a "real time" control of hemodynamic and metabolic parameters and permits a significant reduction of the ischemic time. A trend toward reduction of myocardial damage was observed when compared to CSS. More cases are needed to evaluate the real impact on clinical outcomes, particularly in unfavourable donor-recipient combination. A potential expansion of donors'pool is predictable with this innovative system.

**O71**

**COMPARING DIFFERENT UNLOADING STRATEGIES IN AN OVINE MODEL OF POST-INFARCTION HEART FAILURE**

*Jacobs S[1], Geens J[1], Claus P[2], Rega F[1], Meyns B[1]*
[1]Department of Cardiac Surgery, Catholic University of Leuven, Leuven, Belgium
[2]Department of Cardiovascular Imaging and Dynamics, Catholic University of Leuven, Leuven, Belgium

**Background:** Previous research indicated that partial mechanical support in an model of post-infarction heart failure could induce structural reversed remodeling (ie. decrease in ventricular end–diastolic volumes).
**Aim:** With all commercial available assist devices today being full support devices we sought to analyze the structural reversed remodeling potential of full support assist devices.
**Methods:** Heart failure was induced by permanent ligation of the distal LAD and second diagonal branch and temporary occlusion of the proximal LAD. Six weeks later ventricular dimensions were measured using MRI. Then the sheep were randomized into 2 treatment groups; one group receiving no treatment (n = 4) and the other group had a full support device implanted (n = 7). After 6 weeks both groups underwent a new MRI analysis.
**Results:** In the group without treatment left ventricular end-diastolic volumes increased from 119.3 ml ± 3.9 ml to 135.3 ml ± 4.4 ml after 6 weeks ($p<0.01$). In the group with a full support left ventricular assist device the left ventricular end-diastolic volumes did not change significantly (136 ml ± 33.4 ml vs. 139.1 ml ± 32.9 ml; p = 0.32).
**Conclusions:** These results indicate that full support assist device rather halt further structural remodeling rather than inducing reversed structural remodeling. These findings indicate the importance of the type of unloading strategy in inducing reversed remodeling.

## Symposium: Extracellular Vesicles

**O72**

**CHARACTERIZATION OF EXTRACELLULAR VESICLES IN WHOLE BLOOD: INFLUENCE OF PREANALYTICAL PARAMETERS**

*Fendl B[1,2], Weiss R[1,2], Spittler A[3], Weber V[1,2]*
[1]Christian Doppler Laboratory for Innovative Therapy Approaches in Sepsis, Danube University Krems, Krems, Austria
[2]Center for Biomedical Technology, Danube University Krems, Krems, Austria
[3]Core Facility Flow Cytometry and Surgical Research Laboratories, Medical University of Vienna, Vienna Austria

**Background:** Extracellular vesicles (EVs) are central in intercellular communication and have been described in pathological conditions, such as sepsis.
**Aim:** We aimed to characterize EVs in human whole blood with respect to their cellular origin and interaction with blood cells and assessed the influence of preanalytical parameters, in particular anticoagulation, on vesicle generation.
**Methods:** Freshly drawn blood was anticoagulated with EDTA, sodium citrate, or heparin and the time dependent release was studied at 4°C, 21°C and 37°C. Flow cytometric analysis was performed using a Gallios Flow Cytometer (Beckman Coulter) calibrated with fluorescent polystyrene beads (0.1/0.3/0.5/0.9 µm). Cell/EV interaction was visualized using imaging flow cytometry (ImageStreamX MkII, Millipore). Phosphatidylserine exposing EVs were identified as lactadherin + events and antibodies against cell specific markers for monocytes (CD45+ CD14+), erythrocytes (CD235a+), and platelets (CD41+) were used to identify the cellular origin.
**Results:** EV release in whole blood was dependent on the anticoagulant (EDTA<citrate<<heparin) and EVs were predominantly derived from platelets. EV concentration in plasma obtained by centrifugation at 4°C and 21°C increased with every cycle of freezing and thawing. The increase was more pronounced for samples obtained by centrifugation at 4°C. EVs interact with blood cells, in particular with monocytes and granulocytes, but not with lymphocytes.
**Conclusions:** Anticoagulation with EDTA preserves EV concentration in whole blood, while EV generation is enhanced in citrate and heparin blood. Freezing and thawing of plasma induces EV release, especially for plasma obtained at 4°C, indicating a pre-activation of residual platelets and a facilitated release of EVs during thawing. Whole blood measurement allows for the determination and visualization of cell/EV interaction.

## Session - Biomaterials II: Soft Tissue Replacement

**O73**

**THE INVESTIGATION OF THE INFLUENCE OF THE LASER SOLDER COMPOSITION ON THE WELDS TENSILE STRENGTH**

*Ryabkin D, Rimshan I, Podgaetskii V, Selishchev S, Gerasimenko A*
Biomedical Systems Department, National Research University of Electronic Technology, Moscow, Russian Federation

**Background:** Laser welding of biological tissues is an alternative to traditional methods of their connection. The tissue welds are hermetically sealed to liquids, non-toxic and have small geometric dimensions. The laser welding can be used to weld the skin, cartilage, tendons, vas deferens, veins and arteries. Special laser solders are used for to increase tensile strength and to reduce the postoperative rehabilitation time.
For today about 10 various components are used in laser solders.
**Aim:** The aim of the work is to study the influence of various components of laser solder such as multiwalled carbon nanotubes (MWNTs), single-walled carbon nanotubes (SWCNTs), indocyanine green (ICG), bovine serum albumin (BSA) and collagen for the weld tensile strength.
**Methods:** The device for laser welding of biological tissues was based on a diode laser with a wavelength of 808 nm. The device has a temperature feedback, which controls the temperature of the weld during welding. A group of laser solders based on aqueous dispersions of MWNT, SWCNT, ICG, BSA and collagen was used. The porcine tracheal cartilage was used as a biological

tissue. The laser welds were examined by computed micro tomography and Scanning Electron Microscope.
**Results:** The experiments were carried out using 7 compositions of the laser solders. The highest relative tensile strength (~10%) was achieved using solder based on MWNT - 0.1 wt.%, Albumin - 25 wt.%, ICG - 0.1 wt.%. The weld obtained with the of MWNT-based solder had the highest tensile strength in comparison with solders based on SWCNTs. Also, the addition of ICG to the solder resulted in an increase in the tensile strength of the welds.
**Conclusions:** The use of MWCNTs and ICG in the composition of solders makes it possible to increase the tensile strength of the welds. During the experiments it was achieved the tensile strength of the welds ~10%. This is sufficient for the primary connection of biological tissues with their subsequent regeneration in the weld region.

**O74**
**INVESTIGATION OF BENDABILITY AND ANISOTROPY OF FIBER-BASED VASCULAR GRAFTS UNDER PHYSIOLOGICAL CONDITIONS**
*Bode M, Mueller M, Glasmacher B*
Institute for Multiphase Processes, Leibniz Universität Hannover, Hannover, Germany

**Background:** The development of vascular grafts is subject to stringent requirements. In addition of biocompatibility, specific mechanical requirements are key.
**Aim:** Besides other, two important properties are relevant for suitability as a replacement material - resistance to collapse from kinking under bending stress and physiologically comparable compliance for dampening of pressure peaks. The aim is to establish measuring methods to validate vascular grafts and develop consistent standards for future investigations.
**Methods:** Tubular poly(caprolactone) scaffolds fabricated by electrospinning were used for measurements. The validation methods regarding the indicated criteria are two-fold. One is the development of a tensile testing machine, which allows radial and axial tests in a tempered water bath to imitate physiological environment. The other is the development of a bending test bench which allows the investigation of bending angle influence on kinking behavior under physiological pressure, temperature and flow rate.
**Results:** The tensile tests show that there is a significant difference (anisotropy) between axial and radial alignment of the fibers in regard to the force ($p<0,001$). Additionally, they show highly increased elongation in tempered environment. A 150% elongation is observed at 20°C but when heated to 37°C there is a drastic increase to 1400% elongation. With the results of the bending test, it was proved that temperatures up to 37°C allow a bending angle of more than 150° before exceeding the 50% reduction of flow limit. In contrast, reduced pressure to 40 mmHg allows only 75° bending angle and reduced volume flow rate permits only 110°.
**Conclusions:** The developed tensile testing machine allows testing of specimens in radial and axial direction. Thus, the influence of temperature can be investigated especially on polymeric scaffolds and allows a closer look at their predicted mechanical stability in vivo. With the bending test bench it can be proved that each investigated parameter has a measureable influence on the bending behavior.

**O75**
**THE ANTICALCIFICATION POTENTIAL OF HEPARIN ON HYDROXYAPATITE SEED CRYSTALS**
*Badria A[1,4], Koutsoukos P[2,4], Korossis S[3,4], Mavrilas D[1,4]*
[1]Department of Mechanical Engineering and Aeronautics, University of Patras, Patras, Greece
[2]Department of Chemical Engineering, University of Patras, Patras, Greece
[3]Department of Cardiothoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany
[4]Hannover Medical School, Hannover, Germany

**Background:** Bioprosthetic heart valve calcification is among the principal limiting factors of their reduced long-term survival in vivo. Among numbers of different solutions proposed to overcome the calcification problem so on, sulphated and non sulphated GAGs have shown significant inhibitory potential in vitro.
**Aim:** The aim of this study is to investigate the anticalcification potential of heparin in vitro with respect to hydroxyapatite (HAP) seed crystals.
**Methods:** All experiments were done at conditions of constant solution supersaturation. Experiments were conducted using supersaturated solutions with respect to HAP (7.0° ± 0.1°C, pH 7.400 ± 0.001), inoculated with HAP seed crystals (specific surface area = 44 m2g-1) at different supersaturation ratios (control) and solutions of the same supersaturation containing 0.25-3 ppm heparin. The rates of crystal growth were monitored from the titrants added to maintain solution supersaturation. SEM and XRD analysis were used for the characterization of the crystals grown. Adsorption studies were done by equilibration of solutions saturated with respect to HAP. Adsorption data were obtained from heparin analysis before and after adsorption.
**Results:** Heparin resulted in a clear decrease in crystal growth for concentrations up to 1 ppm before a plateau was reached. SEM images did not show significant effect of heparine in the morphology or the size of the HAP crystals. Adsorption data showed significant adsorption up to heparin concentrations ~15 ppm, supporting that the inhibition of HAP growth was due to blockage of the active sites by the adsorbed heparin molecules.
**Conclusions:** Heparin in calcium phosphate solutions supersaturated with respect to HAP inhibited calcification, attributed to its adsorption at the active crystal growth centers. The adsorption mechanism was confirmed from the respective heparine adsorption isotherms.

**O76**
**THE APPLICATION OF POLY(L-LACTIDE-CO-GLYCOLIDE-CO-TRIMETHYLENE CARBONATE) TO FORMULATE RODS WITH 17-B-ESTRADIOL**
*Turek A[1,2], Borecka A[1,2], Wilinska J[1], Mokshaha-Zarzycki A[1], Kasperczyk J[1,2]*
[1]Chair and Department of Biopharmacy, School of Pharmacy with the Division of Laboratory Medicine in Sosnowiec, Medical University of Silesia, Katowice, Poland
[2]Centre of Polymer and Carbon Materials, Polish Academy of Sciences, Zabrze, Poland

**Background:** 17-β-estradiol (E2) is an important hormone that regulates many of the body's functions. In the last decade, E2 has also been considered for the treatment of neurodegenerative diseases. Long-term administration of E2 is necessary to achieve the therapeutic effect. The proposed concept of biodegradable implantable rods based on poly(L-lactide-co-glycolide-co-trimethylene carbonate) (P(L-LA:GA:TMC)) with E2 would allow to deliver the drug substance in a prolonged manner. In the case of therapeutic systems, it is crucial to obtain a release profile according to the zero-order kinetic model. The release pattern can be optimized by parameters such as molecular weight (Mn) and glass transition temperature (Tg).
**Aim:** The aim was to investigate the influence of degradation on changes in polymer parameters to determine the release pattern of E2 release from P(L-LA:GA:TMC).
**Methods:** P(L-LA:GA:TMC) was synthetized in mass with the use of zirconium (IV) acetylacetonate as an initiator. Rods containing 10% w/w of E2 were formulated by the hot melt extrusion method (105 °C).
Thermal, structural and surface properties were investigated by DSC, NMR, GPC and SEM. The concentration of released E2 was monitored using UV-VIS spectrophotometry (203.5 nm).
**Results:** The extrusion process influenced the decrease of Mn by 22%, whereas the thermal, structural and surface parameters did not change significantly. The degradation had a stable character, a gradual decrease of Tg, Mn was observed. Non-significant changes were noted in the composition, chain microstructure and surface properties of the rods. An analysis of the E2 concentration revealed release according to the zero-order kinetic model ($k = 5,147$; $R2 = 0.9889$) for a period of 113 days.
**Conclusions:** The proposed rods with E2 may be an interesting solution for the treatment of neurodegenerative diseases.

**O77**
**ENHANCED INTERFACIAL BONDING STRENGTH OF HYDROPHOBICALLY- MODIFIED, ALASKA POLLOCK GELATIN-BASED SURGICAL SEALANTS**
*Taguchi T[1,2], Mizuta R[1,2]*
[1]Biomaterials Field, National Institute for Materials Science, Tsukuba, Japan
[2]Graduate School of Pure and Applied Science, University of Tsukuba, Tsukuba, Japan

**Background:** For the treatment of pulmonary air leaks and anastomotic sites between living tissues, surgical sealants have been widely used in clinical field. Fibrin sealant is a typical sealant which consists of human blood components and has excellent biocompatibility and versatile, however, it does not possess sufficient sealing effect because of its low interfacial bonding strength to tissues.
**Aim:** In this study, we have chosen Alaska pollock-derived gelatins (ApGltn) as a base material for surgical sealants. We modified ApGltn with different hydrophobic groups and introduction ratios and evaluated their sealing effects on wet tissues by combining hydrophobically-modified (Hm)-ApGltns with poly(ethylene glycol)-based 4-armed crosslinker (4S-PEG).
**Methods:** The measurement of burst strength for the porcine blood vessel was performed according to the method reported as ASTM (F2392-04). Biodegradability of Hm-ApGltn based sealants was observed by implanting in subcutaneous tissues of mice.
**Results:** The burst strengths of all Hm-ApGltn-based sealants against blood vessel were higher than that of original ApGltn (Org-ApGltn)-based sealant. Highest burst strength of Hm-ApGltn-based sealant was 10-fold higher than that of fibrin sealant and 3-fold higher than that of Org-ApGltn-based sealant. Furthermore, the burst strengths of Lau (C12) and Ste (C18)-ApGltn-based sealant were higher than those of Pro (C3) and Hx (C6)-ApGltn-based sealant. Furthermore, 9.6Ste-ApGltn-based sealant was completely degraded within 8 weeks in the mice subcutaneous tissue. Cell infiltrations into 9.6Ste-ApGltn-based sealants were also observed after 4 weeks.
**Conclusions:** Our surgical sealants composed of Hm-ApGltn and 4S-PEG possess high sealing strength as well as biocompatibility. Therefore, our sealants can be applied in the field of cardiovascular surgery and thoracic surgery. References 1. Taguchi, T. et al., J Biomed Nanotechnol 2016, 12, 128-134.; 2. Mizuta, R., et al., Colloids Surf B 2016, 146, 212-220.

**O78**
**LONG-TERM URINE-RESISTANT ARTIFICIAL BLADDER**
*Mazzocchi T[1], Iacovacci V[1], Cardona A[1], Milani A[1], Pinzi N[2], Ricotti L[1], Menciassi A[1]*
[1]The BioRobotics Institute, Scuola Superiore Sant'Anna, Pisa, Italy
[2]Urology Department, University of Siena, Siena, Italy

**Background:** Radical cystectomy due to tumors or traumas can be surgically addressed through ureterocutaneostomy and eterotopic/orthotopic neobladder reconstruction. The first implies a severe burden on patients' life quality, while reconstruction procedures produce often morbidity as a consequence. The development of an artificial bladder (AB) would be highly desirable since no long-term urine resistant devices able to both expand/contract are available at present.
**Aim:** To design a novel AB featured by variable volume and high resistance to urine encrustation.
**Methods:** The proposed AB is featured by variable volume, biocompatibility and resistance to urine. This latter property is provided by antiadhesive and/or antibacterial coatings. When combining these materials with variable volume polymeric structures, the risk of cracks formation increases, thus acting as a trigger for crystal precipitation and encrustations. To avoid these phenomena, a bi-stable structure able to change its internal volume without undergoing a stretching of the constitutive components was devised. It consists of four segments properly bound together to enable a shape transition due to internal volume changes. Each segment has a multilayered structure including two elastomeric layers, divided by a non-extendable one, and a urine-resistant internal coating.
**Results:** Polydimethylsiloxane was selected as elastomeric material for its biocompatibility and easy shaping whereas polypropylene net was chosen as non-extendable layer. Several materials, showing antiadhesive and/or antimicrobial properties, such as pyrolytic carbon, molybdenum nanoparticles, silver and inert polymers were identified as coating candidates. A preliminary prototype including proper connections with the ureters and the urethra was developed and tested, in vitro and ex vivo.
**Conclusions:** A novel AB featured by a smart structure and urine-resistance in the long-term was reported. The possibility to include volume/pressure sensors, wireless data transfer modules and active squeezing mechanisms is under investigation.

## Session: Blood Trauma

**O79**
**ASSESSMENT OF LEUKOCYTE FUNCTIONALITY IN CONTACT WITH A FOREIGN SURFACE UNDER SHEAR STRESS**
*Radley G[1,2], Pieper I[1,2], Hawkins K[1], Thornton C[1]*
[1]Medical School, Swansea University, Swansea, UK
[2]Research and Development, Calon Cardio-Technology Ltd, Swansea, UK

**Background:** The introduction of a foreign surface and the shear stress encountered by the blood moving through a rotary pump can impair cell viability, count, morphology, and function. Leukocytes are more vulnerable to shear than red blood cells, and as they link both thrombosis and infection, it is important to observe how they are affected by the VAD environment.
**Aim:** To replicate the artificial shear on a foreign surface introduced to the body by ventricular assist devices (VADs) using biomaterial discs attached to a rheometer.
**Methods:** Biomaterial discs: diamond-like carbon coated stainless steel (DLC); single crystal sapphire (Sap); and titanium alloy (Ti) were attached to parallel plates on a rheometer. Whole human blood was sheared for 5 min between all discs at 0 s-1 and 1000 s-1. Complete blood counts were measured. Flow cytometry was used to measure leukocyte activation (L-selectin and CD11b), phagocytosis, ROS, and viability. ELISA was used to measure cytokines of interest after initial proteome profiling (MIF and IL-1α).
**Results:** Data shown as fold from baseline. Leukocyte counts (n = 6) were reduced when sheared on Sap with neutrophils significantly decreased (69.3 ± 21%, p = 0.005). Activation of neutrophils and monocytes was evident through a significant decrease in L-selectin on Sap both at 0 s-1 and 1000 s-1 (n = 9, $p<0.05$). There was no increase in the expression of CD11b or cell death in any biomaterial/shear combination. The functionality of leukocytes in terms of phagocytosis (n = 3) was decreased when in contact with DLC at 0 s-1 (77.3 ± 9.1%) and delayed when sheared at this surface (70 ± 20.1%). There was no significant difference in IL-1α or MIF production in any samples tested.
**Conclusions:** Initial results correlate with previous work using biomaterials in a static environment with leukocytes, particularly monocytes, affected by Sap when static/sheared. This ongoing work may reveal why some pump designs are more susceptible to thrombus formation, particularly at the bearings.

**O80**
**SHEAR STRESS EXPOSURE ALTERS THE ELECTROCHEMICAL AND PHYSICAL PROPERTIES OF ERYTHROCYTES**
*McNamee A[1,2], Tansley G[3], Simmonds M[1,2]*
[1]Biorheology Research Laboratory, Griffith University, Gold Coast, Australia
[2]Menzies Health Institute Queensland, Griffith University, Gold Coast, Australia
[3]School of Engineering, Griffith University, Gold Coast, Australia

**Background:** The capacity of the circulatory system to regulate blood fluidity is dependent on the ability of red blood cells (RBC) to aggregate, disaggregate and deform. The major intrinsic disaggregating force of RBC is their negative charge, determined by charged sialic acids (SA) located within the glycocalyx of the cell membrane.
**Aim:** Given that subhaemolytic mechanical trauma may alter cell morphology and membrane composition, we hypothesise that exposure to supraphysiological shear environments will cleave membrane bound SA, altering the electrochemical and physical properties of RBC.
**Methods:** RBC from 20 healthy donors were collected, isolated and resuspended in Polyvinylpyrrolidinone (PVP; pH 7.4, 290 mOsmol·kg-1, 4 mPa·s) at 0.15 L/L. A Poiseuille shearing system was constructed with polyethylene

tubing (I.D. of 200 µm) and dual syringe pumps. RBC suspensions were exposed to 100 Pa for 1.5 s, with samples being extracted immediately following the first and third exposures. Collected samples were centrifuged to separate RBC from supernatant, and resuspended in autologous plasma at 0.4 L/L.
**Results:** RBC aggregation and the shear rate required to disaggregate rouleaux significantly increased following exposure to shear. Such exposure also increased the ability of RBC to aggregate extrinsic to plasma factors (i.e. RBC aggregability), determined in a standard aggregating solution (3% dextran 70 kDa in PBS) at 0.4 L/L haematocrit. The concentration of SA, measured using the periodate-resorcinol method, significantly increased in the PVP supernatant with shear exposure, and decreased in isolated RBC cell membrane ghosts. The electrophoretic mobility, conducted in a microfluidic chamber with Pt electrodes, significantly decreased following shear exposure, indicating RBC becoming less negatively charged.
**Conclusions:** Supraphysiological shear exposure for 1.5 s may remodel the RBC membrane, removing SA from the glycocalyx, thereby altering the electrochemical and physical properties of RBC. This observation may explain, in part, the increased incidence of microvascular dysfunction and systemic complications observed in patients receiving mechanical circulatory support.

## O81
## NUMERICAL COMPARISON OF SHEAR AND ELONGATIONAL STRESSES IN ROTARY VENTRICULAR ASSIST DEVICES

*Khoo D, Gill R, Cookson A, Fraser K*
Mechanical Engineering, University of Bath, Bath, UK

**Background:** Despite the evolution of Ventricular Assist Devices (VADs), VAD patients still suffer from complications due to damage to the blood by fluid dynamic stress. To date, most numerical models for blood damage are functions of the scalar shear stress (SSS), the second invariant of the strain rate. Since rotary VADs are assumed to exert mainly shear stress, the measurements of blood damage for these models are obtained from shear flow experiments. However, measurements of red cell deformation show elongational and shear stress deform cells differently, and then potentially damage cells differently.
**Aim:** The aim of this work was to use computational fluid dynamics (CFD) to assess the significance of elongational stress, in comparison with shear stress, in rotary VADs.
**Methods:** CFD was used to calculate flow fields in a centrifugal and an axial VAD. The velocity of the blood defined the reference frame, with both stresses computed from the transformed strain rate. Firstly, volumes of the VADs experiencing shear or elongational stress above threshold values were found. And secondly, the cell deformation index (DI = (L-W)/(L + W); given the cell's length, L, and width, W) was set to 0.5, and the regions of the VADs producing DI >0.5 due to shear or elongation stress were compared.
**Results:** Compared with elongation stress, blood in the VADs experiences higher shear stress over a larger volume. However, when comparing the stress using a threshold value for cell deformation, elongational stress occurs in a smaller but significant volume of both VADs (significant elongational stress volumes: centrifugal 0.2 ml, axial 0.15 ml, compared with significant shear stress volumes: centrifugal 0.3 ml, axial 0.5 ml).
**Conclusions:** Although shear stress volumes are larger than elongational volumes for both VADs, the latter are still significant in size. Crucially, given that the axial design reduces the significant elongational stress volume, but increases that for shear stress, more experimental data is needed on elongational stress- induced damage, with which to inform the design of new VADs.

## O82
## OVINE ACTIVATED LEUKOCYTE MICROPARTICLES GENERATED BY THE CENTRIMAG VENTRICULAR ASSIST DEVICE IN VITRO

*Pieper I[1,2], Radley G[1,2], Ali S[1], Christen A[1], Thornton C[2]*
[1]Research and Development, Calon Cardio-Technology Ltd, Swansea, UK
[2]ILS1, Swansea University Medical School, Swansea, UK

**Background:** VADs save heart failure patients lives but have not yet reached their full potential due to the side effects (thrombosis, bleeding, infection). These relate to the activation of blood caused by shear stress/foreign materials. Clinically, VADs cause granulocyte and T cell activation/apoptosis, a decrease in leukocyte count, and leukocyte microparticle (LMP) formation. In vitro, bovine LMPs are formed in various VADs. These examples show that VADs have an impact on leukocytes, but the published data is muddled by different device designs and a lack of lineage markers to demonstrate the cell types of key concern and in what designs. Therefore, in vitro tools to study activated LMP formation are needed.
**Aim:** 1) develop an in vitro method for studying LMPs in ovine blood that can be used by developers during the screening of new device designs, 2) identify the parent cell type and activation status of LMPs formed in vitro in the CentriMag (CMAG).
**Methods:** Directly conjugated antibodies were chosen for their cross-reactivity to sheep, bovine, and human blood, to create a 4-colour panel suitable for translational research of VAD designs. Ovine blood was selected for its novelty and suitability for the in vivo stage as bovine LMPs have already been researched in vitro. The CMAG was used at three different operating conditions and blood was sampled regularly and analysed for haemolysis, haematology, and LMP formation by flow cytometry.
**Results:** The high speed operating condition significantly decreased granulocytes ($p = 0.02$), increased pfHb ($p = 0.02$), and generated two activated LMP populations: CD11bbright/HLA-DRneg ($p<0.01$) and CD11b-dim/HLA-DRpos ($p = 0.03$), likely stemming from granulocytes and T cells, respectively.
**Conclusions:** This is the first evidence of activated LMPs forming during in vitro VAD testing, and the first ovine blood damage profile of the CMAG. Future research will repeat the study in bovine blood and add granulocyte and T cell antibodies for more detailed analysis.

## O83
## EVALUATION OF HEMOCOMPATIBILITY OF A HYDRODYNAMICALLY LEVITATED CENTRIFUGAL BLOOD PUMP USING HYPERSPECTRAL IMAGING IN ACUTE ANIMAL STUDIES

*Kosaka R[1], Sakota D[1], Fujiwara T[2], Murashige T[3], Nishida M[1], Tahara T[2], Ohuchi K[2], Arai H[2], Maruyama O[1]*
[1]National Institute of Advanced Industrial Science and Technology (AIST), Ibaraki, Japan
[2]Tokyo Medical and Dental University, Tokyo, Japan
[3]Tokyo University of Science, Tokyo, Japan

**Background:** We have developed a hydrodynamically levitated centrifugal blood pump. To improve hemocompatibility of the pump, an in-vitro thrombogenesis test and an animal study are performed. However, in these studies, it is difficult to identify how thrombus formation forms inside the pump.
Therefore, we have developed a real-time optical monitoring system for detecting thrombus formation in whole blood using hyperspectral imaging.
**Aim:** In this study, we performed acute animal studies to evaluate hemocompatibility of the developed blood pump using hyperspectral imaging.
**Methods:** Seven acute animal studies were performed. The blood pump was installed extracorporeally. The driving condition was set at a flow rate of 1 l/min without anticoagulation. The thrombus formation inside the pump was monitored using hyperspectral imaging. Seven studies were divided into two groups: a non-coated circuit group (n = 6) and a heparin-coated circuit group (n = 1).
**Results:** In the non-coated circuit group, mean activated clotting time (ACT) was 84 ± 10 s, and mean experimental time was 8.4 ± 2.8 h. During the studies, thrombus formation was suddenly observed inside the pump by hyperspectral imaging. After the experiments, the shape of actual thrombus corresponded to hyperspectral imaging. Since tiny thrombi formed at the gap in the tube connection or within the left ventricle, it is considered that thrombus formation inside the pump was originated from outside of the pump. In the heparin-coated circuit group, mean ACT was 85 ± 10 s, and experimental time was 20.7 h. The thrombus formation was not observed inside the pump and the circuit. Moreover, free-plasma hemoglobin was less than 2.1 mg/dl.
**Conclusions:** We confirmed that a developed blood pump was able to realize high hemocompatibility by monitoring thrombus formation inside the pump using hyperspectral imaging through the acute animal studies.

## Symposium - Numerical Modelling: Design, Optimization and Functional Characterization of Ventricular Assist Devices

### O84
### PAST AND FUTURE OF BLOOD DAMAGE MODELLING IN BIOFLUID MECHANICS LABORATORY

*Goubergrits L*
Institute for Computational and Imaging Science in Cardiovascular Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany

**Background:** Blood damage modelling is of great interest for development and optimization of artificial organs (e.g. heart valves, ventricle assist devices or oxygenators) as well as for study of pathologies (e.g. aortic valve stenosis or coarctation of the aorta).
**Aim:** To give a systematic review of 15 years developments and ideas of blood damage modelling accompanied by experimental studies in the Biofluid Mechanics Laboratory as well as to overview promising developments worldwide. To outline future perspectives of the blood damage modelling and define our next goals.
**Methods:** Systematic analysis of earlier proposed blood damage models and analysis of their effectiveness and usability. Analysis of advantages and disadvantages of known blood damage models and test devices.
**Results:** Current blood damage models independent of the approach (Lagrange or Euler; empirical or mechanistic) are able to take into account major requirements including principle of causality, reproduction of known experimental data, and dependence on load history. However, validation of models as well as the impact of turbulence on the blood damage still unsolved problems. Furthermore, currently no patient- specific model for blood damage was proposed.
**Conclusions:** Based on the review follow conclusions are drawn: the problem of missing data for blood damage due to turbulence should be closed by a development of new blood damaging test devices. New ways of the blood damage modelling tools validation should be proposed. Patient-specific impacts should be incorporated into future models.

### O85
### STRAIN-BASED BLOOD DAMAGE MODELING-CURRENT STATUS AND FUTURE PERSPECTIVES

*Pauli L, Haßler S, Behr M*
RWTH Aachen University, Chair for Computational Analysis of Technical Systems, Aachen, Germany

**Background:** Nowadays, stress-based power law models with Lagrangian particle tracking or Eulerian/field- based approaches are common practice for computational hemolysis estimations in blood pumps. Eulerian approaches have already shown superior numerical accuracy compared to Lagrangian particle tracking.
However, both approaches suffer from the assumption of an instantaneous deformation of red blood cells (RBCs) due to the action of fluid forces.
**Aim:** Since a couple of years, we are developing an efficient simulation tool that allows hemolysis estimations by means of a strain-based model. Such a strain-based model tries to estimate the deformation history of RBCs, when passing the blood pump.
**Methods:** We use the Eulerian approach and a power law to predict free plasma hemoglobin in the blood pump. However, instead of using the instantaneous stress distribution of the flow field, we solve a viscoelastic tensor equation to predict the stresses that are acting on the RBC itself. The tensor equation is mapped to an exponential space, which significantly improves the robustness and computing time of the model.
**Results:** The comparison of stress-based and strain-based models leads to significant differences. Not only the locations of critical shear stresses differ, but also the total hemolytic performance changes its behavior for varying operating conditions of the blood pump.
**Conclusions:** With the current implementation, we are able to apply the strain-based model for the analysis of various medical devices. Validation with several blood experiments is currently on the way and will be presented as well.

### O86
### COMPUTATIONAL FLUID DYNAMIC ANALYSES AND IN VITRO ASSESSMENT OF A NOVEL MICROFLUIDIC FLOW-BASED ASSAY

*Dimasi A[1], Roka-Moiia Y[2], Consolo F[3], Rasponi M[1], Fiore G[1], Slepian M[2], Redaelli A[1]*
[1]Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milan, Italy
[2]Department of Medicine and Biomedical Engineering, University of Arizona, Tucson, USA
[3]Department of Anesthesia and Cardiothoracic Intensive Care, University Vita Salute San Raffaele, Milan, Italy

**Background:** Microfluidic flow-based assays represent potential advancements of current diagnostic approaches for monitoring pro-thrombotic risk of patients, allowing to include shear flow contributions. Such systems allow replication of hypershear conditions of Ventricular Assist Devices. However, design of microfluidic channels is currently based on basic fluid dynamic characteristics (i.e. wall shear stress).
**Aim:** To design and test a microfluidic-flow based assay for assessing platelet activation under dynamic shear stress conditions.
**Methods:** A novel microfluidic platform for the study of platelet response to shear stress was designed using multiphase computational fluid dynamic (CFD) simulations and tested in vitro by comparison to a shearing device, the Hemodynamic Shearing Device (HSD). Platelet response following shear exposure was evaluated by means of: i) the platelet activity state (PAS) assay, ii) scanning electron microscopy (SEM) acquisitions, and iii) flow cytometry for phosphatidylserine (PS) exposure.
**Results:** HSD and microfluidic-stimulated GFP showed similar PAS values and dynamics as measured at 4 time points of shear exposure, demonstrating the reliability of the CFD approach in designing the microfluidic platform. Similar morphological characteristics were observed from SEM images showing microaggregate formation following 9 min shear. Also, analogous distributions of platelets PS exposure were obtained from HSD and microfluidic-stimulated GFP.
**Conclusions:** The study allowed to assess the validity of a CFD-based designing approach of shearing microfluidic channels. Results set the basis for the development of a novel microfluidic flow-based assay for the study of platelet response under dynamic controlled shear stress conditions that can mimic shear stress patterns of cardiovascular devices.

### O87
### NUMERICAL MODELING OF THE THROMBOGENIC POTENTIAL OF ALTERED HEMODYNAMICS AT THE LEFT VENTRICULAR APEX-LVAD INTERFACE BASED ON NON-INVASIVE PATIENT-SPECIFIC IMAGING TECHNIQUES

*Apostoli A[1], Bianchi V[1], Dimasi A[1], Selmi M[1], Melisurgo G[2], Votta E[1], De Bonis M[3], Pappalardo F[2], Slepian M[4], Redaelli A[1]*
[1]Department of Electronics Information and Bioengineering, Politecnico di Milano, Milan, Italy
[2]Department of Anesthesia and Cardiothoracic Intensive Care, University Vita Salute San Raffaele, Milan, Italy
[3]Department of Cardiac Surgery, IRCCS San Raffaele Scientific Institute, Milan, Italy
[4]Department of Medicine and Biomedical Engineering, Sarver Heart Center, University of Arizona, Tucson, USA

**Background:** Left Ventricular Assist Device (LVAD) support, despite affording increased survival for patients with advanced systolic heart failure (HF), remains limited by post-implant pump thrombosis. Thrombus formation has been observed to occur at the Left Ventricle (LV) apex-LVAD inflow cannula interface, where altered hemodynamics is characterized by low Wall Shear Stress (WSS), which may trigger an activated prothrombotic phenotype of endothelial cells (ECs) with associated platelet activation, adherence and progressive thrombosis.
**Aim:** To develop a computational method to compute LV hemodynamics and WSS distribution over consecutive cardiac cycles for both healthy and failing LVs and to evaluate the associated thrombogenic potential.
**Methods:** Patient specific LV geometrical models were reconstructed from 3D TT-ECHO as follows: a) healthy, with ejection volume (EV) of 70 ml; b) failing HF with residual 50% EV (35 ml); c) failing HF with no residual EV + LVAD.

Dynamics of the cardiac cycle were simulated in ANSYS Fluent. Mesh motion User Defined Functions allowed to model LV wall contraction and twist during systole, expansion and untwist during diastole.
**Results:** Reducing the LV contractility resulted in reduced WSS: indeed, WSS in the apical region was one order of magnitude lower for the HF LVs (with/without LVAD) compared to the healthy LV. The HF LV + LVAD model revealed a further decrease of WSS. The presence of the LVAD cannula largely altered the LV apex hemodynamics: the velocity magnitude was <0.1 m/s, revealing the presence of a region of stagnation - i.e. a critical prothrombotic condition.
**Conclusions:** Hemodynamics in the LVAD-implanted LV showed the highest thrombogenic potential, consistent with clinical observations. Our model provides mechanistic insights into the thrombogenic risk of LVAD patients and the significance of the LV apex-LVAD interface as a nidus of thrombosis.

## O88
## NUMERICAL DESIGN IMPROVEMENT AND EXPERIMENTAL TESTING OF A SMALL VAD

*Tyler A, Fraser K*
Department of Mechanical Engineering, University of Bath, Bath, UK

**Background:** Computational Fluid Dynamics is a useful tool for developing Ventricular Assist Devices (VADs). However, the results are not necessarily trusted, and validation studies are essential to increase confidence. Validation studies usually require expensive, time consuming, for example Particle Image Velocimetry (PIV). Simpler validation methods, which could be incorporated more naturally into the design process, are therefore desirable.
**Aim:** The aim of this work was to investigate the extent to which design changes in the computational domain produced measureable effects on the experimental pressure-flow characteristics, with a view to using rapid prototyping of early design iterations to increase confidence in CFD.
**Methods:** A small pump, similar to a VAD, was designed using CAD. The geometry was meshed and CFD calculated using ANSYS CFX. Mesh studies were conducted, and several turbulence methods were investigated, to assess errors. Transient simulations were performed to estimate the steady flow pressure- flow curves for a range of speeds. Based on examining the results a series of manual design changes were made and the simulation results were updated for each design iteration. A physical prototype of the pump was created from 3D printed parts; these fitted together allowing replacement of individual components.
The pump was driven with an external motor and shaft. The pump is currently being tested in a custom designed rig.
**Results:** For the original design the operating speed to reach the design point (100 mmHg at 5 l/min) was 10,500 rpm. At this speed the design iterations resulted in changes to the pressure head of between 10 and 200 mmHg; alternatively speed changes of 600 to 5000 rpm were required to produce the design point.
**Conclusions:** These pressure differences are greater than both CFD and transducer measurement errors, meaning the design changes should produce measurable effects. However, rapid prototyping also has inherent errors. Good agreement between CFD and experimental pressure-flow curves in early design iterations could be extrapolated to assume good agreement at the later design stages.

## O89
## INFLUENCE OF PUMP DESIGN VARIATIONS ON HYDRAULIC PERFORMANCE AND BLOOD DAMAGE: A COMPUTATIONAL FLUID DYNAMICS ANALYSIS

*Wiegmann L[1], Boës S[2], de Zélicourt D[1], Schmid Daners M[2], Meboldt M[2], Kurtcuoglu V[1,3]*
[1]The Interface Group, Institute of Physiology, University of Zurich, Zurich, Switzerland
[2]Product Development Group Zurich, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland
[3]Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland

**Background:** Many adverse events observed in patients with ventricular assist devices (VAD), including bleeding, thrombosis and strokes, are thought to be closely related to flow conditions inside the VAD. Consequently, optimization of the pump design is indicated.
**Aim:** We aimed to systematically investigate the impact of centrifugal pump design variations on selected hydrodynamic and hemocompatibility measures using a reproducible baseline geometry.
**Methods:** We developed a generic pump design based on industrial design guidelines, obtaining a pump comparable to current clinical VADs in size and performance. We considered 4 clearance gaps (50-500 µm), 4 blade numbers (4-7) and open as well as shrouded impeller designs. We assessed, using computational fluid dynamics, hydraulic performance, blood damage metrics and their relative correlations: flow, hydraulic efficiency, shear stress thresholds for hemolysis, platelet activation and VWF cleavage, stagnation/recirculation areas, hemolysis index (HI) and spanwise vorticity.
**Results:** Higher clearance led to decreased flow, efficiency and stagnation areas, but increased HI. Larger numbers of blades increased the flow rate and thrombogenicity measures, while efficiency and HI stayed constant. The shrouded impeller yielded a higher flow rate, efficiency, HI and more stagnation areas than the open one. Available models correlating flow metrics to hemocompatibility gave conflicting results.
**Conclusions:** Smaller gaps and a shrouded impeller may be beneficial in terms of hydraulic performance, but less favorable in terms of hemocompatibility. Similarly, more blades may be disadvantageous in terms of blood damage. Our results also highlight the need for better characterization of the relationship between flow metrics and blood damage.

## O90
## ROBUST COMPUTATIONAL TOOLS TO IMPROVE THE DEVELOPMENT PROCESS OF MECHANICAL CIRCULATORY SUPPORT

*Kaufmann T, Groß-Hardt S, Boehning F, Hesselmann F, Steinseifer U*
Cardiovascular Engineering, Institute of Applied Medical Engineering, RWTH Aachen University and University Hospital Aachen, Aachen, Germany

**Background:** While the rise of mechanical circulatory support has been ongoing for several years, there are still burdening complications for patients such as bleeding and thrombosis, as well as limited exercise capacity and reduced quality of life.
**Aim:** In order to overcome these limitations of current technology, a lot of effort is put into more hemocompatible and more physiological devices. However, designers and developers of novel mechanical circulatory support systems face long and costly development, testing and certification processes.
**Methods:** Computational modeling is often sought to fasten early stage developments and reduce the number of physical prototypes being tested. Additionally, it is commonly used to better understand the interaction with medical devices and the human body. Specifically, the interfaces between mechanics and biology are often the weakest link in the chain. Lastly, current research focuses on better prediction of hemocompatibility at early stages to avoid re-iteration of device designs after in-vivo validation.
**Results:** This talk highlights current developments, chances, limitations and threats for computational modeling as a tool for device development. It will present current and ongoing research, describe necessary next steps and required improvements.
**Conclusions:** In the end, the question will be asked when and how computational modeling will ever be able to support not only the development, but also the certification of medical devices.

## Symposium: Nanomedicine

### O91
### IMMOBILIZATION STRATEGIES WITH GLYCOSAMINOGLYCANS-POLYMERIC DRUG CONJUGATE ON BIOMATERIALS FOR ANTI-INFLAMMATORY PURPOSES

*Al-Khoury H[1,2], Heyroth F[2], Syrowatka F[2], Chatterjee C[1], Aguilar M[3], Espinosa E[3], Gomez A[3], San Román J[3], Schmidt G[2], Groth T[1,2]*
[1]Department of Biomedical Materials, Institute of Pharmacy, Halle, Germany
[2]Interdisciplinary Center of Materials Science, Institute of Physics, Halle, Germany
[3]Department of Biomaterial, Polymer Science and Technology, Madrid, Spain

**Background:** Biomaterial implantation induces a series of interactions jointly called the foreign body response, which can impair the longevity of the biomaterial. Therefore, material surfaces are modified here with multilayer coatings to obtain potential anti-inflammatory characteristics. Hence, poly(ethylene imine) (PEI) in combination with other polyelectrolytes such as heparin (Hep), chitosan (Chi) and polymeric drug conjugates as nanoparticles (NPs) are used as a synergistic system to control inflammatory response. The NPs are based on a pseudo-block copolymer composed of a hydrophilic shell (imidazole residue) which covers and protects the core domain of the covalently bound hydrophobic drug (naproxen residue) to increase the therapeutic effect towards bioactive components.
**Methods:** Thirteen single layers were assembled in which NPs were adsorbed for 60 min, while PEI was adsorbed for 30 min and Hep and Chi for 15 min. The multilayers were characterized toward topography by atomic force and scanning electron microscopy and the thickness with profilometry. In addition, cell experiments were conducted to determine foreign body giant cells (FBGCs) formation.
**Results:** NPs with dimension of 89 nm in solution resulted in a homogeneous distribution across the model surfaces obtaining a certain roughness. However, larger particle dimensions, e.g. 342.8 nm, resulted in aggregations and heterogeneous adsorption and distribution of the particles. However, the increase in thickness was an indicatior of the successful immobilization in both cases. In addition, smaller FBGCs containing fewer nucleuses were found on surfaces assembled with NPs in comparison to plain PEI control surfaces.
**Conclusions:** The synergetic effects between the nonsteroidal anti-inflammatory drug (NSAID) naproxen and the glycosaminoglycan Hep with anti-inflammatory potential could help to diminish the inflammatory process after biomaterial implantation.

### O92
### ELECTROSPINNING OF FIBRES FOR NANOMEDICAL APPLICATIONS

*Repanas A[1,2], Mavrilas D[3], Müller M[2], AL Halabi F[2], Glasmacher B[2]*
[1]Biomedical Materials Group, Institute of Pharmacy, Martin-Luther Universität Halle-Wittenberg, Halle, Germany
[2]Institute for Multiphase Processes, Leibniz Universität Hannover, Hannover, Germany
[3]Laboratory of Biomechanics and Biomedical Engineering, Mechanical Engineering and Aeronautics, University of Patras, Patras, Greece

**Background:** Nanomedicine is an interdisciplinary field that combines basic principles of Engineering, Biology and Medicine. Different types of materials and methods are utilized to create high quality formulations, including particles, films and fibres. Nanofibres have the advantage to mimic the extracellular matrix (ECM) and have a positive effect on cell adhesion, growth and differentiation. One of the most frequently used techniques to create multi-layered polymeric fibrous scaffolds is electrospinning.
**Aim:** In this study, we performed a multi-parameter study and investigated the influence on morphological, physical and mechanical properties, related to our own custom-made device. The goal is to produce tailor- made fibres with desired properties that could be used in tissue engineering and drug delivery.
**Methods:** Coaxial electrospinning using a custom-made nozzle was performed under room temperature. The structural and morphological properties were studied using a scanning electron microscope (SEM). The surface properties were investigated performing a static water contact angle assay. Mechanical properties were studied using a uniaxial tensile testing bench.
**Results:** Solution and process parameters affect the morphological and mechanical properties of the fibres in a similar manner compared to blend electrospinning. Linear relationships between structural properties (such as fibre diameter) and physical properties (such as electrical conductivity and hydrophilicity) were determined. Polymer concentration was the most versatile parameter in order to optimize the fibres' characteristics.
**Conclusions:** The knowledge gained from this study can be used to design a bio-artificial system based on electrospun fibres that can act as both a scaffold for structural support, as well as a carrier that can modulate the release of growth factors and promote cell differentiation.

### O93
### VASCULAR GRAFTS WITH DEFINED FIBER ORIENTATIONS

*Grasl C[1,2], Stoiber M[1,2], Enayati M[2,3], Bergmeister H[2,3], Schima H[1,2,4]*
[1]Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria
[2]Ludwig Boltzmann Cluster for Cardiovascular Research, Vienna, Austria
[3]Department of Biomedical Research, Medical University of Vienna, Vienna, Austria
[4]Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria

**Background:** During conventional electrospinning the charged jet is exposed to multiple instabilities. Therefore the fibers are deposited in a random fashion.
**Aim:** Higher control of fiber deposition is necessary to have a tool for better mimicking the layered structure of the vascular wall. The anisotropic behavior shall be replicated by defined orientations of the electrospun fibers.
**Methods:** Tubular vascular grafts with an inner diameter of 2 mm were electrospun from polyurethane. Orientation and fiber alignment was controlled by auxiliary electrodes using electrodynamic deflection of the jet. Grafts with one and two orientation layers were prepared. The morphology and structure of the electrospun scaffolds were examined by scanning electron microscopy and by measuring the radial compliance of these constructs in the physiological range.
**Results:** A macroscopically fiber alignment in the predominant deposition direction of each selected orientation angle was observed. Although, with the used methods and materials it was not possible to electrospin completely straight fibers. The grafts with longitudinal fiber orientation had a compliance of 18.6 ± 2.8%/100 mmHg, whereas the prostheses with circumferential orientation showed the lowest compliance of 7.1 ± 2.6%/100 mmHg. Grafts with random fiber orientation were inferior to the longitudinal grafts. Cavities with large pore volumes were formed at the interface between layers of different fiber orientation.
**Conclusions:** The used electrodynamic steering method allows to electrospin grafts with different pre- defined fiber orientations.

## Symposium: Regulatory Affairs

### O94
### IMPACT OF NEW EUROPEAN MEDICAL DEVICE REGULATION (MDR) ON ARTIFICIAL ORGANS REGULATORY APPROVAL

*Wallstab U[1], Grothues J[2]*
[1]Engineering Office, Institute of Medical Technology, Overath, Germany
[2]RegDev Ltd, Colchester, UK

**Background:** Artificial Organs (AO) are mostly regulated as medical devices (MD) in Europe. The MD regulation was established in Europe (EU) in 1993 by the Directive 93/42 EEC (MDD) and became effective in 1996. The core legal framework consists of 3 directives, the AIMD, MDD and IVDD respectively. These 3 main directives have been supplemented by several modifying and implementing directives and the last significant change was implemented by directive 2007/47/EC. Significant changes in the regulatory framework for MD in EU have been extensively discussed, since the EU Commission adopted a proposal for a EU Regulation on MD and on in vitro diagnostic MD in 2012. The proposed two new regulations will repeal the existing three MD directives. On February 22, 2017, the final draft of the new MDR was

published and the final adaptation is expected during the first semester of 2017. The MDR is structured in 10 Chapters and extending to 123 Articles on approximately 300 pages and 17 Annexes with 200 additional pages. From clinical perspective, the most important is the Chapter VI Clinical evaluation and clinical investigations that outlines in articles 61 to 82 requirements concerning clinical evaluation and clinical trials. Requirements on vigilance and market surveillance, described in article 83 to 100, will also influence the clinical user of a medical device. Many of existing MD will be moved to a higher risk class caused by revised risk classification rules which will have significant impacts on the extended conformity procedures and clinical evaluations. AO regulated as MD are typically classified as class IIb or class III. For certain class III and class IIb devices clinical evaluation consultation procedure is required. The competent authority could request the application of the scrutiny procedure for these MD. The most important upcoming changes in the regulatory framework for MD in EU are presented and show the impact on development, clinical evaluation and clinical use of Artificial Organs regulated as MD.

**O95**
**CLINICAL EVALUATION OF ARTIFICIAL ORGANS REGULATED AS MEDICAL DEVICE**
*Wallstab U[1], Grothues J[2]*
[1]Engineering Office, Institute of Medical Technology, Overath, Germany
[2]RegDev Ltd, Colchester, UK

**Background:** Artificial organs (AO) are mostly regulated as Medical Devices (MD). A Clinical Evaluation (CE) is an important element within the conformity assessment (market approval) for MD in Europe (EU). The guidance document MEDDEV 2.7/1 describes the requirements regarding the CE and the completely revised fourth edition was published 2016. Notified Bodies and Competent Authorities expect full compliance of a CE with the 4th edition (ed.) for market approval. The 4th ed. defines the CE in a 5-stage process and each stage needs detailed planning, conduction, and documentation. The process begins with scoping of CE follows by identification of pertinent data, appraisal of pertinent data, analysis of the clinical data and results in clinical evaluation report. The 4th ed. clarifies that the CE should be conducted and documented within a defined scope with clear objectives that are linked to specific safety, performance, and risk-benefit endpoints and with respect to the state of the art and all available treatment options. This includes establishing the safety and performance of the device under Investigation (DUI), it's claimed equivalent(s), other similar MD, as well as the risks and benefits of other available treatment options including pharmaceutical options. It is no longer sufficient to list several MD that are similar to the DUI and include those MD in the search of the clinical literature. Now a manufacturer may only select one MD for equivalence and must provide a comprehensive equivalence analysis on the basis of clinical, technical and biological characteristics that includes detailed specification of both MD. The CE by "literature route" is only acceptable for DUI where an equivalent MD used in equivalent indication already exists, otherwise clinical investigation (study) is requires to satisfy with the CE requirements established by the 4th ed. The CE for AO MD should be planned and conducted by a multidisciplinary team with expertise in biostatics, medicine, and technology in the specific field of the AO that is subject of evaluation.

**O96**
**3D PRINTED MEDICAL DEVICES UNDER THE PERSPECTIVE OF EU REGULATION**
*D'Avenio G, Daniele C, Grigioni M*
Center for Innovative Technologies in Public Health, Italian National Institute of Health, Rome, Italy

**Background:** 3D printing technologies allow to create patient-specific medical devices (MDs), flexibly and inexpensively. The ease of constructing complex devices with 3D printing can, however, overshadow the need for a strict evaluation of their characteristics.
**Aim:** To emphasize the need for an accurate characterization of the specific risks of 3D printed MDs, as well as to highlight the critical aspects of the European regulation of MDs.
**Methods:** The technologies used for printing MDs were reviewed. The European regulatory framework pertaining to such devices was also considered, owing to the increasing diffusion of such technologies and the difficulty in controlling their introduction in the market.
**Results:** Apart from the series production of printed MDs (with similar regulatory status as traditional MDs), a more interesting case is the printed MD created for a particular patient, to be considered as a custom- made device, according to the MD Directive (MDD). In this case, the manufacturer is only required to provide a declaration (Annex VIII of the MDD), with a statement about conformity of the MD to the essential requirements, indicating, if the case, which of the latter have not been fully met. The regulatory status of such devices is similar to that of Class I MDs (the intervention of a Notified Body is not requested), whereas the functional and structural complexity of printed MDs can easily reach remarkable levels.
**Conclusions:** The European MDD does not explicitly considers the peculiarity of printed MDs, so that they can easily be assigned to the category of custom-made devices, originally introduced in the MDD to deal with low-risk MDs. Hence, it may be said that there is a risk of weak regulatory oversight, given the complexity attainable by printed MDs. The new MD Regulation, which will soon replace the MDD, does not provide substantial changes with respect to the latter: the definition of custom-made devices in the new Regulation is essentially the same, and the manufacturers will still be allowed to market such devices without third-party assessments.

**O97**
**CURRENT STATUS OF THE REDEMPTION PRICE OF THE MEDICAL DEVICES IN JAPANESE INSURANCE SYSTEM DURING 2015-2016**
*Akagawa E, Tatsumi E*
Intellectual Asset Management, National Cerebral Cardiovascular Center, Osaka, Japan

**Background:** How the prices of medical devices to be commercialized are determined is different between Europe, the United States and Japan. The price of medical devices in Japan cannot be set by companies themselves, and it is also set publicly in consideration with that of medical devices in foreign countries and cost of material, development, distribution and so on. On the other hand, there are not so much report which has been analyzed the tendency of recent redemption prices of medical devices in Japan.
**Aim:** The objective of this study is to obvious recent trends of redemption price of the medical devices in Japanese insurance system.
**Methods:** As for medical devices which redemption prices were listed in Japanese medical insurance system, 45 cases which were extracted from the recent published data from 2015 to 2016 were analyzed. In particular, these insurance redemption price, foreign average price, and corporate desired redemption price were focused and were examined.
**Results:** The redemption prices listed in Japanese insurance system were about 0.77 times the corporate desired redemption prices, and the redemption prices tended to linearly increase with rise in corporate desired redemption price ($r = 0.98$). In addition, the redemption price listed in Japanese insurance system were about 0.87 times the foreign average prices, and the redemption prices tended to linearly increase with rise in the foreign average prices ($r = 0.94$).
**Conclusions:** It was suggested that the redemption price listed in Japanese insurance system was correlated with corporate desired redemption price and with foreign average price.

**O98**
**NANOSTRUCTURED MEDICAL DEVICES: THE NEED FOR A SPECIFIC ROADMAP OF THE REGULATORY FRAMEWORK**
*Grigioni M[1], D'Avenio G[1], Daniele C[1], Condello M[2], Bozzuto G[2], Pietrantoni A[1], De Berardis B[1], Superti F[1], Molinari A[2]*
[1]TISP (Innovative Technologies in Public Health), Italian National Institute of Health, Rome, Italy
[2]CNRVF National Center, Italian National Institute of Health, Rome, Italy

**Background:** Nanomaterials (NM) - materials with at least one dimension <100 nm - are gaining popularity in the medical devices (MD) domain. The peculiar characteristics of such materials (above all, the tunability of their physico-chemical properties as a function of their size) are drawing much interest in the biomedical area, in view of enhancing the biocompatibility of MD. Besides the theoretical advantages, though, also the associated risks must be considered.

**Aim:** To pinpoint possible mechanisms of cell-NM interaction, and to highlight how NM are considered in the current European regulatory framework for MD.
**Methods:** The cell damage potential of some NM (ZnO, Ag) already used in the fabrication of MD was comparatively assessed by means of different techniques (MTT, electric cell-substrate impedance sensing (ECIS), SEM, TEM). The European regulatory framework was also examined to consider the provided guidance in dealing with NM-associated risks.
**Results:** The need for oversight of MD containing NM is reflected by the new Regulation on MD, which states that MD incorporating or consisting of NM are in class III unless the NM is encapsulated or bound so that it cannot be released into the patient's or user's body when the MD is used within its intended purpose (Rule 19). It is generally agreed that the ISO 10993 series must be revised in order to consider the specificity of biocompatibility and toxicity of NM. In our experience, standard cytotoxicity assays showed a good agreement with ECIS data, whose real-time measurement of cell viability provides essential information on the mechanisms of cell damage by NM. The results were very sensitive to NM concentration, showing the necessity of defining a clear threshold for each NM and contact type.
**Conclusions:** Nanotechnology can give MD remarkable properties. A cautionary approach about NM, though, is suggested by the new EU regulatory framework, in view of the remaining knowledge gaps.

## Symposium: Blood Damage in Rotary Assist Devices

### O99
### VISUALIZED ERYTHROCYTE'S SHEAR INDUCED DAMAGE PROCESS UNDER HIGH SHEAR FLOW

*Watanabe N, Shimada T, Hakozaki M, Hara R*
Department of BioScience and Engineering, College of Systems Engineering and Science, Shibaura Institute of Technology, Tokyo, Japan

**Background:** In order to understand subhemolytic damage process of erythrocyte, it is desirable to develop the experimental system, which enable the direct observation against individual blood cell under shear flow.
**Aim:** The purpose of this study is firstly to develop such shear device which make it possible to visualize individual blood cell, and secondly to visualize the shear induced blood damage process leading to hemolysis.
**Methods:** We prototyped original shear flow chamber with counter-rotating mechanism of acrylic cone and glass plate for the generation of quasi-Couette high shear flow. The measured surface roughness of acrylic cone resulted in 0.08 micrometers. The flow chamber was mounted on the inverted microscope. And the 350 W metal halide lamp was further incorporated in this setup. Using this experimental system, we visualized blood cells, which was diluted within the high viscous polyvinyl pyrrolidone phosphate buffered saline solution, under high shear stress over 100 Pa.
**Results:** Erythrocytes deformed into ellipsoidal shapes under the high shear flow as their normal intact response, and later they showed the abnormal rheological behavior, finally up to collapsing. In addition, ellipsoidaly elongated some erythrocytes, started undulating their membrane surface, and some of them showed the segmentation through the collision of such abnormal erythrocytes with other cell. Time series their elongation levels were quantified through the image analysis. It was resulted that the greater shear stress and the longer exposure time, the quantified their elongation level as evaluated by major axis of ellipsoidal shape decreased and also their standard deviation became bigger. These results suggested increase of red cell's fragmentation with the increase in time and shear stress. Such tendency agreed with the conventionally known knowledge on shear induced hemolysis.
**Conclusions:** Our prototyped experimental system successfully made it possible to visualize the erythrocytes' rheological behavior.

### O100
### RED BLOOD CELL RESPONSES TO SHEAR STRESS EXPOSURE IN PATIENTS UN/LIKELY TO RECEIVE MECHANICAL CIRCULATORY SUPPORT

*Simmonds M[1,2], Meiselman H[3], Detterich J[4]*
[1]Biorheology Research Laboratory, Griffith University, Gold Coast, Australia
[2]HealthTechX, Menzies Health Institute Queensland, Gold Coast, Australia
[3]Department of Physiology and Biophysics, University of Southern California, Los Angeles, USA
[4]Division of Cardiology, Children's Hospital Los Angeles, Los Angeles, USA

**Background:** Absolute tolerance of red blood cells (RBC) to shear stress (SS) is well defined; hemolysis may occur when exposure reaches ~400 Pa for ~1 s. The functional tolerance of RBC to SS, however, is also important, given many complications of mechanical circulatory support (MCS) may be explained due to microcirculatory impairment.
**Aim:** We recently performed a comprehensive experiment that defined the functional tolerance of RBC to SS. We subsequently extended this model to patients with heart failure who are potential recipients of future MCS. We also investigated the effect of acute and chronic blood transfusion on the relative tolerance of RBC to SS in a group excluded from various MCS (i.e., sickle-cell disease; SCD).
**Methods:** The deformability of RBC was examined in: i. healthy controls, ii. heart failure, and iii. SCD patients with/without a history of blood transfusion; the transfused patients were tracked before and after acute simple transfusion. A Couette-shearing system was used to expose RBC suspensions to discrete magnitudes of SS (1-64 Pa) for specific durations (1-64 s), immediately prior to RBC deformability being measured.
**Results:** The response of healthy RBC to SS confirmed our recent findings that the upper limit of RBC to short-term SS exposure was ~80 Pa, with relative tolerance reaching an asymptote of ~38 Pa for infinite SS exposure. Patients with heart failure demonstrated impaired tolerance to SS. Patients with SCD were more susceptible to SS; however, chronic transfusion improved tolerance to SS to near normal levels.
**Conclusions:** Current strategies to define hemocompatibility may be improved by exploring functional tolerance of RBC through the method described herein. Further discussion is required to the in/exclusion criteria for MCS, based on the results presented in the present paper.

### O101
### INVESTIGATION OF SHEAR-INDUCED PLATELET DAMAGE WITH A COUETTE SHEAR DEVICE

*Lommel M, Affeld K, Kertzscher U*
Laboratory for Biofluid Mechanics, Charité Berlin, Berlin, Germany

**Background:** In the last years continuous flow left ventricular assist devices (LVADs) have evolved from short time therapy into permanent or destination therapy. Critical complications in long term usage are thromboembolic events, caused by activated or damaged platelets, which are presumably attributed to shear-induced interference on the coagulation system.
**Aim:** In our study, we investigate the impact of shear stresses similarly occurring in rotary blood pumps on blood. For these Investigations a novel shear device especially fitted to rotary blood pumps with high dynamic and repetitive stresses was developed. With these investigations we want to establish new evaluation criteria, which are directly regarded to the commonest complications of LVADs.
**Methods:** The blood is 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 50 repetitions. The effect on platelets are investigated with various standard methods used in clinical assessment of platelet function.
**Results:** 50 samples of citrate human whole blood were taken from 4 different healthy donors with informed consent. Damaging models based on the power law including shear stress and exposure were derived.
**Conclusions:** The shear device enables investigations of shear stresses occurring in rotary blood pumps on blood under controlled conditions. Here the influence on the function of platelets is investigated. Objective for

future work is to generate a model to predict the influence of short time stresses on other blood parameters and to derive design criteria for rotary blood pumps.

**O102**
**VON WILLEBRAND FACTOR AND A CORRELATION TO TURBULENCE**
*Affeld K, Schüle C, Thamsen B, Yevtuchenko P, Kertzscher U*
Laboratory for Biofluid Mechanics, Charité - Universitätsmedizin Berlin, Berlin, Germany

**Background:** A number of patients with ventricular assist devices (VAD) suffer from adverse events, some of them being internal bleeding. It is believed, that turbulence and the connected high shear stresses in the rotational ventricular assist device cause the partial destruction of the von Willebrand factor-vWF. Little data is available on the behavior of the von Willebrand molecule under shear stress. However, there is a naturally occurring patho-physiological event that can provide a relation between vWF damage and flow quantities-this is the flow through an aortic valve stenosis. Such a jet flow is characterized by turbulence and shear stresses that go with it.
**Aim:** Objective of this study is to investigate a correlation of turbulence and the damage of the vWF.
**Methods:** As basis clinical data from Vincentelli2003 and Natorska2011 are taken. These authors have investigated patients with an aortic stenosis. They have documented the decrease of molecular weight of vWF as a function of pressure drop caused by the stenosis. An attempt is made to connect these data with an experimental and a numerical model flow of the flow in a typical aorta with a stenosis. This model is based on CT data of a natural aorta. A model of an aortic root with stenosed aortic valve is designed and converted into a mesh for CFD simulation. Five aortic stenosis geometries with different stenosis diameters were used. Turbulence was modeled with Large eddy simulation (LES).
**Results:** Clinical data from both authors scatter considerably, so does the effect of vWF damage on bleeding. Apparently there are large interpersonal difference in vWF function and stability. But a coarse correlation of turbulent shear stress and decrease of vWF molecular weight could be achieved.
**Conclusions:** With the clinical data available from two clinical studies a dependence of von Willebrand factor molecular weight decrease and turbulent shear stresses could be assessed. The flow quantities in an aortic root with stenosed aortic valve were calculated.

**O103**
**CAN WE PREDICT THE THROMBOTIC RISK IN PATIENTS WITH LEFT VENTRICULAR ASSIST DEVICES?**
*Consolo F[1,2], Dimasi A[2], Pieri M[3], De Bonis M[4], Rasponi M[2], Zangrillo A[1,3], Fiore G[2], Slepian M[5], Pappalardo F[1,3], Redaelli A[2]*
[1]Anesthesia and Cadiothoracic Intensive Care, Università Vita Salute San Raffaele, Milan, Italy
[2]Department of Electronic Information and Bioengineering, Politecnico di Milano, Milan, Italy
[3]Anesthesia and Cadiothoracic Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy
[4]Cardiac Surgery, IRCCS San Raffaele Scientific Institute, Milan, Italy
[5]Department of Medicine and Biomedical Engineering, Sarver Heart Center, The University of Arizona, Tucson, USA

**Background:** Assessment of shear-mediated platelet activation (SMPA) in patients with Left Ventricular Assist Devices (LVADs) and how it correlates with thrombotic complications remain a blind spot, preventing the possibility for tailoring antithrombotic therapeutic (AT) strategies to reduce the likelihood of adverse events.
**Aim:** To correlate the dynamics of SMPA as measured via the Platelet Activity State (PAS) assay with thrombotic complications in LVAD patients, and to translate PAS assay on a clinical reliable point-of-care AT diagnostic tool.
**Methods:** The progression of SMPA was evaluated in vivo in a cohort of 44 LVAD patients: PAS was measured preoperatively, early-post-implant, and at long-term follow-up or at the time of a thrombotic adverse event. For the second aim, we developed a microfluidic platform for monitoring SMPA in response to LVAD-like shear stress stimulating conditions.
**Results:** We observed significant elevations of PAS in patients sustaining thrombotic events. These patients also exhibited higher baseline PAS values, suggesting PAS as a potential thrombotic risk predictor. The microfluidic device allowed to properly resembling the dynamics of platelet prothrombotic activity, also discriminating between different platelet inhibitory effects induced by different AT drugs and maintenance doses.
**Conclusions:** Monitoring of SMPA emerged as an important advance for the prediction, prevention and diagnosis of platelet damage and thrombosis. The microfluidic platform will be exploited for the identification of patients with a specific activated prothrombotic profile who might benefit tailored AT strategies.

**O104**
**INFLUENCE OF DYNAMICALLY CHANGING OPERATING CONDITIONS ON THE HEMOCOMPATIBILTY OF ROTARY BLOOD PUMPS**
*Thamsen B[1], Boes S[1], Granegger M[2], Schmid-Daners M[1], Meboldt M[1]*
[1]ETH Zurich, Zurich, Switzerland
[2]Children's Hospital Zurich, Zurich, Switzerland

**Background:** The flow through a rotary blood pump (RBP) depends on the pressure difference across the pump, the speed setting and the pump characteristics, altogether defining the operating point. As a consequence of dynamically changing pressures especially in the left ventricle, flow through the pump permanently varies. The design of rotary blood pumps however, targets one specific operating point with highest efficiency and expectably lowest blood trauma. Off-design operation consequently leads to decreased efficiency and an unfavorable flow field within the pump. Therefore, the varying operating conditions might have a huge impact on flow induced blood trauma and related adverse events.
**Aim:** Aim of this talk is to discuss effects of dynamic operating conditions on the hemocompatibility of RBPs and design challenges in this regard.
**Methods:** First, the theoretical background of the behavior of the flow within rotary pumps including effects of partload and overload operation will be described with the help of CFD simulations. According to established metrics for assessing blood trauma and thrombosis the potential consequences will be discussed. Further, an in-vitro method to evaluate more realistically hemocompatibility of RBPs will be presented. A newly developed pulsatile blood test bench, which consists of two pressure reservoirs connected to a RBP, enables the application of realistic aortic and ventricular pressures at the inputs and outputs of the pump depending on different pulsatile operating conditions. Without causing any blood damage by itself, blood trauma of a RBP can be measured at typical physiologic conditions and realistic waveforms in partial and full support.
**Results:** These investigations allow the evaluation of the effect of realistic operating conditions on blood damage and thereby closing the gap between in-silico and in-vivo studies.
**Conclusions:** This will provide insight into the optimal operating range of rotary blood pumps and a better understanding of the factors influencing it leading to more reliable design criteria.

**O105**
**A MODIFIED CHANDLER-LOOP AS A BENCHMARK FOR HEMODYNAMIC SIMULATION STUDIES**
*Engel S[1], Mueller M[2], Berg P[1], Knigge S[2], Krolitzki B[2], Rusiecki T[2], Voß S[1], Thévenin D[2], Glasmacher B[1]*
[1]Laboratory of Fluid Dynamics and Technical Flows, Otto-von-Guericke University Magdeburg, Magdeburg, Germany
[2]Institute for Multiphase Processes, Leibniz Universität Hannover, Hannover, Germany

**Background:** Flow simulations are used to reduce experimental resources for investigating blood trauma, such as hemolysis. The validation of such simulations still requires time-consuming and expensive experiments. Studies available in the literature often lack in detailed information on the experimental setup and their results. This is, based on our experiences, the main reason for the major limitations of blood damage modeling.
**Aim:** This study aims to assess whether a modified Chandler-Loop can be used to quantify sublethal blood damage. The system would repeatedly strain samples with intermittent reliefs. This procedure could be used to assess

hemolysis in low-stress conditions while considering elastic deformation of erythrocytes.
**Methods:** Tygon tubes with an inner diameter of 4 mm were cut to a total length of 600 mm. One set was modified by inserting two small titanium tubes (l = 10 mm, i.D. 3 mm). The tubes were filled with 3 ml heparinized porcine blood and closed to loops. Dynamic hemocompatibility testing (20 rpm) was performed for 1 h at 37 °C. Blood parameters (HCT, THb, PHb, platelets) were measured before and after the experiment. Index of hemolysis was calculated to assess damage of the erythrocytes.
**Results:** Unmodified tubes showed an index of hemolysis of 0.07% (n = 14); this shows that nearly no blood damage was induced by the material, nor by the system itself. By inserting small titanium tubes, the index of hemolysis was increased to 0.23%. Number of platelet decreased to 90% and 87%, respectively.
**Conclusions:** The results of this study show the ability of a modified Chandler-Loop to induce controlled blood damage by changing the set-up of the loops. It is possible to detect clearly small changes in blood parameters, because the system itself induces a very low background activation. In a next step, corresponding experimental results will be used for validating flow simulations based on Computational Fluid Dynamics.

## Symposium: Dialysis of Today and Tomorrow

### O106
### CARBON BLOCK COLUMN (CB) FOR REGENERATION OF DIALYSATE IN CVVHD

*Ash S[1,2], Sullivan T[1]*
[1]R&D, HemoCleanse Technologies, Lafayette, USA
[2]Department of Nephrology, Indiana University Health Arnett, Lafayette, USA

**Background:** CVVHD provides generally effective fluid and toxin removal in AKI, but there is considerable time, effort and cost in replacing bags of dialysate. The dialysate flow rate is set so low it becomes the limiting factor for chemical clearances (usually 20-40 ml/min). Excess removal of small uremic toxins like K+ often occurs, and altering chemical concentrations of sterile dialysate is time-consuming and expensive.
**Aim:** We propose placing a CB in the CVVHD circuit to remove organic toxins, increasing dialysate flow to 300 ml/min, and recirculating fluid from 5 liter dialysate bags. We report here in vitro tests of a variety of CB to see if they would be safe and effective when used in a CVVHD circuit.
**Methods:** Hydraulic resistance and fine release-standard tests. Creatinine clearance-decrease in concentration in 40 liter tanks with starting concentration of 15 mg% (by spectrophotometry and chemical assay). MM clearance-removal of reactive red dye, acetaminophen and phenobarbital from 40 liter tanks (spectrophotometry). Water purity-by GCMS and AA.
**Results:** CB have low hydraulic resistance, less than 80 mm Hg pressure drop at 300 ml/min for dialysate or albumin solution. CB can be sterilized with gamma radiation, without loss of binding of creatinine. Release of charcoal fines into dialysate is minimal. CB effluent meets or exceeds AAMI-AANSI water standards.
Middle molecule removal was high for some types of CB, low for others. Creatinine removal efficiency was nearly 100% for all CB by chemical assay, but smaller CB appeared to generate a creatinine-like product with altered absorbance spectrum after some hours of use (apparently creatol). 300 grams of carbon should regenerate CVVHD fluid effectively for 24 hours.
**Conclusions:** The addition of CB column to regenerate dialysate in a CVVHD system should be safe and effective in removal of uremic toxins. With a CB and higher dialysate flow, clearance of organic uremic toxins would be greatly increased. Clearance of small uremic toxins would be controlled by the frequency of exchange of dialysate bags.

## Session: Tissue Engineering and Regenerative Medicine II

### O107
### AN INFLUENCE OF THE ZINC OXIDE NANOPARTICLES ON PROPERTIES OF THE ENDOTHELIAL CELLS CULTURED UNDER PHYSIOLOGICAL FLOW

*Ciechanowska A[1], Hoser G[1], Sabalinska S[1], Kawiak J[1], Kaminski A[2], Ladyzynski P[1]*
[1]Department of Biomedical Systems and Technologies, Nalecz Institute of Biocybernetics and Biomedical Engineering, Warsaw, Poland
[2]Department of Transplantology and Central Tissue Bank, Medical University of Warsaw, Warsaw, Poland

**Background:** Nanoparticles can deeply penetrate the human tissue. Due to its properties the zinc oxide nanoparticles (ZnO-NPs) are used in cosmetology and medicine. An important problem is to determine their cytotoxicity.
**Aim:** The main objective of the study was to analyze the effect of ZnO-NPs on properties of the Human Umbilical Vein Endothelial Cells (HUVECs) cultured in a capillary bioreactor under shear stress conditions simulating the natural conditions in the blood vessel.
**Methods:** We seeded 60,000 HUVECs/cm$^2$ in the culture flasks under static condition (SC) and in the polysulfone capillary membranes with the surface area of 16.3 cm$^2$ under dynamic condition (DC), i.e. physiological shear stress. After 24 h, ZnO-NPs were introduced in the concentration of 0, 2.5, 5 or 20 μg/ml. The flow cytometry-based analysis was used to study cellular proliferation. Cells' viability was analyzed using Annexin V. Microscopic visualization of HUVECs was made after staining HUVECs with hematoxylin and eosin. Analyses were made after 72 h of the culturing.
**Results:** The viability analysis showed a higher percentage of cells in early apoptosis in cultures carried out in DC (9.2% for 2.5 μg/ml of ZnO-NPs, 26.3% for 5 μg/ml of ZnO-NPs) than in SC (5.5% for 2.5 μg/ml of ZnO-NPs, 6.0% for 5 μg/ml of ZnO-NPs). Increasing concentration of ZnO-NPs resulted in slower proliferation of cells cultured in SC and DC. Microscopic visualization showed that cells cultured in DC and treated with ZnO-NPs were in worse condition than those cultured in SC. We speculate that the shear stress causes friction of ZnO-NPs at cells' membrane leading to easier access of ZnO-NPs into the cells and damage of their cytoskeleton.
**Conclusions:** ZnO-NPs decrease proliferation and increase apoptosis and damage of HUVECs. These effects are more pronounced in cells cultured in DC than in those cultured in SC.

### O108
### MATERIAL-DRIVEN ASSEMBLY OF FIBRONECTIN (NANO) NETWORKS IN 2D SUBSTRATES AND 3D SCAFFOLDS: EFFECT OF CHEMICAL CROSSLINKING ON FIBRONECTIN ORGANIZATION

*Sabater i Serra R[1,2], León-Boigues L[1], Sánchez-Laosa A[1], Gómez-Estrada L[3], Gómez Ribelles J[1,2], Salmeron-Sanchez M[4], Gallego Ferrer G[1,2]*
[1]Centre for Biomaterials and Tissue Engineering, Universitat Politècnica de València, València, Spain
[2]Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine, (CIBER- BBN), Zaragoza, Spain
[3]Ikasia Technologies SL, València, Spain
[4]Division of Biomedical Engineering, School of Engineering, University of Glasgow, Glasgow, UK

**Background:** Certain materials, such as of poly(ethyl acrylate), PEA, are able to induce the organization of fibronectin (FN) in biomimetic (nano) networks, which have been shown to be recognized by cells. This ability to organize FN has been demonstrated in 2D and 2.5D environments (fibres), but not yet in 3D scaffolds, which incorporate 3-dimensionality and chemical crosslinkers that may influence its fibrillogenic potential.
**Aim:** The aim of this work is to engineer PEA-based 3D scaffolds that sustain the organization of FN in their pores into physiological-like (nano) networks in the same way as in 2D and 2.5D environments.
**Methods:** PEA 2D-substrates were obtained by radical polymerization with different amount of crosslinker and characterized by DSC, DMA and TGA. PEA

3D-scaffolds were polymerized inside a template of poly(vinyl alcohol), which was subsequently removed by leaching. Scaffolds morphology was studied by SEM. FN organization on both 2D substrates and scaffolds were investigated by AFM and ELISA assay.
**Results:** The organization of FN after adsorption and the availability of the FN cell-binding domain were found to be dependent on crosslinking density. Surface mobility was identified as a key parameter for FN organization. FN (nano) networks were assembled on the walls of scaffolds prepared by 2% of crosslinker.
**Conclusions:** In this work we show that while three-dimensionality does not interfere with PEA-induced FN fibrillogenesis, crosslinking does. PEA-based scaffolds are able to induce FN fibrillogenesis in 3D environments as long as the amounts of crosslinker is low enough. Acknowledgement: Project MAT2015-69315-C3-1-R supported by MINECO (Spain) and FEDER funds.

**O109**
**MICROSPHEROID ASSEMBLIES: LEVITATING PCL –IO SPHEROIDS IN BIOMATERIAL APPLICATIONS-INSIGHTS FROM RESPIROMETRY**
*Fernandez F, Beeran AE, Varma H*
Division of Bioceramics, BioMedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum, India

**Background:** 2-D cell culture models have been the workhorse to understand cell biology & cell physiology with direct application in the fields of material discovery, biocompatibility and toxicity testing. Recognizing the limits of traditional 2D (Two-Dimensional) methods, evolution of 3D (three dimensional) tissue mimics has been accelerated. The ability to generated structured cellular structures resembling native tissues in form and function is key to modeling natural architecture of tissues and elucidating tissue response to challenges (1).
**Aim:** Cellular clusters developed so far range from traditional clot cultures, droplet based aggregation systems to self-assembling & self-organizing smart systems. The persistent challenge has been the development of three-dimensional systems that offer fine-grained control over assembly and function. Using non-contact force systems ensures control and acceptable levels of process security. The ability of these systems to ensure rapid agitation via directed force levels also provides a micro-flow system.
Circulating fluids, layered cellular structures and interaction at a tissue level are key to the success of any 3D system for testing or modeling purposes.
**Methods:** Spheres were loaded with cell systems and evaluated for cell viability, structure and function. The spheres were demonstrated to be cytocompatible, demonstrated to perform as a assembled spheroid system for use in drug testing, three dimensional interaction analysis. The spheroids are capable of executing magnetic field guided agitation and organized levitation in media. Respirometry analyses were carried out to elucidate cell stressors to identify markers for compatibility at a sub-cellular level.
**Results:** The constructs exhibited excellent cell loading abilities and performance in standard culture systems.
**Conclusions:** Circulation and creation of micro-flow systems via controlled motion will mimick vascular supply and dispersal of metabolites. Future studies include evaluation of theranostic abilities and conjugation.

**O110**
**HUMAN INDUCED PLURIPOTENT STEM CELLS-BASED STRATEGIES FOR BONE TISSUE ENGINEERING AND REGENERATION.**
*Ogrin L[1,2], Stetco A[1,2], Redl D[1,2], Marolt Presen D[1,2]*
[1]Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria
[2]Austrian Cluster for Tissue Regeneration, Vienna, Austria

**Background:** Regeneration of bone defects presents significant clinical and scientific challenges, particularly in elderly patients suffering from chronic conditions.
**Aim:** The aim of our project is to develop functional bone tissue substitutes from human induced pluripotent stem cells and to test their potential to enhance bone defect regeneration.
**Methods:** We used human induced pluripotent stem cells to derive embryonic-like mesenchymal progenitors (hiPSC-MPs) with high proliferation and osteogenic differentiation potential. hiPSC-MPs were seeded on bone scaffolds and cultured in perfusion bioreactors to support new tissue formation in vitro. Tissue development was investigated using biochemical, molecular and histological methods and by micro- computed tomography (micro-CT) imaging over the duration of bioreactor culture and after 12-week subcutaneous implantation in immunodeficient mice. More recently, the effects of hiPSC-MP-derived tissue components on the regenerative potential of endogenous bone populations are being evaluated.
**Results:** Bioreactor culture yielded bone-like tissue constructs with significantly higher cellularity, alkaline phosphatase activity and osteopontin release into the culture medium as compared to static culture controls. Dense bone matrix formation was evidenced by the positive staining of collagen, osteopontin, bone sialoprotein and osteocalcin. Micro-CT analysis revealed a significant increase in tissue mineralization. Furthermore, engineered bone tissue displayed stable phenotype after 12-week implantation in vivo. Histological analyses demonstrated the presence of human cells, as well as ingrowing host vasculature and osteoclasts, suggesting an initiation of tissue remodeling.
**Conclusions:** Our studies demonstrate the potential of hiPSC-MPs for engineering of functional bone tissue substitutes with enhanced regenerative properties and could represent a basis for a new treatment alternative for elderly patients.

**O111**
**OSTEOGENIC DIFFERENTIATION OF HUMAN MESENCHYMAL STEM CELLS UNDER PHYSIOLOGICAL FLUID SHEAR STRESS**
*Clementi A, Egger D, Kasper C*
Department of Biotechnology, University of Natural Resources and Life Science, Vienna, Austria

**Background:** Obtaining physiological fluid shear stress during the cultivation of three dimensional (3D) cell- scaffolds for optimizing 3D cell culture processes is a crucial but challenging task. Therefore, we used a recently developed miniaturized perfusion bioreactor together with a specialized incubator system to achieve conditions for osteogenic differentiation of human adipose derived mesenchymal stem cells (hASCs) on a 3D scaffold.
**Aim:** In our study we wanted to compare static and dynamic osteogenic differentiation of MSC on 3D Sponceram® scaffolds regarding cell number, alkaline phosphatase activity (ALP, an early osteoblast marker), glucose consumption and lactate production.
**Methods:** Cells were seeded on a three-dimensional macro-porous zirconium dioxide ceramic scaffold and cultivated in osteogenic media. To investigate the effect of controlled application of physiologic fluid shear stress a flow rate of 1.5 ml/min was used to cultivate MSCs in a self-developed perfusion bioreactor. For static conditions, the scaffolds were cultivated in polystyrene 6 well plates. The experiment was performed over 21 days at 37°C, 5% $CO_2$ and normoxic conditions with regular media changes and sample collection of conditioned media. The samples were analyzed for ALP activity, glucose and lactate concentrations. As an end point measurement, cell number of each scaffold was determined via a DNA quantification.
**Results:** It could be shown that under dynamic conditions, cells show a higher specific lactate production and specific glucose consumption compared to static conditions. ALP activity under dynamic conditions is elevated in the first 12 days of culture. At the same time, cell number after 21 days is higher under static conditions, which correlates with microscopy images of DAPI stainings.
**Conclusions:** These findings show that dynamic and thus more physiological conditions affect cell metabolism and and strongly underline the effects of mechanical stimulation on osteogenic differentiation of hASCs.

## Symposium: Artificial Lung

### O112
### INTRACORPOREAL MEMBRANE CATHETER FOR $CO_2$ REDUCTION IN THE BLOOD-MEMBRANE CONTACTOR

*Harasek M[1], Haddadi B[1], Jordan C[1], Gföhler M[2], Janeczek C[2], Karabegovic A[2], Futter L[2], Krenn C[3], Neudl S[4], Ullrich R[3]*
[1]Department of Chemical Engineering, TU Wien, Vienna, Austria
[2]Department of Engineering Design and Logistics Engineering, TU Wien, Vienna, Austria
[3]Critical Core Technologies, Vienna, Austria
[4]Medical University of Vienna, Vienna, Austria

**Background:** An approach to prevent acute respiratory distress syndrome (ARDS) is to reduce $CO_2$ concentration in blood before it reaches the lungs. This can be achieved using an intracorporeal membrane catheter in which $CO_2$ is transferred from blood side to the other fluid which is pumped to outside of the body. $CO_2$ is removed and the secondary fluid is then pumped back into the body in a closed loop.
**Aim:** The main challenge is to design the membrane module in a way that is small enough to be implanted into the patient body and at the same time can provide the required $CO_2$ removal capacity from the blood.
**Methods:** There are different approaches for testing membrane designs and investigating the influence of key parameters on the performance of such units. Computational fluid dynamics (CFD) is a method using the solution of fluid flow equations based on numerical approaches with time and space resolution. In this study an open-source CFD platform (OpenFOAM®) was used for development of a new solver for 3D and 1D membrane modeling. Driving forces for mass transfer - partial pressure differences - are calculated based on local information. The code was validated against measurements and other 1D simulation tools.
**Results:** Using the new code the flow structure in the shell side of a suggested membrane module for $CO_2$ removal was simulated and the flow pattern and residence time of the blood in the shell was studied. The simulation shows how flow and pressure are distributed in the membrane and main design factors which causes pressure drops and also non ideal flow distribution can be detected and improved.
**Conclusions:** A membrane based device was suggested for removal of $CO_2$ from blood. This device needs to be small enough for implantation and at the same time remove enough $CO_2$ from blood. For this optimization purpose a CFD solver was developed and design and operation parameter variation for the membrane model was performed.

### O113
### IN VITRO CHARACTERIZATION OF THE PITTSBURGH PEDIATRIC AMBULATORY LUNG DEVICE

*Orizondo R[1], May A[1,2], Madhani S[1,3], Frankowski B[1], Burgreen G[4], Wearden P[1,5,6], Federspiel W[1,2,3,7]*
[1]McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, USA
[2]Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburgh, USA
[3]Bioengineering, University of Pittsburgh, Pittsburgh, USA
[4]Computational Fluid Dynamics Group, Center for Advanced Vehicular Systems, Mississippi State University, Starkville, Mississippi, USA
[5]Department of Cardiothoracic Surgery, University of Pittsburgh, Pittsburgh, USA
[6]Cardiac Center, Nemours Children's Hospital, Orlando, USA
[7]Critical Care Medicine, University of Pittsburgh, Pittsburgh, USA

**Background:** Acute and chronic respiratory failure is a significant source of pediatric morbidity and mortality. Current means of respiratory support used to bridge these children to lung recovery or transplantation typically render them bedridden, a condition that can worsen long-term patient outcomes.
**Aim:** The Pittsburgh Pediatric Ambulatory Lung (P-PAL) is a wearable pediatric blood pump and oxygenator integrated into a single compact unit that enables patient ambulation. The P-PAL is intended for long-term use and designed to provide up to 90% of respiratory support in children weighing 5-25 kg.
**Methods:** Pressure-flow curves were obtained at various impeller rotation rates using a blood analog fluid. Oxygen exchange rates were obtained in blood in accordance with ISO standard 7199. The normalized index of hemolysis (NIH) was measured over a 6-hour period at blood flow rates of 1 and 2.5 L/min.
**Results:** The P-PAL provided blood flows of 1-2.5 L/min against the pressure drop associated with its intended-use pediatric cannulas. An oxygen exchange rate of 108 mL/min was achieved at a blood flow rate of 2.5 L/min, thereby meeting our respiratory support design target. Device-induced hemolysis was low with NIH values of 0.014-0.024 g/100L in the intended blood flow rate range.
**Conclusions:** The current P-PAL design met our pumping, oxygenation, and hemolysis specifications and has the significant potential to improve treatment for pediatric respiratory failure. Future work includes in vivo evaluation of the P-PAL in acute and chronic animal studies.

### O114
### RAS-Q-A NOVEL PASSIVE RIGHT HEART ASSIST SYSTEM

*Kaufmann T[1,2], Borchardt R[2], Verbelen T[3], Sonntag S[2], Ritter P[2], Steinseifer U[1], Mouzakis F[4], Kashefi A[4], Mottaghy K[4], Meyns B[3]*
[1]Department of Cardiovascular Engineering, Applied Medical Engineering, RWTH Aachen University and University Hospital Aachen, Aachen, Germany
[2]enmodes GmbH, Aachen, Germany
[3]Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium
[4]Institute of Physiology, RWTH Aachen University and University Hospital Aachen, Aachen, Germany

**Background:** RAS-Q is a novel passive right heart (RH) and respiratory assist device which supports and protects the right ventricle by reducing afterload and dampening pressure spikes. RAS-Q is connected between the pulmonary artery (PA) and left atrium (LA) by vascular grafts. Blood flows passively through the device driven by PA/LA pressure gradient. RAS-Q combines an integrated compliance to reduce the RH's afterload with gas exchange technology to support the lungs' function. The internal compliance is adjustable during operation, allowing for adaption to patient conditions, exercise and weaning.
**Aim:** In this study, we present first in-vitro and in-vivo results of RAS-Q as a RH assist system.
**Methods:** RAS-Q was designed to reduce right heart afterload by 35% while maintaining sufficient gas exchange within the pulmonary bypass. Compliance and pressure gradients across RAS-Q were measured using mock loops. Gas exchange was analyzed in blood trials following ASTM standards. RAS-Q was tested in acute animal studies, focusing on reduction of right ventricular afterload. RH failure was induced by PA banding in sheep, which resulted in pulmonary hypertension and consecutive RH failure.
**Results:** In-vitro studies showed a compliance of 5.8 ± 0.2 ml/mmHg, which is comparable to the native lungs. Blood trials revealed highly efficient gas exchange ($VO_2$ >60mL$O_2$/L blood $VCO_2$ >50 mL$CO_2$/L blood). In vivo studies in sheep (53 ± 7 kg) confirmed the mock results. Baseline CO of 3.06 ± 0.50 l/min was reduced to 1.70 ± 0.57 l/min in acute RH failure. With RAS-Q, CO was restored to 2.95 ± 0.16 L/min. Right ventricular afterload was reduced by 41.1% ± 9.9%, resulting in overall improved and restored cardiac function.
**Conclusions:** RAS-Q possesses great potential as a gentle and effective RHassist system. Its long-term impacts will be analyzed in chronic animal trials this year.

### O115
### CONTROLLED BLOOD RECIRCULATION ENHANCES OXYGENATION EFFICIENCY IN AN ARTIFICIAL LUNG

*Madhani SP[1,2], Frankowski BJ[1,2], Antaki JF[3], Burgreen GW[4], Federspiel WJ[1,2]*
[1]McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, USA
[2]Department of Bioengineering, University of Pittsburgh, Pittsburgh, USA
[3]Department of Biomedical Engineering, Carnegie Mellon University, Pittsburgh, USA
[4]Computational Fluid Dynamics Group, Center for Advanced Vehicular Systems, Starkville, Mississippi, USA

**Background:** Device size is dependent on hollow fiber membrane (HFM) bundle surface area (SA). Augmenting oxygenation with increased efficiency

allows SA reduction. Efficiency is dependent on blood flow velocity in the HFM bundle. Strategies including moving elements effectively increase efficiency, however complex flow features in the HFM bundle can cause hemolysis.
**Aim:** By increasing the recirculation rate we precisely control blood velocity through the HFM bundle thus controlling hemolysis. This study investigates blood recirculation in the Pittsburgh Ambulatory Artificial Lung (PAAL).
**Methods:** A model predicting oxygenation as a function of recirculation flowrate was developed using a semi-empirical mass transfer correlation. In-vitro testing was conducted on a 0.38 m2 HFM bundle device. Oxygenation was measured at a constant 3.5 L/min blood flow while recirculation flowrate varied (0, 2.5, 4.5 and 6.5 L/min). Hemolysis was measured at 3.5 L/min blood flow and 6.5 L/min recirculation flow and represented as a normalized index of hemolysis (NIH). An optimized design was developed using computational fluid dynamics (CFD) analysis.
**Results:** The model predicted oxygenation capacity within 7%. Oxygenation up to 180 ml/min was achieved with a surface area of 0.38 m2. The NIH contribution of the fiber bundle was 0.012 g/100 L. The CFD analysis showed the device could pump over 250 mmHg while maintaining 3.5 L/min blood flow and 6.5 L/min recirculation flow. Maximum shear in the optimized device was low (300 pa).
**Conclusions:** Blood recirculation achieved efficiency over 470 ml/min/m2 while meeting performance requirements. This design allows a fiber surface area over 3.4 times smaller than the clinical standard. The optimized design from our CFD analysis will be manufactured for bench testing in the near term.

### O116
### INVESTIGATIONS OF THROMBUS DISTRIBUTION AFTER LONG TERM ECMO AND BLOOD FLOW DISTRIBUTION USING CFD IN AN OXYGENATOR

*Katagiri N, Tsukiya T, Mizuno T, Takewa Y, Tatsumi E*
Department of Artificial Organs, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan

**Background:** Some of membrane oxygenators in ECMO systems have been demonstrated durability for over 1 week continuous use. Blood-gas data is measured during ECMO, and used as an index of management. On the other hand, thrombus distribution is extremely difficult to evaluate during ECMO.
**Aim:** Purpose of this study is systematic evaluation of the changes of thrombus formation in a hollow fiber membrane oxygenator (BIOCUBE2000) due to conditions of anticoagulant therapy and ECMO period by quantifying the thrombus distribution in the oxygenator after ECMO using an image processing.
**Methods:** VA-ECMO using the oxygenator and ROTAFLOW pump was conducted on 8 adult goats (19-30 kg). Four groups (n = 2 each) were determined from the combination of 2 types of anticoagulant therapy (continuous heparin administration (H group) or no continuous anticoagulation (N group)), and 2 types of ECMO periods (2 or 5 weeks). After each experiment, we took section images of inlet side, middle and outlet side of blood passage in the oxygenator. The red thrombus area was distinguished by converting each image to black and white, and ratio of red thrombus area to all area was calculated. On the other hand, the blood flow distribution in the oxygenator was calculated by CFD.
**Results:** The average area ratios of red thrombus at inlet side, middle and outlet side were 0.002, 0.000 and 0.000 in the group of H for 2 wks, 0.049, 0.001 and 0.013 in the group of N for 2 wks, 0.052, 0.001 and0.000 in the group of H for 5 wks, 0.147, 0.178 and 0.249 in the group of N for 5 wks, respectively. Estimated blood flow distribution in the oxygenator showed low velocity in a wake of hollow fiber bundle at the outlet side.
**Conclusions:** The change of thrombus formation in the oxygenator could be evaluated quantitatively by expressing thrombus distribution as the area ratio at each section. The estimated flow characteristics were thought to be consistent with the increment of thrombus at the outlet even in the cases without thrombus in the middle of bundle.

### O117
### IN-VITRO AND IN-VIVO STUDIES OF AN INTEGRATED, WEARABLE BLOOD PUMP- LUNG

*Madhani S[1,2], Frankowski B[1,2], Ye S[1,2], Burgreen G[3], Antaki J[4], Kormos R[1,5], Wagner W[1,2,5], D'Cunha J[1,5], Federspiel W[1,2]*
[1]McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, USA
[2]Department of Bioengineering, University of Pittsburgh, Pittsburgh, USA
[3]Computational Fluid Dynamics Group, Mississippi State University, Starkville, Mississippi, USA
[4]Department of Biomedical Engineering, Carnegie Mellon University, Pittsburgh, USA
[5]Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, USA

**Background:** Clinical studies show improved outcomes in ambulated lung failure patients. Implementing ambulation necessitates development of a compact wearable respiratory support device. The Pittsburgh Ambulatory Assist Lung (PAAL) is being designed for ambulating lung failure patients during treatment.
**Aim:** We previously published in-vitro and acute in-vivo results of our PAAL. The PAAL design was optimized using CFD analysis and in-vitro tested in this study. We then evaluated the PAAL for five days in sheep.
**Methods:** Flow paths were optimized using CFD analysis. The PAAL was tested on the bench for hydrodynamic performance and hemolysis. Five day in-vivo studies (n = 5) with the PAAL were conducted in 50-60 kg adult sheep after heparinization and cannulation with a 27 Fr. Avalon Elite dual lumen cannula. The animals moved freely in a stanchion while device flow, bundle resistance, and animal hemodynamics were recorded hourly. Oxygenation, plasma free hemoglobin (PfHb) were measured daily. Platelet activation, blood chemistry and blood counts were assessed pre-operatively, and on POD 0, 3 and 5.
**Results:** CFD optimization retained design elements from our first prototype while reducing in-vitro hemolysis by 70%. All animals survived the surgery and three survived the study duration. Two animals were terminated early (POD 0, 3). PfHb remained at baseline for all animals and blood left the device 100% oxygenated. CD62-P expression was under 10%. Minimal thrombus was seen in devices at explant.
**Conclusions:** Initial blood compatibility of the PAAL is promising. There were no device related complications over the study course. 30-days studies are planned in the near term.

## Session: Computational Fluid Dynamics I

### O118
### EVALUATION OF NUMERICAL MODELS IN SIMULATION OF INTRAVENTRICULAR FLOW PATTERN WITH LEFT VENTRICULAR ASSIST DEVICE SUPPORT

*Ghodrati M[1], Aigner P[2], Moscto F[1,2], Stoiber M[1,2], Schima H[1-3]*
[1]Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria
[2]Ludwig Boltzmann Cluster for Cardiovascular Research, Vienna, Austria
[3]Department for Cardiac Surgery, Medical University of Vienna, Vienna, Austria

**Background:** The evaluation of the left ventricular assist devices (LVADs) performance requires understanding details of intraventricular flow pattern with LVAD support. Computational Fluid Dynamics (CFD) can be a powerful tool to simulate flow field that leads to access more details where experimental approach is stretched to its limit.
**Aim:** The aim of this study is to evaluate different numerical methods to simulate the intraventricular flow patterns and compare these to experimental tests using Particle Image Velocimetry (PIV).
**Methods:** Four different CFD methods (laminar, standard k-omega (SKO), Shear Stress Transport (SST) and realizable k-epsilon(RKE)) were utilized to simulate the intraventricular flow field with LVAD support. The boundary conditions were extracted from PIV data (Pump Speed 2800 rpm, Flow rate

2 lit/min). For comparison with PIV tests, the flow velocities from the CFD models at five different cross sections from mitral inflow to Lvad cannula were compared to PIV measurements and a validation metric E (mean velocity differences between CFD and PIV divided by PIV velocity) applied (E = 0 is exact simulation).
**Results:** All models could reproduce the main flow patterns of the PIV within some limitations. The SST performed best with the lowest differences, (SST E = 0.38, RKE E = 0.46, SKO E = 0.55, Laminar E = 0.89). At the mitral position the lowest velocity difference was achieved with SST turbulence model (E = 0.34). RKE method showed better agreement with PIV velocity at the LVAD cannula insertion position (E = 0.36).
**Conclusions:** Selection of turbulence models is critical and can result in completely different flow pattern. For the flow patterns predicted by Laminar, SKO and SST methods the main differences with PIV data occurred on the area around the LVAD inflow cannula, while for RKE method was seen at the middle part of the ventricle.

## O119
## THE EFFECT OF INFLOW CANNULA INSERTION LENGTHS ON THE RISK OF VENTRICULAR THROMBOSIS IN A MULTISCALE NUMERICAL MODEL

*Liao S[1,2], Neidlin M[3], Li Z[1], Simpson B[4], Gregory S[1,4]*
[1]Institute of Health and Biomedical Innovation (IHBI), Queensland University of Technology, Brisbane, Australia
[2]ICETLAB, The Prince Charles Hospital, Brisbane, Australia
[3]Helmholtz Institute, RWTH Aachen University, Aachen, Germany
[4]School of Engineering, Griffith University, Brisbane, Australia

**Background:** Left ventricular assist devices (LVADs) are mechanical pumps used to assist failing hearts. LVADs can affect flow dynamics within the left ventricle (LV) which can cause thrombosis and neurological dysfunction. Many studies have assessed inflow cannulae but in highly simplified numerical models, assuming LV symmetry, steady boundary conditions (BC) and rigid walls.
**Aim:** The aim was to investigate the risk of LV thrombosis as a result of differences in inflow cannula insertion lengths due to variances in apical wall thicknesses using a multiscale numerical model.
**Methods:** A severely dilated LV was modelled from computed tomography imaging data. Inflow cannula geometry was modelled from a HeartWare HVAD. Four insertion lengths were assessed: 5 mm (apical hypertrophy), 19/24 mm (higher/lower bound of typical wall thicknesses) and 50 mm (trial length). The BC of the fluid was one-way coupled to a lumped parameter network (LPN), tuned to represent a patient with heart failure. Heart wall motion was applied using one-way fluid-structure interaction. A mitral valve was controlled by the LPN. Thrombus risk was evaluated over a cardiac cycle at the apex in terms of dynamic pressure and blood stagnation.
**Results:** The average dynamic pressure at the apex before the atrial kick, as an example, was 24, 6, 5 and 21 Pa for 5, 19, 24 and 50 mm cannula insertion lengths, respectively. Based on a stagnation threshold, the 5 and 50 mm lengths did not have any stagnation. The 19 and 24 mm insertion lengths had 6 and 14 µL of stagnation, respectively, found at the interface between the cannula and endocardium.
**Conclusions:** It was found that both a short and long insertion length has the potential to minimise thrombosis. The knowledge obtained from the multiscale numerical model may help with future designs of inflow cannulae. To optimise LV flow in a wide group of patients, variable length inflow cannulae may be needed.

## O120
## COMPARISON OF AN UNSTEADY-REYNOLDS-AVERAGED AND A VERY-LARGE- EDDY SIMULATION REGARDING THEIR POTENTIAL TO PREDICT HEMOLYSIS WITH STRESS-BASED HEMOLYSIS MODELS

*Konnigk L[1], Torner B[1], Hallier S[1], Wisniewski A[2], Medart D[2], Wurm F[1]*
[1]Institute for Turbomachines, University of Rostock, Rostock, Germany
[2]Berlin Heart GmbH, Berlin, Germany

**Background:** It is important to estimate hemolysis in the design and optimization process of Ventricular Assist Devices (VADs). Nowadays, this is mostly done by computational fluid dynamics in combination with numerical hemolysis prediction models. The results are significantly influenced by the choices of the hemolysis prediction model and the simulation method. The latter one can greatly affect the accuracy of the calculated shear stress field.
**Aim:** Aim of the study was to analyse two different numerical methods for the flow calculation within a VAD. For this purpose, the stress fields of an Unsteady-Reynolds-Averaged Navier-Stokes Simulation (URANS) and a Very-Large-Eddy Simulation (VLES) were compared.
**Methods:** An URANS and a VLES of one single operating point were carried out on the same mesh of an axial VAD with 16 million nodes under consideration of a Newtonian and single-phase fluid. A globally integrated hemolysis index, volumetric shear stress histograms and potential damage sources were analysed. Furthermore, all results were compared to an LES on a finer mesh (101 million nodes) to state out, how far both methods differ from this simulation, where the real flow physics are expected to be reflected more accurately.
**Results:** Flow fields and pressure head in both simulations are in good agreement. However, the hemolysis predicted with URANS was significantly lower in contrast to the fine LES, whereas the deviations between VLES and LES are substantially smaller. The computational time of the VLES was only moderately higher than for the URANS.
**Conclusions:** Since LES methods resolve velocity gradients more accurately, the VLES method calculates higher stress fields in contrast to URANS on identical meshes. Therefore, URANS systematically underestimates shear stresses whereas the results of the VLES are more similar to the fine LES results. In conclusion, VLES could provide a reasonable alternative to classical URANS methods for hemolysis prediction.

## O121
## NUMERICAL MODELLING OF LEUKOCYTE DEFORMATION IN VENTRICULAR ASSIST DEVICES

*Fraser K[1], Pieper I[2]*
[1]Mechanical Engineering, University of Bath, Bath, UK
[2]Caloncardio Inc. Swansee, UK

**Background:** Despite the evolution of Ventricular Assist Devices (VADs), VAD patients still suffer from complications, often due to damage to the blood components by fluid dynamic stress. Damage to the leukocytes may contribute to infections, one of the biggest post-surgical problems. In experiments destruction of leukocytes was found to depend on impeller speed, flow rate and the type of leukocyte.
**Aim:** The aim was to develop a numerical model for leukocyte deformation to help explain differences in damage levels between VAD operating conditions and between different cell types.
**Methods:** The cell was modelled as a spherical compound liquid drop with concentric nucleus. The Navier- Stokes equations were solved using the finite volume code OpenFOAM, with a Volume of Fluid method to calculate fluid volume fractions. The surface tension of the fluids represented the membranes. The effects of shear stress and elongational stress, on cells with nuclei of different sizes, representing either neutrophils (small nucleus) or lympohcytes (large nucleus), was investigated.
**Results:** Under both elongational and shear stress the cells with the smaller nuclei deformed more than those with the larger nuclei. This could help to explain why neutrophils are damaged more than lymphocytes in VADs.
**Conclusions:** A numerical model of leukocyte deformation has been created and used to investigate cell deformation under elongational and shear stresses.

## O122
## AN EXTENSIVE COMPARISON OF POWER-LAW-BASED HEMOLYSIS MODELS FOR THE BLOOD PUMP OF THE FDA'S CRITICAL PATH CHALLENGE

*Engel S, Janiga G, Thévenin D*
Laboratory of Fluid Dynamics and Technical Flows, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany

**Background:** In the development of blood-wetted devices, such as ventricular assist devices, the numerical simulation of the flow field (CFD) is a valuable tool. However, it is still highly challenging to use flow simulations to predict blood trauma, such as hemolysis. The Critical Path initiative conducted by the FDA recently has published data of experiments assessing the

flow and hemolysis within an academic blood pump. Among other aims, this initiative aims at improving simulation methods and models to characterize hemodynamic flows.
**Aim:** The FDA's published measurements of hemodynamics of an academic blood pump constitute a suitable test case to validate - or debunk - current engineering approaches used to simulate such conditions. The present study will present a benchmark of CFD-based hemolysis predictions using recent models, comparing these with the results of the FDA's experimental study.
**Methods:** The FDA pump has been operated under six test conditions. These have been modeled numerically by using the published geometry and boundary conditions. The flow simulations were performed with the CFD-solver Star-CCM+ V11 using a sliding mesh approach and RANS-turbulence modelling. The geometry has been discretized with a fully structured hexahedral mesh. The hemolysis models are implemented in Eulerian transport equations with respective source terms.
**Results:** The predicted hemolysis rates of each model differ substantially from each other. The underlying model parameters very heavily impact hemolysis predictions. Moreover, the structure of the applied models results in a high dependency on the employed discretization.
**Conclusions:** The results indicate that current models should be implemented with care, and the results must be considered with caution. A direct, absolute prediction of hemolysis still leads to a very large level of uncertainty. Moreover, depending on the model used, additional efforts are necessary to minimize numerical errors associated to discretization in CFD.

### O123
### DEVELOPMENT OF PREDICTION METHODS OF SHEAR INDUCED THROMBUS FORMATION BY CFD METHOD INCLUDING CONCENTRATION TRANSPORT AND AGGREGATION PROCESS AND BY THROMBUS VISUALIZATION METHOD

*Tamagawa M, Yi Y, Hirayama C, Sanjo Y, Nakata S*
Graduate School of Life Science and System Engineering, Kyushu Institute of Technology, Kitakyushu-shi, Japan

**Background:** To suppress the hemolysis and avoid the thrombus is very important and serious problem in developing the rotary blood pumps. In our previous studies, effects of the thrombus formation rate on wall were examined by observation of thrombus formation and CFD. And it was found that the thrombus formation rates increasing linearly with shear rates. In spite of many proposed CFD models, the proper model has not been established yet. To understand this relation in detail, it is necessary to establish the computational model of thrombus formation including concentration transport and platelet aggregation.
**Aim:** This investigation describes the hybrid method to combine concentration transport process of species by FDM and platelet aggregation by DPD.
**Methods:** Computational objects are 5 types of pipe flows through an orifice. Especially concentration of activated platelets is predicted and the deposition of activated platelets is also predicted by FDM. In our newly proposed model, dissipative particle (DPD) method is applied to express the aggregation process of platelet on the wall. In this novel model, the activation platelets turn on when shear rate is more than threshold and concentration of related species is more than other threshold. And number of aggregated and activated platelets is evaluated.
**Results:** It was found that the concentration of activated platelet is high at the front of orifice and near the reattachment point of recirculation area. By using probability of deposed platelets on the wall, the total number history of activated and aggregated platelets was obtained. The rate of aggregated platelets was compared with our previous experiments of thrombus formation rate. It was found that the predicted rate of aggregation increases with shear rate.
**Conclusions:** It is concluded that the deposited and aggregated rate of platelets on the wall depends on the shear rate.

## Session: Transplantation Related Aspects of Dialysis

### O124
### EFFECT OF DOUBLE-FILTRATION PLASMAPHERESIS FOR ANTIBODY-MEDIATED REJECTION REGARDING COAGULATION PARAMETERS AND THROMBIN GENERATION

*Malvezzi P[1], Marlu R[2], Seyve L[2], Jouve T[1], Maurizi J[1], Defendi F[3], Carron P[1], Polack B[2], Rostaing L[1]*
[1]Department of Nephrology, Dialysis, Apheresis and Transplantation, CHU Grenoble, Grenoble, France
[2]Laboratory of Hemostasis, CHU Grenoble, Grenoble, France
[3]Laboratory of Immunology, CHU Grenoble, Grenoble, France

**Background:** Donor-specific alloantibodies (DSAs) cause kidney-allograft loss (chronic antibody-mediated rejection (CAMR)). Treatment relies on blocking antibody-producing cells and removing DSAs by apheresis: e.g., double-filtration plasmapheresis (DFPP).
**Aim:** To determine the impact of DFPP (6 or 8 sessions/patient) on clotting factors and natural anticoagulants, and on thrombin generation.
**Methods:** Six CAMR kidney-transplant patients received DFPP plus rituximab therapy.
**Results:** Within the first DFPP session, mean levels of high molecular-weight factors (fibrinogen, FV, FVIII, FXI, FXIII, von Willebrand factors) decreased significantly to <50% of baseline values, whereas levels of low molecular-weight factors (<100 kDa) were not significantly modified, except for protein S. Of note, binding-protein (BP) of protein S, i.e., C4BP, was significantly decreased. Over the course of successive DFPP sessions, both high molecular-weight and lower molecular-weight proteins (<100 kD) with longer half- lives (>2 days, prothrombin and factor XII) were significantly decreased. DFPP also affected thrombin generation. After the first DFPP session, mean endogenous thrombin potential (ETP) and peak of thrombin (PH) significantly decreased when the thrombin generation assay was performed without thrombomodulin (respectively, 67 ± 4% for ETP and 74 ± 9% for PH compared to baseline). In the presence of thrombomodulin, there was no significant decrease in ETP and PH. ETP ratio (with/without thrombomodulin) significantly increased after the first DFPP session.
**Conclusions:** DFPP significantly affected some clotting factors and thrombin generation. High molecular- weight factors were most prone to being removed. DFPP also decreased thrombin generation and induced thrombomodulin resistance.

### O125
### EFFICACY AND SAFETY OF CINACALCET THERAPY FOR RENAL TRANSPLANT PATIENTS WITH SECONDARY HYPERPARATHYROIDISM - A SYSTEMATIC REVIEW AND META-ANALYSIS

*Lu Y, Zhang P, Cheng J, Chen J*
Kidney Disease Center, The First Affiliated Hospital of Zhejiang University, Wenzhou, China

**Background:** Secondary hyperparathyroidism (SHPT) is one of the complications of chronic kidney disease with increases in Ca, P and PTH as the performance, may cause bone and complications of cardiovascular system. Although renal transplant kidney function returned to normal, but CKD-MBD may continue to deteriorate after renal transplantation. Existing studies have confirmed that Cinacalcet can obviously reduce the PTH and Ca of kidney transplant recipients with SHPT, but its effect on renal function is not yet clearly.
**Aim:** To evaluate the efficacy and safety of Cinacalcet therapy for renal transplant patients with secondary hyperparathyroidism.
**Methods:** Up to December, 2016, Medline, Embase and Cochrane Library were systematically searched for observational studies and RCTs that studied with Cinacalcet therapy's effects on renal transplant patients with SHPT. 23 studies met the criterion, including 21 observational studies and 2 RCTs. The data analysis software was Review Manager 5.3.
**Results:** Totally 23 studies of 610 patients were included. Compared with pre-treatment, Cinacalcet significantly decrease patients' serum Ca (MD = 0.29 mmol/L, 95% CI = 0.26 to 0.33, P<0.00001), PTH (MD = 91.60 pg/mL, 95% CI = 66.57 to 116.62, P<0.00001), and eGFR (MD = 3.61 mL/min/1.73 m2, 95% CI = 1.57 to 5.65, P = 0.0005). Cinacalcet significantly increase patients'

serum P (MD = 0.14 mmol/L, 95% CI = 0.10 to 0.18, P<0.00001). However, no significant effects were found in serum ALP or serum Cr. Further subgroup analysis found that, when the follow-up period was shorter than 6 months, the Cinacalcet therapy had significant reduction on eGFR (MD = 2.21 mL/min/1.73 m2, 95% CI = 0.38 to 4.04), while no significant change was found when the follow-up period was longer than 6 months.
**Conclusions:** Cinacalcet has significant curative effects for renal transplant patients with SHPT, while renal function decrease in the early stage and recover later. The mechanism of Cinacalcet's effect to renal function needs further study.

**O126**
**TACROLIMUS DOSE REQUIREMENT BASED ON THE CYP3A5 GENOTYPE IN RENAL TRANSPLANT PATIENTS**
*Qu L, Xie Z, Ying M, Huang H, Jiang H, Chen J*
Kidney Disease Center, Zhejiang University, Wenzhou, China

**Background:** Tacrolimus and cyclosporine A (CsA), two immunosuppressive drugs, are widely used to protect graft function after renal transplantation.
**Aim:** The aim of the present study is to determine whether CYP3A5*A and CYP3A5*G genotype is a predictive index of tacrolimus dose requirement, and also the selection yardstick of tacrolimus or CsA treatment.
**Methods:** We tested archival peripheral blood of 218 kidney recipients for CYP3A5 genotyping with PCR- SSP. The doses and blood concentrations of tacrolimus and CsA for recipients were measured at day 7, 1st month, 3rd month, 6th month and 12th month after kidney transplantation, as well as liver and graft function. In addition, we also observed the incidences of acute rejection happening in these recipients.
**Results:** 123 patients received tacrolimus treatment and 95 patients received CsA treatment after renal transplantation. In the tacrolimus treatment group, the frequency of CYP3A5*AA, CYP3A5*AG, and CYP3A5*GG was 11/123, 47/123, 65/123 respectively. Genotype CYP3A5*GG was associated with low tacrolimus dose-adjusted concentration, showing a lower acute rejection rate compared to the CYP3A5*AA/AG group but with no significant difference (4/65 vs. 8/58, p = 0.154). The CYP3A5*GG group took shorter time to get the target therapeutic concentration and maintain a stable dose-adjusted concentration with lower tacrolimus expenses than the CYP3A5* AA/AG group. Tacrolimus dose-adjusted concentration at all these time points poses no significant effect on liver and graft function. In the CsA treatment group, the frequency of CYP3A5*AA and CYP3A5*AG was 9/95 and 34/95 respectively, including 16/43 patients switching to tacrolimus treatment after CsA treatment for several years. The frequency of CYP3A5*GG was 52/95, including 20/52 patients switching to tacrolimus treatment. There was no significant difference in the acute rejection rate between CYP3A5*AA/AG and CYP3A5*GG (10/52 vs. 6/43, P = 0.494). CYP3A5*AA/AG patients in tacrolimus treatment group occurred similar acute rejection rate with CsA treatment group (8/58 vs. 6/43. P = 0.982), and the tacrolimus treatment patients took longer time to get a stable immune situation than CsA treatment patients.
**Conclusions:** These results indicate that CYP3A5*AA/AG carriers need higher tacrolimus dose than CYP3A5*GG homozygote to achieve the target blood concentration. CYP3A5*GG carriers preferred to tacrolimus treatment and CYP3A5*AA/AG carriers preferred to CsA treatment depended on the incomes. CYP3A5 genotyping is a new approach to detecting tacrolimus dose requirement and a predictive index for the tacrolimus or CsA treatment selection in the kidney recipients.

## Session: Clinical Reports and Exercise

**O127**
**ACUTE AND LONG-TERM EFFECTS OF LVAD SUPPORT ON RIGHT VENTRICULAR FUNCTION IN CHILDREN WITH PEDIATRIC PULSATILE VENTRICULAR ASSIST DEVICES**
*Iacobelli R, Di Molfetta A, Filippellis, Toscano A, Drago F, Amodeo A*
Department of Pediatric Cardiology and Cardiac Surgery, Pediatric Hospital Bambino Gesù, Rome, Italy

**Background:** Right ventricular failure (RVF) is a significant issue when considering LVAD implantation in pediatrics.
**Aim:** The aim of this study was to evaluate the effects of LVAD on RV function in children.
**Methods:** We retrospectively reviewed clinical and echocardiographic data of children who underwent Berlin Heart EXCOR LVAD focusing on RV function before and after implantation (1, 3 and 6 months follow up).
**Results:** An isolated LVAD was used in 27 patients (pts). Median age was 11 months (IQR: 5-24 months), with a median weight of 6.3 Kg (IQR: 5-9 Kg). Median time on VAD support was 147 days (IQR: 86-210 days). 20 patients were successfully bridged to OHT (74%), 6 patients died (22%) and also1 (4%) recovered the heart function. Before LVAD implantation, 9 pts (33%) showed a right ventricular fractional area change (RVFAC) ≤30%. After implantation, mean RVFAC increased up until the 3-month follow up (43.13%, p = 0.033) and then slightly decreased. In a subgroup of 18 patients, the average strain value increased after the 1-month follow up (p = 0.022). 33% of patients developed RVF before the 1-month follow- up and 7.4% experienced RVF at the 6-month follow-up. No patient required BiVAD.
**Conclusions:** In our population, pulsatile-flow LVAD in children allows optimal RV decompression and function post-LVAD as measured by improvement in RV function at Echo particularly at 1 month and 3 month follow-up. At long-term follow up, the beneficial effects of LVAD on RV function seem to be reduced as some patients may develop signs and symptoms of late RVF despite LVAD support.

**O128**
**SHORT AND LONG TERM CHANGES IN VENTRICULAR LOADING CONDITION IN LVAD PATIENTS: PULSATILE VS CONTINUOUS FLOW LVAD**
*Di Molfetta A[1], Casadio L[2], Fresiello L[3], Iacobelli R[1], Filippelli S[1], Perri G[1,2], Ferrari G[4], Guccione P[1], Meyns B[3], Amodeo A[1]*
[1]Pediatric Cardiology and Cardiac Surgery, Pediatric Hospital Bambino Gesù, Rome, Italy
[2]Department of Cardiac Surgery, Catholic University of Rome, Rome, Italy
[3]Department of Cardiac Surgery, Catholic University of Leuven, Leuven, Belgium
[4]Institute of Clinical Physiology, Italian National Research Council, Pisa, Italy

**Background:** Heart remodeling is an important determinant of heart recovery in LVAD patients.
**Aim:** To study the evolution of ventricular loading in pulsatile and continuous flow LVAD patients (PVAD and CVAD).
**Methods:** Normalized clinical and echocardiographic data of 19 pediatric PVAD patients were retrospectively collected and compared to literature data on clinical and echocardiographic data of 35 young adult CVAD patients at the baseline and at the follow up of 1, 3 and 6 months.
**Results:** In CVAD, left ventricular end diastolic and end systolic diameters (LVEDD, LVESD) decreased progressively over time, respectively from 58,4 ± 22,8 mm to 52,7 ± 9,3 mm (9%, p = ns) and 54,3 ± 21,2 mm to 40,1 ± 13,8 mm (26,1%, p = 0,04) in six months. On the contrary, in PVAD LVEDD and LVESD decreased significantly at 1 month follow up from 46,4 ± 9,2 mm to 34,2 ± 6,6 mm (26,2%, p = 0,000001) and from 40,9 ± 10,5 mm to 29,2 ± 7,4 mm (28%, p = 0,00001), respectively but then a new enlargement of the left ventricle was observed coming almost at the same diameters measured at the baseline. In CVAD, right ventricular function and dimensions decreased progressively, while in PVAD right ventricular dimensions progressively increased and right ventricular function starts to deteriorate since the three months follow up.
**Conclusions:** At the short term follow up the left ventricular unloading is higher in PVAD than in CVAD population, on the contrary at the long term follow up the left ventricular unloading provided by the CVAD is higher than in the PVAD population. Finally, right ventricular function and dimensions are improved by CVAD, while they are worsened by PVAD.

**O129**

**DO LVADS PROVIDE SUFFICIENT CARDIAC SUPPORT DURING PHYSICAL EXERCISE WHEN DRIVEN AT CONSTANT SPEED?**

*Gross C[1,2], Marko C[3], Mikl J[4], Schlöglhofer T[1,2,5], Wiedemann D[5], Zimpfer D[2,5], Schima H[1,2,5], Moscato F[1,2]*

[1]Center for Medical Physics and Biomedical Engineering, Medical University Vienna, Vienna, Austria
[2]Ludwig-Boltzmann-Cluster for Cardiovascular Research, Vienna, Austria
[3]PVA Center for Ambulatory Rehabilitation Vienna, Vienna, Austria
[4]PVA Rehabilitation Center Felbring, Muthmannsdorf, Austria
[5]Department of Cardiac Surgery, Medical University Vienna, Austria

**Background:** Improvement in physical capacity of patients with a left ventricular assist device (LVAD) implanted remains limited.
**Aim:** Aim of this work was to investigate hemodynamics during exercise in LVAD patients using enhanced monitoring of pump data.
**Methods:** Estimated pump flow and derived parameters such as heart rate and aortic valve opening were continuously monitored from 16 patients during maximal bicycle ergometry stress-testing (n = 24), sub- maximal 6-minute walk tests (n = 16) and medical training sessions (bicycle ergometry (n = 100), walking (n = 137), strength training (n = 71) and mobilization training (n = 134). Statistical comparisons were performed by student's t-test with Bonferroni correction and a type I error of 5%.
**Results:** At a constant LVAD impeller speed, exercise responses during bicycle stress-testing showed a LVAD flow increase of 0.9 ± 0.5 L/min and increase in heartrate of 16.9 ± 12.1 bpm at a peak workload of 44.7 ± 20.7 W. Only mobilization training showed a significantly less increase in LVAD flow compared to maximal bicycle stress testing. Peak heartrate was significantly lower during strength training and mobilization training compared to bicycle stress testing. Aortic valve opening at peak exercise occurred most during 6-minute walk testing (88% of patients) followed by bicycle stress-testing (79% of patients). Furthermore multiparameter linear regression analysis identified increase in LVAD flow as the least contributing parameter to predict peak-$VO_2$ during maximum bicycle ergometry training.
**Conclusions:** With current constant-speed pump management, the pump flow increase during exercise is limited and even insensitive to exercise intensity. These findings seem thus to indicate that LVADs do not provide sufficient cardiac support during maximal physical exercise.

**O130**

**EXERCISE CAPACITY IN VAD AND HEART TRANSPLANTED PATIENTS: A COMPARATIVE STUDY**

*Fresiello L[1,2], Petit T[3], Claeys M[3], Van Cleemput J[4], Droogne W[4], Meyns B[1]*

[1]Department of Cardiac Surgery, KU Leuven, Leuven, Belgium
[2]Institute of Clinical Physiology, CNR, Pisa, Italy
[3]Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium
[4]Unit of Cardiology, University Hospitals of Leuven, Leuven, Belgium

**Background:** Ventricular assist devices (VADs) are used both as a bridge to transplantation and as a destination therapy. The current research turns towards secondary end points such as daily life activity and exercise capacity.
**Aim:** In this work we want to assess exercise capacity of patients with a VAD and compare it with patients that received heart transplantation (HTX).
**Methods:** 36 VAD patients (4 HVAD and 32 HeartMate II) and 12 HTX patients were enrolled at the University Hospitals of KU Leuven. Patients performed a spirometry test and a maximal cardiopulmonary exercise test 6 months after surgery. Patients had to cycle at 10 + 10/min watts or 20 + 20/min watts until exhaustion (defined as dyspnea or legs fatigue). Data were averaged and compared with a Student's t-test or a Mann–Whitney test.
**Results:** HTX and VAD groups do not differ in terms of age (53 ± 14 and 52 ± 15 years, p = 0.849), body mass index (27.2 ± 4.4 and 25.3 ± 3.2 kg/m2, p = 0.109) and gender (17% and 33% were females, p = 0.705). The spirometry test and the exercise test showed the following results for HTX and VAD patients: functional vital capacity 103 ± 19% and 79 ± 11% of the predicted value (p<0.001), forced expiratory volume in 1 second 91 ± 17% and 77 ± 10% of the predicted value (p = 0.004), heart rate (HR) 96 ± 11 bpm and 82 ± 14 bpm at rest (p = 0.003), HR 135 ± 21 bpm and 133 ± 25 bpm at peak exercise (corresponding to 81 ± 12% and 81 ± 14% of the predicted value, p = 0.875), peak oxygen uptake 67 ± 17% and 54 ± 13% of the predicted value (p = 0.008), ventilation over carbon dioxide slope 37.2 ± 7.0 and 41.8 ± 8.8 ml/ml (p = 0.175).
**Conclusions:** Both VAD and HTX patients show chronotropic incompetence and a reduced ventilation efficiency. But HTX patients have a better exercise capacity and lung function than VAD patients. More efforts should be conducted to improve exercise capacity in VAD patients. This work was supported by the Belgian Fund for Cardiac Surgery.

**O131**

**THE CLINICAL RESULTS, ADVERSE EVENTS, AND CHANGE OF END-ORGAN FUNCTION IN ELDERLY PATIENTS WITH HEARTMATEII LVAD - JAPANESE MULTICENTER STUDY**

*Yoshioka D[1], Toda K[1], Ono M[2], Nakatani T[3], Saiki Y[4], Shiose A[5], Matsui Y[6], Yamazaki K[7], Matsumiya G[8], Sawa Y[1]*

[1]Cardiovascular Surgery, Osaka University, Osaka, Japan
[2]Cardiovascular Surgery, Tokyo University, Tokyo, Japan
[3]Cardiovascular Surgery, National Cardiovascular Center, Osaka, Japan
[4]Cardiovascular Surgery, Tohoku University, Sendai, Japan
[5]Cardiovascular Surgery, Kyusyu University, Fukuoka, Japan
[6]Cardiovascular Surgery, Hokkaido University, Hokkaido, Japan
[7]Cardiovascular Surgery, Tokyo Women's Medical School, Tokyo, Japan
[8]Cardiovascular Surgery, Chiba University, Chiba, Japan

**Background:** Advanced age has an adverse impact on clinical results in left ventricular assist device (LVAD) patients.
**Aim:** To compared the clinical results of patients older than 60-year-old with younger patients using Japanese national database.
**Methods:** Between 2013 and 2016, 300 patients underwent HeartMateII implantation. Of these, 37 patients were older than 60-year-old at LVAD implantation, and the clinical results of these patients were compared with the other 263 patients younger than 60-year-old.
**Results:** The on-device survival was 95%, 91% in younger patients, and 85%, 75% in older patients, at 1 and 3 years, respectively (p = 0.016). However, the multivariate analysis revealed not age but C-reactive protein and blood urea nitrogen as risk factors. There was no statistical difference between the groups in incidence of various adverse events except stroke. In the propensity matching cohort, the incidence of stroke was significantly higher in older patients (p = 0.047). Although renal function improved after LVAD implantation in both groups, its improvement in older patients was transient and there was no improvement later than 3 months after LVAD implantation. Serum albumin level was significantly lower in older patients at 3, 6 months and 1 year, even after preoperative albumin level matching cohort.
**Conclusions:** Although older age was not a significant risk factor of survival after LVAD implantation as a BTT, there were significant differences in the incidence of strokes and recovery of end-organ functions after LVAD implantatio. These results may indicate patient' selection in future destination therapy in Japan become more crucial.

**O132**

**VIENNESE EXPERIENCE WITH THE HEARTMATE III LEFT VENTRICULAR ASSIST DEVICE**

*Dimitrov K[1], Riebandt J[1], Wiedemann D[1], Moayedifar R[1], Angleitner P[1], Schlöglhofer T[1,2], Schima H[1,2], Laufer G[1], Gross C[2], Zimpfer D[1]*

[1]Department of Surgery, Division of Cardiac Surgery, Medical University of Vienna, Vienna, Austria
[2]Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria

**Background:** HeartMate III is a newer generation fully magnetically levitated continuoaus flow left ventricular assist device (LVAD) that is commercially available in Europe since 2014.
**Aim:** The aim of this study is to summarize our institutional experience with the HeartMate III LVAD as one of the pioneering centers using this novel pump.
**Methods:** Data from patients that received the HeartMate III LVAD at the Medical University of Vienna and had completed 30 day follow up was retrospectively analyzed.

**Results:** Thirty-nine patients were included in the study. Mean age at LVAD implant was 62.7 ± 9.3 (42-76) years, 89.7% were male and 52.5% were in interagency registry for mechanically assisted circulatory support (INTERMACS) level 4. Indication for LVAD implant was destination therapy in 35% and bridge to decision in the rest of the patients. Simultaneous valve procedures were performed in 32.5% and 22.5% received temporary extracorporeal circulatory support as a right ventricular assist device. Median LVAD support was 332 (164; 504) days. Thirty-day mortality was 5% and in-hospital mortality was 15%. One patient (2.6%) suffered pump thrombosis, but there was 0% clinically relevant hemolysis. Gastrointestinal bleeding occurred in 5 patients (12,8%) with a rate of 0,222 events per patient year. Stroke occurred in 13 patients (33.3%) and was associated with infection in 8 patients (20.5%).
**Conclusions:** Early experience with the HeartMate III LVAD shows survival outcomes that are similar to allready published data and are consistent with outcomes characteristic modern generations implantable LVADs. This novel technology seems to afford less pump thrombosis than previous generations commercially available devices and lack of clinically significant hemolysis. However, other complications related to LVAD therapy such as stroke and infection are common and remain a considerable burden.

## Session: Computational Fluid Dynamics II

### O133
### FLUID-STRUCTURE INTERACTION (FSI) HEMODYNAMIC OPTIMIZATION OF CORWAVE ENDOVASCULAR CARDIAC ASSIST DEVICE

*Cornat F, Monticone P, Moniotte T*
R&D, CorWave, Paris, France

**Background:** Heart Failure is the first cause of hospitalization for people above 65 and is routinely treated using cardiac assist devices that imply a heavy surgery and other important drawbacks for patients. To minimize it, CorWave is developing a unique endovascular partial-support cardiac pump implantable with mini-invasive surgery. A magnetic actuator is imposing an alternative linear displacement to a membrane fin that deforming in a wave motion displace the blood pumping it through the outlet. However, the small size of the device might limit its hydrodynamic performances required to ensure a pulsatile support.
**Aim:** In this work, we present the results of design optimization to improve hydraulic performances using FSI simulations and experimental in vitro validations.
**Methods:** A fully parametrized 2D-model of the pump is developed providing the ability to systematically evaluate the effect of each parameter on the hemodynamic. We focused on the inlet dimensions where the flow is separated and the magnet oscillating but also the walls dimensions. The finite element code of COMSOL 5.1 is used to evaluate the mechanical variables within the membrane and the flow as the magnet is moved by applying an imposed displacement. The FSI is solved coupling time-dependent Navier-Stokes equations for the fluid and a hyperelastic model for the membrane. Finally, a merit function is defined to optimize hemodynamic performances. Also, a test bench is created to validate experimentally the design improvements: the pump is tested in a circulatory mock-up loop where pressure and flow are monitored in dynamics conditions.
**Results:** The simulations allowed to spot sources of pressure and velocity losses and improve the design. For example, the distance between the membrane and wall showed a huge impact on the pressure which was drastically improved from 40 to 220 mmHg.
**Conclusions:** Mechanical evaluation of the interplay between membrane and fluid is an important consideration in the process of the pump optimization. Ultimately this method will be updated to include hemocompatibility among the optimization criteria.

### O134
### ROTORDYNAMIC ANALYSIS OF AN ARTIFICIAL AXIAL-FLOW CARDIAC-PUMP USING BOND-GRAPH METHODOLOGY

*Kumar J[1], Richert H[2], Wurm F[1]*
[1]Institute of Turbomachinery, University of Rostock, Rostock, Germany
[2]R&D Magnetic Engineering, Berlin Heart GmbH, Berlin, Germany

**Background:** The design targets of a cardiac-pump are specified as limited blood damage, higher efficiency and low acoustic radiations. The axial-flow pump efficiency can be increased by reducing clearance between rotating and stationary parts. As a consequence hemolysis is utmost high at these gaps. The eccentricity, gyroscopic effect and CFD excitation forces add more instability and increase hemolysis. High synchronous vibration and sub-synchronous rotor instability are common issues in rotordynamics.
Thus, it is important to estimate transient dynamic response to design the cardiac pumps for their smooth performance.
**Aim:** An integrated model is required for transient rotordynamic analysis of the cardiac-pumps to estimate orbital amplitude accurately for full range of operational speed. The model should be generic to perform parametric study for optimization of the pump design.
**Methods:** A detailed bond-graph model is created for each mechanical components (journal bearing, shaft, axial impeller, magnetic bearing etc.) and they are connected using causality to create an integrated model of a system. The gyroscopic effect and imbalance are incorporated in the model. CFD loads are estimated based on URANS simulations of a cardiac pump using CFD tools.
**Results:** A model is created for an axial-flow pump supported by a different combination of bearing technologies. It is observed that at higher speed, all mass centers are rotating in phase, even for out of phase eccentricities. No tilting vibration is observed for full range of operational speeds. It is shown that journal-bearing is significantly reducing the overall orbital amplitude.
**Conclusions:** Bond-graph methodology is able to model rotordynamics accurately. This paper presents the transient dynamic behaviors of an artificial axial-flow pump. It is observed that viscosity and damping coefficient are playing crucial role for vibration amplitudes. The clearance between rotating and stationary parts must be accurately estimated for less blood damage and high efficiency of a cardiac-pump.

### O135
### A NOVEL GENERIC MODEL FOR THE INVESTIGATION OF INTRAVENTRICULAR FLOW PATTERNS IN INDIVIDUAL HEARTS

*Hugenroth K[1], Sonntag S[2], Neidlin M[1], Schmitz-Rode T[3], Steinseifer U[1], Kaufmann T[1,2]*
[1]Cardiovascular Engineering, Institute of Applied Medical Engineering, Aachen, Germany
[2]enmodes GmbH, Aachen, Germany
[3]Institute of Applied Medical Engineering, Aachen, Germany

**Background:** Abnormal flow inside the left ventricle is associated with heart dysfunction, resulting in a higher risk for clotting and poor outcomes in device therapy. Understanding the complex flow patterns inside the ventricle under physiological and pathological conditions may improve therapies and support device development.
**Aim:** The goal of this work is to establish a generic model of the left ventricle adjustable to individual patient conditions. It is used to analyze flow features during physiological and heart failure conditions using fluid- structure interaction simulations.
**Methods:** The geometric layout of the model is based on clinical studies of left ventricular and mitral dimensions. Key indicators for left ventricular condition, such as volume and ejection fraction, are parameterized. With this, ventricular geometries in different heart failure stages were generated. The movements of ventricle wall and mitral leaflets were derived from 3D and 4D echocardiographic data and coupled to flow simulations to create a fluid-structure interaction framework. Flow patterns were analyzed and compared to published patient data.
**Results:** Ventricular wall displacement and mitral valve movement correspond to clinical values. The model reproduces the commonly known aspects of intraventricular flow fields. The flow exhibits a vortex ring descending from the mitral valve at early diastole and a central vortex at end-diastole. The pattern is disturbed in the pathologically dilated hearts, resulting in a decrease in intraventricular kinetic energy of up to 60% and reduced washout with a potential risk for thrombosis.

**Conclusions:** Overall, the developed generic model allows the investigation of intraventricular hemodynamics in individual ventricles. The model can be used to analyze effects on the flow field caused by diseases, iatrogenic flow changes or progressive remodeling towards cardiac dysfunction, posing a great platform for novel device developments.

**O136**

**CFD MODELING OF IABP-INDUCED ABDOMINAL OCCLUSIONS AND STATISTICAL ANALYSIS OF EFFECTS ON HEMODYNAMICS**

*Caruso M, Fragomeni G*
Medical and Surgical Sciences Department, Magna Grecia University, Catanzaro, Italy

**Background:** Intra-aortic balloon pump (IABP) is a therapy used as circulatory support in case of cardiovascular diseases. Technical guidelines indicate that the balloon must be chosen according to the patient's height and the tip must be positioned 2 or 3 cm from left subclavian artery (LSA) emergency.
Some studies have highlighted different clinical complications if these recommendations are followed.
**Aim:** A statistical analysis of computational data was performed in order to investigate the effects of different IABP-induced abdominal occlusions on hemodynamics in aorta.
**Methods:** Three patients with similar height were chosen and their aorta models were reconstructed starting from CT images. Two possible sizes (25 and 34 cc) (2 and 3 cm from LSA) of LINEAR 7.5 Fr were considered, creating four abdominal occlusions cases (I: 25 cc and 2 cm; II: 34 cc and 2 cm; III: 25 cc and 3 cm; IV: 34 cc and 3 cm). IAB inflation/deflation and two locations behavior was numerically reproduced. The same boundary conditions were applied to all simulations in order to analyze the flow changes only due to the occlusions.
**Results:** For the three patients, a hypoperfusion of visceral arteries and of legs happen when the abdominal occlusion increases with balloon counterpulsation. At the same time, an increase of flow occurs in the head and in the arms due to the presence of IAB in the descending aorta. Considering the mean values, the flow reduction was of 2.7% (I vs II), 5.4% (I vs III) and 3.2% (I vs IV) in the abdominal vessels and of 3.5% (I vs II), 16.7% (I vs III) and 20.8% (I vs IV) in the iliac arteries. Comparing case I and IV, a cerebral hyperperfusion was obtained, with a mean increase of blood flow of 8.5%. Moreover, the results indicate that the abdominal flow is similar in case II and IV (mean values of 24.0% vs 23.9% respect to the cardiac output).
**Conclusions:** The obtained results are in agreement with the literature, highlighting as balloon positioning and size have a key role in the induced abdominal occlusion and, so, in clinical complications and patient's outcome.

**O137**

**EFFECT OF INFLOW CANNULAS SIDE-HOLE NUMBER ON DRAINAGE FLOW CHARACTERISTICS: FLOW DYNAMIC ANALYSIS USING NUMERICAL SIMULATION**

*Goto T[1], Tanabe T[2], Inamura T[2], Shirota M[2], Fumoto K[2], Saito Y[3], Fukuda W[3], Fukuda I[3], Daitoku K[3], Minakawa M[3]*
[1]Clinical Engineer, Hirosaki University School of Medicine and Hospital, Hirosaki, Japan
[2]Intelligent Machines and System Engineering, Faculty of Science and Technology, Hirosaki University, Hirosaki, Japan
[3]Thoracic and Cardiovascular Surgery, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

**Background:** Venous drainage in cardiopulmonary bypass is a very important factor for safe cardiac surgery. While there are various kinds of commercially available venous cannulas with diverse shapes, it is not yet known what type of cannula is optimal for effective venous drainage.
**Aim:** In the present study, we evaluated the effect of side-hole number under the fixed total area and venous drainage flow to elucidate the effect of increasing side-hole numbers.
**Methods:** Computed simulation of venous drainage was performed. Cannulas were divided into six models: an end-hole model (EH) and models containing four (4SH), six (6SH), eight (8SH), 10 (10SH) or 12 side-holes (12SH). Total orifice area of side-holes was fixed to 120 $mm^2$ on each side-hole cannula. End- hole orifice area was 36.3 $mm^2$. The total area of the side-holes was kept constant when the number of side-holes was increased.
**Results:** Mean venous drainage flow rate of the EH, 4SH, 6SH, 8SH, 10SH and 12SH was 2.57, 2.52, 2.51, 2.50, 2.49, 2.41 L/min, respectively. The mean flow rate decreased in accordance with increased number of side-holes. The wall shear stress area appeared on the most proximal side-hole area, the maximal wall shear stress magnitude was 64.8 Pa.
**Conclusions:** We speculate that flow separation at the proximal of the side-holes induces stagnation of flow and induces energy loss. This flow separation may hamper the main stream from the end-hole inlet, which is most effective with low shear stress. The EH cannula was associated with the best flow rate and flow profile. However, an end-hole cannula may fail secondary to obliteration of the single end-hole. Therefore, the 4SH may be most advantageous for minimal reduction of flow loss combined with favorable safety.

**O138**

**MODELING MATURATION OF PATIENT-SPECIFIC ARTERIOVENOUS FISTULA'S USING COMPUTATIONAL FLUID DYNAMICS**

*Colley E[1], Carroll J[1], Thomas S[2,3], Barber T[1]*
[1]Mechanical and Manufacturing Engineering, University of New South Wales, Sydney, Australia
[2]Department of Vascular Surgery, Prince of Wales Hospital, Sydney, Australia
[3]School of Medicine, University of New South Wales, Sydney, Australia

**Background:** After an Arteriovenous Fistula (AVF) creation, the vein undergoes rapid remodeling and then eventually matures. Current research has been limited in this area due to traditional imaging modalities such as CTA and MRA required for computational fluid dynamics (CFD) being costly and invasive. There is a need to understand what happens in this time period so that a higher patency can be achieved for patients with end-stage kidney disease on dialysis.
**Aim:** We propose to investigate the weekly vascular changes due to remodeling after an arteriovenous fistula creation using 3D freehand ultrasound to obtain the geometry and computational fluid dynamics to study the flow. We will visually demonstrate and compare two cases: Successful maturation and maturation needing intervention.
**Methods:** We have built a 3D freehand ultrasound system which optically tracks the vascular probe as we sweep down the arm and spatially aligns each 2D B-mode image, creating a volume similar to a DICOM stack. The vasculature is segmented from the volume and the hemodynamics are analyzed using CFD. We scan each patient pre-creation and then at weekly intervals for 8 weeks.
**Results:** Case 1 (successful maturation): the vein dilated to at least three times in size immediately after creation, and then steadily increased at a small rate until matured. Case 2 (intervention needed): the vein dilated until 2 weeks where a slight narrowing occurred in the swing segment. The vein was fully occluded by the following week and a juxta-anastomotic stent was inserted. We compare the full flow analysis of each case using CFD, showing streamlines and wall-shear stress and their affects associated to the weekly changes observed.
**Conclusions:** We are able to successfully monitor and analyze the maturation period of an AVF using freehand 3D ultrasound, and show the timeline of successful remodeling, and additionally, the onset of stenosis leading to total occlusion.

## Session: Tissue Engineering and Regenerative Medicine III

**O139**

**FABRICATION OF PROANTHOCYANIDIN CROSS-LINKED CHITOSAN-GELATIN HYDROGEL SCAFFOLDS FOR TISSUE ENGINEERING**

*Encerrado Flores A, Scotchford C, Campbell Ritchie A*
Mechanical, Materials and Manufacturing Engineering, University of Nottingham, Nottingham, UK

**Background:** Studies have shown that the behaviour of anchorage dependent cells is influenced by the substrate stiffness on which they rest. Mechanical signals are as fundamental to gene expression and cell response as chemical signals. Hydrogel properties can be modified to match the requirements of the tissue engineering application.
**Aim:** This project investigates the biocompatibility and mechanical properties of proanthocyanidin (PA) cross-linked gelatin-chitosan hydrogels and examines the response of cells grown on these hydrogels.
**Methods:** Chitosan and Gelatin solutions were prepared by solution in acetic acid. These solutions were mixed then neutralised with NaOH. The mixture was then cross-linked by gradual addition of PA. Gels were prepared in petri dishes and cooled overnight at 4°C. Cast hydrogels were washed with distilled water then neutralized before rinsing with PBS. Prepared Gels were sterilized by UV radiation. 24 hrs prior to use gels were protein conditioned in fresh media. 3T3 fibroblasts, MG63 Osteosarcoma and Breast Adenocarcinoma (MDA-MB) were seeded onto the hydrogels. The samples were incubated for 2 hours to allow cell attachment. Media was changed every 48 h.
**Results:** Cell growth on hydrogels showed proliferation comparable to controls on tissue culture plates. By day 7 cells had covered the total sample surface for must formulations, Morphological evaluation of the cell cultures revealed no discernible difference between control and test groups. By changing the ratios of cross- linker, chitosan and gelatin, it was possible to deliver hybrid hydrogels with suitable mechanical properties, demonstrating the superior biomimetic properties of the cross-linked blend compared with uncross linked hydrogels.
**Conclusions:** Cells proliferated and migrated very favourably on the cross-linked hydrogels. The cytocompatibility implies that PA cross-linked hydrogels are suitable substrates for tissue engineering of connective tissues. The results also show that PA is an effective, non-toxic cross-linking agent.

## O140
## FABRICATION OF POROUS POLY(TRIMETHYLENE CARBONATE) MEMBRANES FOR LUNGS-ON-CHIPS

*Pasman T[1], Grijpma D[1,2], Stamatialis D[1], Poot A[1]*
[1]Biomaterials Science and Technology, University of Twente, Twente, The Netherlands
[2]Biomedical Engineering, University Medical Centre Groningen, Groningen, The Netherlands

**Background:** In vitro models for lung research greatly improved with lung-on-a-chip technology. In general, in these chips, lung epithelial and endothelial cells are grown on opposite sides of a flat membrane, often made of poly(dimethyl siloxane) (PDMS), which provides support and nutrient transport. However, unlike the membranes, alveoli are three-dimensional structures.
**Aim:** Membranes in lungs-on-chips can be improved. In this study, poly(trimethylene carbonate) (PTMC), a more biocompatible polymer was processed with evaporation-induced phase separation (EIPS) to prepare porous 3D membranes.
**Methods:** Membrane preparation: PTMC was dissolved in chloroform. Ethanol, propanol, butanol or hexanol was added as a non-solvent for PTMC. Poly(ethylene oxide) (PEO) was included as a pore stabilizer. Lastly, crosslinking agents were added. The polymer solution was cast on a silicon wafer without or with microstructures. Phase separation was initiated by evaporation. The membranes were cross-linked with UV-light, washed with demi-water and dried. Gel content: Samples were submerged in chloroform for 2 days. Gel content is defined as the percentage of remaining dry weight after chloroform compared to the original weight. Permeability: Ultrapure water was introduced to the membranes at different water pressures.
**Results:** Including more alcohol or a larger alcohol increased the pore size and permeability. Since there is more alcohol present, it can coalesce more during phase separation. PEO was essential to make membranes porous, suggesting a role as pore stabilizer. Gel contents of the membranes were above 85% in all conditions. EIPS was able to accurately replicate microstructures with similar dimensions as those of the mould.
**Conclusions:** EIPS yields membranes with tuneable porosity and permeability. Microstructures can also be incorporated. These membranes can serve as adaptable environments for organs-on-chips.
**Acknowledgments:** The Lung Foundation Netherlands is gratefully acknowledged for financial support (project 6.1.14.010).

## O141
## RAPAMYCIN INHIBITS EPITHELIAL-TO-MESENCHYMAL TRANSITION OF PERITONEAL MESOTHELIUM CELLS THROUGH REGULATION OF RHOGTPASES

*Shilong X*
Kidney Center, The First Affiliated Hospital of Zhejiang University, Wenzhou, China

**Background:** Long-term peritoneal dialysis patients often develop progressive peritoneal fibrosis. EMT of peritoneal mesothelial cells (MC) is a key process of peritoneal fibrosis. The mTOR inhibitor rapamycin has been previously shown to inhibit the EMT of peritoneal MCs and preventing peritoneal fibrosis.
**Aim:** The purpose of this study was to investigate the undefined molecular mechanisms by which rapamycin inhibit EMT of peritoneal MCs.
**Methods:** In vivo, a long-term 4.25% glucose dialysis solution infusion PD model was used. The administration of rapamycin was received from wk 4 to 6 daily intragastrically. The peritoneal function was evaluated and the peritoneal tissues were performed to observe the pathological changes and the expression levels of α-SMA and TGF-β1. In vitro, RPMCs were treated with high glucose (30, 60, 120 mM) to induce EMT, and/or rapamycin (10, 100 nM) for indicated time. The expression of EMT markers and the cell motility was examined. The activation of PI3K-Akt-mTOR pathway and RhoGTPases were then examined. Furthermore, the cytoskeletal rearrangement was examined by immunofluorescence staining.
**Results:** In vivo, the HG group showed decreased ultrafiltration volume and obvious fibroproliferative response, with markedly increased peritoneal thickness, as well as higher expression of α-SMA and TGF-β1. Rapamycin significantly ameliorated those pathological changes in a dosage-dependent manner. In vitro, rapamycin significantly inhibited HG-induced EMT, which manifests as increased the expression of α - SMA, fibronectin and collagen I, decreased expression of E-cadherin and increased mobility. HG increased the phosphorylation of PI3K, Akt and mTOR. Importantly, rapamycin inhibits the RhoA, Rac1 and Cdc42 activated by HG. Moreover, rapamycin repaired the pattern of F-actin distribution induced by HG, reducing the formation of stress fiber, focal adhesion, lamellipodia and filopodia.
**Conclusions:** High glucose activates the PI3K-Akt-mTOR pathway and induces EMT of peritoneal MCs and peritoneal fibrosis. Rapamycin shows an obvious protective effect on the process, by inhibiting the activation of RhoGTPases.

## O142
## DECELLULARIZED LIVER EXTRACELLULAR MATRIX GEL PROMOTES RESOLUTION OF LIVER FIBROSIS IN MICE

*Hussein K[1-4], Park K[1-4], Lee Y[1,4], Woo H[1,3,5]*
[1]Stem Cell Institute, Kangwon National University, Chuncheon, Gangwon, Republic of Korea
[2]Research Institute for Veterinary Science, College of Veterinary Medicine, Seoul National University, Seoul, Republic of Korea
[3]College of Veterinary Medicine, Kangwon National University, Chuncheon, Gangwon, Republic of Korea
[4]Adult Stem Cell Research Center, College of Veterinary Medicine, Seoul National University, Seoul, Republic of Korea
[5]Renal Division, Brigham and Women's Hospital, Harvard Medical School, Harvard Stem Cell Institute, Boston, USA

**Background:** Liver fibrosis is the excessive accumulation of extracellular matrix (ECM) proteins that distorts the hepatic architecture. Advanced fibrosis results in cirrhosis and liver failure that often requires liver transplantation. Decellularized liver tissue contains different structural proteins with growth factors that mimic the natural hepatic environment. We hypothesize that decellularized ECM extract can replace the necrotic hepatocytes and damaged ECM.
**Aim:** To develop antifibrotic therapy for resolution the liver fibrosis in thioacetamide-induced hepatic fibrosis in mice.
**Methods:** Mouse liver was decellularized and processed to form a hepatic matrix extract. We tested the ability of the matrix to enhance the migration of hepatocytes and endothelial cells. Then, the matrix gel was injected into liver parenchyma in mouse after induction of liver fibrosis using thioacetamide.

**Results:** The resulting liver ECM maintained a complex composition, including glycosaminoglycan, collagen, elastin and growth factors content. Hepatocytes and endothelial cells were shown to migrate towards the liver matrix in vitro. The matrix was delivered successfully in a minimally invasive procedure. The results of in vivo tests showed that the matrix gel was able to enhance the neovascularization and cell migration toward the fibrotic regions.
**Conclusions:** We have demonstrated that liver matrix gel could be utilized as an injectable scaffold for liver tissue engineering to promote neovascularization and reduce the fibrosis degree.
**Acknowledgments:** This work was carried out with the support of "Cooperative Research Program for Agriculture Science & Technology Development (Project No. PJ0110022015)", Rural Development Administration, Korea.

**O143**
**TOWARDS A FULLY IMPLANTABLE AUTONOMOUS ARTIFICIAL PANCREAS**
*Iacovacci V, Ricotti L, Tamaddon I, Tortora G, Perri C, Dario P, Menciassi A*
The BioRobotics Institute, Scuola Superiore Sant'Anna, Pisa, Italy

**Background:** Typical Type 1 diabetes therapy implies daily fingerpricks and insulin injections. This approach fails in satisfactorily controlling blood glucose levels and strongly affects patients' life quality. Artificial Pancreas (AP) represents a technological solution combining a sensor for continuous glucose monitoring and an insulin pump, connected through a closed-loop controller. Despite recent advancements, current AP (mainly portable ones) still have some limitations.
**Aim:** To demonstrate the feasibility of a fully implantable long-term autonomous AP based on a non- invasive insulin refilling and battery recharging strategy and exploiting the intraperitoneal supply route to enable a more physiological insulin profile.
**Methods:** The proposed device is conceived to be implanted close to an intestine loop. This enables to implement a non-invasive refilling procedure based on sensorized ingestible insulin capsules. These can go through the gastrointestinal tract, where they are revealed and reversibly captured by the implanted AP. The insulin can be thus transferred to the device reservoir. The AP prototype was based on mechatronic components enabling capsule docking, insulin transfer to the reservoir and intraperitoneal microinjection. A variable volume Nylon reservoir was fabricated to guarantee insulin stability. Long-term powering can be guaranteed by embedded batteries, wirelessly rechargeable, through non-radiative energy transfer.
**Results:** A docking mechanism based on magnetic switchable device (MSD) was designed, developed and tested. Two under-actuated mechanisms each including a stepper motor and a train of gears were embedded in the system for the activation of the MSD/capsule punching and the suction/injection system, respectively. The Nylon reservoir limited insulin aggregation for at least two weeks. A 4 coils-based wireless recharging system was designed and preliminarily tested.
**Conclusions:** The authors demonstrated the feasibility of a fully implantable autonomous AP, guaranteeing an intraperitoneal insulin supply. Results are encouraging in view of in vivo translation.

## Session: Uremic Toxins II

**O144**
**EXPLORING PROTEIN BINDING OF DIFFERENT URAEMIC TOXINS**
*Deltombe O[1], de Loor H[2], Glorieux G[1], Dhondt A[1], Van Biesen W[1], Meijers B[2], Eloot S[1]*
[1]Renal Division, Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium
[2]Department of Nephrology, University Hospitals Leuven, Leuven, Belgium

**Background:** Protein-bound uremic toxins (PBUTs) remain an intriguing group as their removal during dialysis is still limited. Unfortunately, little is known about potential differences in binding characteristics in patients with chronic kidney disease versus healthy controls. The question arises whether this difference is attributed to (1) elevated levels of competing uremic toxins, and/or (2) post-translational modifications (PTMs) of albumin. In most binding studies, binding characteristics of PBUTs are described without reaching saturation of binding sites and/or in the presence of commercial human serum albumin, lacking the uremic characteristics.
**Aim:** Our goal was to gain more insight into the protein binding of PBUTs in serum from hemodialysis (HD) patients and healthy controls.
**Methods:** We evaluated the binding characteristics of hippuric acid (HA), indole-3-acetic acid (IAA), indoxyl sulphate (IS), and p-cresylsulphate (pCS) to human albumin by deriving a binding curve in three types of pools: 1) serum from healthy controls (healthy serum), 2) blank serum from HD patients (blank HD serum; i.e. cleared from uraemic toxins), and 3) non-treated serum from HD patients (HD serum). Additionally, the mutual binding competition of these uraemic toxins was studied in pairs. The percentage protein binding (%PB) of each PBUT was calculated from the measured free and total PBUT concentrations.
**Results:** For all four compounds, the binding capacity in healthy serum was higher than in blank HD serum, which was comparable to non-treated HD serum, except for HA. Competition experiments revealed that at high uraemic concentrations, mutual competition was observed for the strongly bound PBUTs IS and pCS. The%PB of the weakly bound HA and IAA was lower (trend) only when added to blank HD serum already spiked with the strongly bound IS or pCS.
**Conclusions:** We conclude that competitive binding is only relevant for the strongly bound PBUTs at high uraemic concentrations and at least part of the impact on%PB must be attributed to PTMs of albumin.

**O145**
**MODELLING UREMIC TOXICITY: FURTHER STEPS TOWARDS A PRECISE IN VITRO DETECTION OF TOXIC EFFECTS CAUSED BY UREMIC RETENTION SOLUTES**
*Vollmer T[1], Glorieux G[2], Jankowski V[3], Jankowski J[3], Stegmayr B[1]*
[1]Department of Public Health and Clinical Medicine, Umea University, Umea, Sweden
[2]Department of Internal Medicine, University of Ghent, Ghent, Belgium
[3]Institute for Cardiovascular Research, RWTH Aachen University, Aachen, Germany

**Background:** Uremic substances in CKD alter cellular integrity and function. We developed a feasible in vitro method that uses human spermatozoa to predict uremic toxicity. Defining exact functional characteristics of the primary cells is crucial to unravel the influence of retained substances.
**Aim:** We show how decay of function over time can be discriminated from toxic effect. We give insight about the usage of a uremic toxin mix (UTM) that imitates uremic conditions. We aimed to find out if specific portions of ultrafiltrate gained from dialysate influences cell function.
**Methods:** A microscopic counting method estimated motility. Staining via Eosin and Nigrosin determined viability. UTM contained uric acid (147 mg/ml), xanthine (3.44 mg/ml), uridine (32.6 µg/ml) and uracil (0.45 µg/ml). Ultrafiltrate was separated via elution into 6 fractions from most hydrophobic (1) to most hydrophilic (6). Linear regression, correlation and Mann Whitney testing were used.
**Results:** A steady decline (-0,28×) of motile function was observed (60 min: 89,3% ± 8,8%; 90 min: 80,7% ± 11,8; 120 min: 72,2% ± 14,2; 180 min: 55,0% ± 23,7%). Viability at 300 minutes correlates to motility at 180 minutes (spearman ro = 0.83, p = 0.042). UTM causes an immediate arrest and long-term decrease of function in 1:1 (p = 0,003) and even higher 1:8 dilution (p = 0,009). UTM also diminishes cell viability (p = 0,024). Solely hydrophobic fractions 1-5 (p≤0,05), but not the most hydrophilic fraction 6 elicits toxicity (p>0,9).
**Conclusions:** In this study we define ways to mimic uremia in vitro. We charatcterize physiological decline of function to detect changes induced by substances as outliers from the non-toxic curve. The introduced UTM and the toxic effect of the more hydrophobic portions underline the sensitivity of this model and implicate clinical relevance. Single substances can easily be applied to this system.

**O146**

**NOT CREATININE BUT PROTEIN-BOUND URAEMIC TOXINS ARE PREDOMINANT IN THE PREDICTION OF QOL IN CHILDREN WITH CKD**

*Snauwaert E[1], De Bruyne E[1], Van Herzeele C[1], Raes A[1], Van Biesen W[1], Glorieux G[1], Van Hoeck K[2], Roels S[3], Vande Walle J[1], Eloot S[1]*
[1]Ghent University Hospital, Ghent, Belgium
[2]Antwerp University Hospital, Antwerp, Belgium
[3]Ghent University, Ghent, Belgium

**Background:** In children with chronic kidney disease (CKD), uraemic toxins accumulate while poorer quality of life (QoL) has been reported.
**Aim:** We explored the associations between concentrations of different uraemic toxins and QoL.
**Methods:** In 23 children (11.0[6.9;14.6]years, 61% boys) with non-dialysis CKD stage1-5, plasma concentrations of small solutes (asymmetric & symmetric dimethyl arginine, creatinine), middle molecules (β2microglobuline, complement factor D), and protein-bound solutes [p-cresylglucuronide, hippuric acid (HA), indole acetic acid (IAA), indoxyl sulfate, p-cresylsulfate, and 3-carboxy-4-methyl-5-propyl-furanpropionic acid (CMPF)] were measured. Their parents were asked to fill in the general (PedsQLTM 4.0 Generic Core: total score, physical & education subscale) and disease-specific QoL questionnaire (PedsQLTM End Stage Renal Disease (ESRD): disease & fatigue subscale). Lasso regression was used as explorative method to select a set of predictive uraemic toxins (when β≠0) in models for the PedsQL questionnaires.
**Results:** The mean estimated GFR was 50.4[31.2;74.5]mL/min/1.73 m². CMPF was found to predict total PedsQL (β = -0.34) and physical PedsQL subscale score (β = -1.19). Besides CMPF, IAA was predominant in the prediction of total PedsQL and physical PedsQL subscale score(respectively β = -0.84 and β = -1.26); and HA in the education PesdsQL subscale (β = -0.31). The disease subscale of the PedsQL ESRD questionnaire was predominantly predicted by HA (β = -1.18) and IAA (β = -2.30). Using this model, creatinine was for none of the questionnaires selected as a possible predictor.
**Conclusions:** This model selected CMPF, IAA and HA as promising predictors for the hard end-outcome QoL in children with CKD. Moreover, creatinine was not selected as a possible predictor for any of the QoL measures. A more extensive longitudinal study is necessary to strengthen our findings about the impact of uraemic toxins on the QoL in children with CKD.

**O147**

**ALKALINE PHOSPHATASE AND COMBINED ALKALINE PHOSPHATASE AND IPTH INFLUENCES CLINICAL OUTCOME IN PERITONEAL DIALYSIS PATIENTS**

*Chen Z[1], Zhang X[1], Han F[1], Xie X[1], Qureshi A[2], Lindholm B[2], Chen J[1]*
[1]Kidney Disease Center, The First Affiliated Hospital College of Medicine, Zhejiang University, Wenzhou, China
[2]Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet, Solna, Sweden

**Background:** Alkaline phosphatase (ALP) is usually used as a biomarker to monitor the chronic kidney disease-mineral bone disorder (CKD-MBD) in CKD patients. With regard to PTH, high PTH levels were also reported to be related to mortality in CKD patients.
**Aim:** We conducted this longitudinal cohort study to evaluate the interaction of PTH and ALP, and to evaluate the associations between ALP and PTH with all-cause and cardiovascular mortality in a large contemporary cohort of peritoneal dialysis patients.
**Methods:** In 1276 PD patients baseline serum ALP values and ALP values around 3, 6, 12 and 24 months after initiation of PD were enrolled. Demographic and metabolic measurements potentially linked to CKD- MBD were also analysed. The association of total serum ALP levels with all-cause and cardiovascular mortality was assessed using multivariable-adjusted Cox models. For ALP and ALP-average, their predictive power, represented by area under the curve (AUC), was assessed by ROC analysis.
**Results:** Patients with high tertile of ALP were older and had higher serum albumin, ALT, AST, total bilirubin, iPTH and lower levels of uric acid and calcium. The CVD mortality rate was significantly higher among patients with high ALP tertile than with middle + low ALP tertile. After full adjustment, the highest alkaline phosphatase quartile was significantly associated with higher hazard ratio for all-cause mortality and cardiovascular mortality. For baseline ALP and time-averaged ALP, their predictive power (AUC), high ALP associated with higher cardiovascular and all-cause mortality. In multivariate Cox analysis, the interaction of the combination of high ALP and low iPTH was independently associated with all-cause and cardiovascular mortality.
**Conclusions:** Elevated ALP levels and combined ALP and iPTH are independent risk factors for all cause mortality and cardiovascular mortality in PD patients.

**O148**

**CLINICAL INVESTIGATION OF 120 PERITONEAL DIALYSIS PATIENTS COMBINED WITH EXTRAOSSEOUS CALCIFICATION**

*Wang S, Chen Z, Zhang X, Yin X, Chen J*
Kidney Disease Center, The First affiliated Hospital of Zhejiang University, Wenzhou, China

**Background:** The extraosseous calcification is a kind of severe chronic complication.
**Aim:** To investigate the extraosseous calcification of peritoneal dialysis (PD) patients.
**Methods:** in 1243 PD patients followed up more then 12 months. Demographic and metabolic measurements were enrolled. Calcification of PD patients was assessed by X-ray.
**Results:** 120 (69 males and 51 females, age 63.24 ± 12.18 (29-87) years) of 1243 (9.65%) PD patients underwent extraskeletal calcification. Among them, 38 (31.67%) were diabetic nephropathy, 21 (17.5%) were hypertensive nephropathy, 98 cases (81.67%) had atherosclerosis. 21 cases of them had valvular calcification; 99 cases of them had coronary and/or aortic calcification. 30 out of 120 patients were found extraosseous calcification before dialysis, and, 90 of them were found calcification between 5 and 158 months after dialysis. The serum Phosphate levels were higher in 46 patients (38.33%) (2.17 ± 0.37 (1.81-3.38) mmol/L), and the serum calcium levels were higher (2.75 ± 0.22 (2.61-3.47) mmol/L) in 15 cases (12.5%). 23 cases (19.17%) had higher iPTH levels (1206.75 ± 609.43 (640.20-2846.00) pg/ml), 37 cases (30.83%) had lower iPTH levels (56.85 ± 34.45 (2.50-125.00) pg/ml), and the iPTH levels were 300.00 ± 121.28 (134.00-576.00) pg/ml in 49 cases (40.83%) Among them, 11 patients had parathyroid hyperplasia.
**Conclusions:** Diabetic nephropathy, hypertensive nephropathy, high phosphorus, high calcium and the lower iPTH are important causes of extraosseous calcification in peritoneal dialysis patients.

**O149**

**NUMERICAL MODELLING OF MICROCIRCULATION FLUID EXCHANGES IN UREMIC PATIENTS ACCOUNTING FOR THE NON-LINEAR EFFECT OF LYMPHATIC SYSTEM**

*Possenti L[1], Casagrande G[1], Costantino M[1], Zunino P[2]*
[1]Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Milan, Italy
[2]Department of Mathematics, Politecnico di Milano, Milan, Italy

**Background:** A large social and medical impact is associated to end stage renal disease (ESRD). Patients need to be treated to remove toxins and excess fluids from their body and the most common treatment is haemodialysis. The water overload is treated by withdrawing fluids from blood, and a proper blood volume has to be restored trough plasma refilling: extracellular fluids must return to vascular region through microcirculation and lymphatic system.
**Aim:** Numerical models of fluid exchanges in microcirculation can be found in the literature but they consider only a linear effect of lymphatic system. Since a strong non-linear effect on lymphatic flow rate due to interstitial pressure is known, aim of this study was to develop a numerical model of fluid exchanges in a capillary bed and interstitium including a non-linear model of the lymphatic system.
**Methods:** A finite element model considering both extravascular space (3D) and capillary bed (1D) was considered. The non-linear effect of the lymphatic system was modeled using a sigmoidal function of interstitial pressure. Simulations with both physiological and pathological conditions were ran to study the peripheral variations in mean interstitial pressure and filtration flow rate.
**Results:** Interstitial pressure and filtration were coherent with expected ranges. The proposed non-linear model allowed to study the dynamic equilibrium

between fluids, modelling the capillary filtration counterbalanced by the action of lymphatic system. In addition, the model highlights variations between physiological and pathological conditions in terms of interstitial pressure or filtration rate, caused by oncotic interstitial pressure and filtration coefficient alterations.
**Conclusions:** A non-linear model of the lymphatic system was included in a numerical model of the peripheral fluid exchanges. This model allows to study different fluid exchange conditions at a microcirculatory level in a 3D portion of tissue.

**O150**
**WHICH UREMIC TOXINS ARE AFFECTING VASCULAR CALCIFICATION?**
*Holmar J[1], Sanati M[1], Orth-Alampour S[1], Jankowski J[1,2]*
[1]Institute for Molecular Cardiovascular Research (IMCAR), University Hospital RWTH Aachen, Aachen, Germany
[2]School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands

**Background:** Around 8-10% of the adult population suffers from kidney damage, and the death rate of complications related to chronic kidney disease (CKD) is still high. The leading cause of death is cardiovascular complications at which vascular calcification (VC) is prevailing in CKD patients.
**Aim:** This systematic review analyzed original research papers on uremic toxins and vascular calcification and determined which uremic toxins affect vascular calcification processes.
**Methods:** The authors performed a PubMed literature search to identify eligible studies. A combination of the search terms "chronic kidney disease", "uremia", "end-stage renal disease", "dialysis", "chronic renal failure", "chronic kidney failure", "vascular calcification", "calcification", "uremic toxin(s)", "uremic retention solute(s)", "cardio-renal toxin(s)", "cardiovascular toxin(s)", "toxin(s)" was used. The systematic review was registered in the PROSPERO database, and PRISMA guidelines were followed.
**Results:** The literature search resulted in 92 papers. After removing non-English and review articles, the titles and abstracts of the remaining 50 papers were screened by two reviewers. The remaining 36 papers were given a full-text examination and 33 papers identified as relevant for narrative synthesis. Altogether 43 solutes were studied: 20 low- and 14 middle molecular weight, 7 protein bound uremic toxins and 6 other solutes/factors. In 22 cases no significant effect on VC processes was revealed (e.g. calcium, creatinine, and urea); 17 solutes were found to have inducers of VC (e.g. phosphate, indoxyl sulphate and beta-2 microglobulin) and 7 substances inhibited VC processes (e.g. paricalcitol and drugs AST-120 and Sevelamer).
**Conclusions:** Researching the effect of uremic toxins on VC gives valuable information which toxins levels should be reduced in CKD patients and gives hints to the developers of dialysis techniques. Since the effect of many solutes on VC is still not analyzed, there is a need for further research.

## Session: Tissue Engineering and Regenerative Medicine IV

**O151**
**STRATEGIES FOR THE EXPANSION AND DIFFERENTIATION OF HUMAN MESENCHYMAL STEM CELLS UNDER PHYSIOLOGICAL CONDITIONS**
*Kasper C*
Department for Biotechnology, University of Natural Resources and Life Sciences, Vienna, Austria

**Background:** "Classical" standard cell cultivation is still performed under static conditions (5% $CO_2$ at 37°C) incubators in 2 D plastic well plates in ambient atmosphere. These conditions do not mimic physiological in vivo conditions for human primary cells including stem and progenitor cells. For improving cell "quality" and thus also functionality cultivations should be performed in a bioreactor in/or on 3 D scaffolds under dynamic conditions resulting in optimized transport of nutrients and metabolic waste as well as in monitoring and control of the tissue microenvironment.
**Aim:** Physiological stem cell expansion and differentiation towards functional 3 D tissues also includes the cultivation under "hypoxic" (less than 20% oxygen) conditions. Moreover, recently disposable bioreactors and bioprocess strategies for automation have been developed enabling GMP conform production of cells for cell therapy and tissue engineering applications. The lecture shall give an update on current research activities within the field of bioreactor developments for the cultivation of stem cells in 3 D structures under physiological conditions for the production of clinical relevant cell quantity and quality for cell based therapies and tissue engineering applications.
**Methods:** MSC from adipose tissue and umbilical cord were isolated by explant cultures. Cells were cultured in an expansion bioreactor based on a rotating bed and a meander bioreactor system. Furthermore, MSC were cultured for bone tissue engineering on macroporous zirconium dioxide discs and sucessfully differentiated into osteogenic lineage (Zellwerk GmbH).
**Results:** Cells were successfully expanded maintaining stem cell characteristics. Medium consumption was significantly decreased in comparison to "classical" expansion in T-flasks/cell factories and time for generating comparable cell number was reduced. MSC were seeded onto macroporous and successfully differentiated into osteogenic lineage.
**Conclusions:** The bioreactor platform ZRP(R) was used for expansion of MSC under physiological conditions and for bone Tissue Engineering using MSC on macroporous ceramics.

**O152**
**3D OXYGEN TRANSPORT MODEL IN STRIPS OF OVARIAN CORTICAL TISSUE: A BASIC TOOL FOR ASSISTED REPRODUCTION TECHNIQUES**
*Catapano G[1], Falvo D'Urso Labate G[1], Sudhakaran S[2], Rango G[1], Di Nardo M[2], Gualtieri R[2], Talevi R[2]*
[1]Department of Environmental and Chemical Engineering, University of Calabria, Rende (Cosenza), Italy
[2]Department of Biology, University of Naples "Federico II", Naples, Italy

**Background:** Cryopreservation of ovarian tissue strips followed by thawing, in vitro culture, fertilization and re-implantation is a promising regenerative strategy to restore fertility in women with ovarian failure or malignancies. In in vitro culture of ovarian strips it is difficult to keep follicles viable and guide their maturation. Optimal dissolved oxygen concentration ($pO_2$) near follicles may favour their viability and progression.
**Aim:** To predict perifollicular $pO_2$ as a function of strip geometry and $pO_2$ at strip surfaces by a $O_2$ transport model.
**Methods:** Ovarian tissue was modeled as pseudo-homogeneous layers representing the subdomains of ovarian cortex, varying for geometry, stromal cell and fiber density, in which follicles are embedded.
Follicles at different stages were represented as spheres with mass-impermeable core (oocyte) surrounded by a pseudo-homogeneous granulosa cell layer (GCL). Oocyte, GCL geometry and GC number varied with stage. 3D $O_2$ transport in each subdomain and GCL was described in terms of diffusion-reaction equations for Michaelian oxygen consumption kinetics. The 22 geometric and kinetic parameters were estimated from experiments or literature data for bovine tissue. The model was validated vs. own or literature experiments.
**Results:** Model-predicted strip oxygen consumption rate agreed well with respirometry or literature data. The model predicted higher perifollicular $pO_2$ at decreasing strip thickness, for cubic than elongated strips, and at increasing strip sphericity. Comparison to literature culture data shows that, under conditions favouring higher $pO_2$s, follicles were more viable and grew faster. This suggests that optimal perifollicular $pO_2$ favours follicle viability and guide their progression.
**Conclusions:** The $O_2$ transport model predicts $pO_2$s in agreement with experiments and may be used to optimize strip geometry, enhance viability and guide progression of follicles in vitro.

**O153**

**FIBER SIZE AND COMPOSITION AS TOOLS TO MANIPULATE WETTABILITY AND COMPLIANCE OF ELECTROSPUN TUBULAR SCAFFOLDS TO ENHANCE TISSUE REGENERATION**

*Mueller M[1], Bode M[1], Pfeiffer D[2], Lang I[2], Glasmacher B[1]*
[1]Institute for Multiphase Processes, Leibniz Universität Hannover, Hannover, Germany
[2]Institute for Cell Biology, Histology and Embryology, Medical University Graz, Graz, Austria

**Background:** Cellular attachment and mechanical properties strongly depend on the size and composition of the fibers of electrospun scaffolds.
**Aim:** This study aims to investigate the influence of scaffold microstructure and material on wettability, compliance and cell migration.
**Methods:** Tubular scaffolds were electrospun using solutions with different concentrations of polycaprolactone (PCL) as well as blends with polylactide acid (PLA) or polyethylene glycol (PEG) and PLA. Specific surface was calculated based on average fiber diameters. Surface energy was determined via contact angle measurements using captive bubble method. Compliance was analyzed with a custom- made test bench. Preliminary cell seeding studies were performed for 7 d with human Amnion-derived mesenchymal stem cells.
**Results:** Fiber diameter of PCL scaffolds increased with increasing concentration (1.1 to 2.45 µm). Blending with PLA or PLA/PEG led to fiber diameters of 1.05 and 1.15 µm. Specific surface increased with decreasing fiber size (1.39 to 2.4 m2/g). Surface energy of PCL scaffolds increased with increasing fiber diameter (41 to 54 J/m2). Blending with PLA or PLA/PEG led to a further increase (60 J/m2). Compliance was significantly influenced ($p<0.001$) by fiber size, with a compliance of 13.05% (small fibers) and 2.9% (big fibers). The addition of PLA or PLA/PEG led to a significant decrease ($p<0.001$) compared to pure PCL (small fibers) with values of 2.7 and 2.1%, respectively. Cell seeding showed a high cell migration for scaffolds with big fibers and high wettability as well as a confluent cell coverage for small fibers and high wettability.
**Conclusions:** This study demonstrates, that important scaffold properties be manipulated by changing the size or the composition of the fibers. It is possible to independently tailor these properties to the requirements at the implantation site and hence to enhance efficient tissue regeneration.

**O154**

**LASER ENGRAVING PROMOTES THE REPOPULATION OF DECELLULARIZED ARTICULAR CARTILAGE**

*Schneider C[1,2], Rieder B[3], Teuschl A[2,3], Zehetner J[4], van Osch G[5], Redl H[1,2], Wolbank S[1,2], Nürnberger S[1,2,6]*
[1]Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria
[2]Austrian Cluster for Tissue Regeneration, Vienna, Austria
[3]University of Applied Sciences Technikum Wien, Vienna, Austria
[4]University of Applied Sciences Vorarlberg, Dornbirn, Austria
[5]Erasmus Medical Center, Rotterdam, The Netherlands
[6]Medical University of Vienna, Vienna, Austria

**Background:** Decellularized allogenic cartilage is considered to be a promising biomaterial for the treatment of large chondral defects. However due to the exceptionally dense matrix of articular cartilage, it has never been possible to repopulate more than the very edges of the matrix. In our study we used lasers to create channels to support cell migration.
**Methods:** Articular cartilage biopsies were either devitalized or decellularized and subjected to glycosaminoglycan (GAG) depletion. Different lasers were tested to engrave holes, furrows or grid patterns into the scaffold surface. Scaffolds were seeded with adipose-derived stromal cells (ASC) or chondrocytes to evaluate cell adhesion, chondrogenic differentiation and in vivo performance in a nude mouse model.
**Results:** Lasers were found to be suitable for engraving fine structures into articular cartilage, bearing the advantage of reproducibility and speed. In vitro cells and newly produced matrix filled up the spaces in scaffolds of either pretreatment, but in GAG-depleted scaffolds the integration was better than in those which were only devitalized. Chondrogenic differentiation of ASC could be achieved by the addition of growth factors. In vivo implanted scaffolds were well integrated in all cases and chondrocytes as well as cells in co-culture deposited cartilage-like matrix.
**Conclusions:** Our approach proved that laser-engraved decellularized articular cartilage may be used as scaffold and contribute to advanced regeneration by providing homologous matrix architecture and mechanical stability to allow earlier joint loading for patients.

**O155**

**REGENERATION AND OSTEOINTEGRATION OF THE ANTERIOR CRUCIATE LIGAMENT USING A NOVEL SILK FIBER BASED SCAFFOLD**

*Teuschl A[1,2,5], Heimel P[1,3,5], Nuernberger S[4,5], Redl H[1,5], Nau T[1,5]*
[1]Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, AUVA Research Center, Vienna, Austria
[2]Department of Biochemical Engineering, University of Applied Sciences Technikum Wien, Vienna, Austria
[3]Karl Donath Laboratory for Hard Tissue and Biomaterial Research, Medical University of Vienna, Vienna, Austria
[4]Department of Trauma Surgery, Medical University of Vienna, Vienna, Austria

**Background:** In ACL regeneration, a structured scaffold with ideal mechanical properties, cells from different sources, and mechanical as well as biological factors are needed. The optimal scaffold is regarded to be biocompatible and biodegradable to allow tissue ingrowth, but also provides the right mechanical properties to provide immediate mechanical stability.
**Aim:** It was the aim to test a novel silk based scaffold with the mechanical properties close to the natural ACL in regards to the ability to regenerate ligament tissue following ACL resection and reconstruction under in vivo conditions. We also tested if additional cell seeding of the scaffold leeds to an increased regenerative activity.
**Methods:** 33 mountain sheep underwent ACL resection and randomisation in 2 experimental groups: 1) ACL reconstruction with scaffold alone (SA), and 2) ACL reconstruction with cell seeded scaffold (CS). Histological evaluation of the intra-articular portion as well as of the intra-osseous part was performed after 6 and 12 months.
**Results:** After 6 months, connective tissue surrounded the silk scaffold with ingrowth in some areas. The cell seeded scaffold had significant lower silk content compared to the unseeded scaffolds and demonstrated higher content of newly formed tissue. After 12 month, the density of the silk fibers decreased significantly, and the ingrowth of newly formed tissue increased in both groups. No differences between the two groups regarding silk fiber degradation and regenerated new tissue were found anymore. Osteointegration also increased from 6 to 12 months.
**Conclusions:** The novel silk fiber scaffold was able to stimulate ACL regeneration and osteointegration. Additional cell seeding was beneficial for 6 months, not anymore after 12 months.

**O156**

**DEVELOPMENT OF INJECTABLE CELL SCAFFOLD FOR CELL THERAPY**

*Furuzono T[1], Sato H[2], Fukumoto S[3]*
[1]Department of Biomedical Engineering, B.O.S.T., Kindai University, Osaka, Japan
[2]QOL Research Center, Gunze Limited, Osaka, Japan
[3]Department of of Premium Prevention Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

**Background:** Cell therapy for angiogenesis aims to improve limb perfusion by enhancing neovascularization using autologous bone marrow mononuclear cells (BMNCs), stem cells, etc. The mechanism for neovascularization by cell therapy depends on regulation of the secration of proangiogenic factors and endotherial differentiation. The clinical efficiency of cell-based therapeutic angiogenesis in diabetic patients with peripheral arterial disease (PAD), unfortunately, has not been satisfied because approximately 80% of the transplanted cells were estimated to disappear early from the injection site.
**Aim:** It is necessary for maintaining transplanted cells in place in order to enhance the therapeutic efficiency. In this report, the injectable cell scaffold (ICS) microsphere, that was hydroxyapatite (HAp) nanoparticles coated bioabsorbable poly(L-lactide-co-caprolactone) (PLCL), was developed and evaluated the efectiveness for angiogenesis therapy in vivo.
**Methods:** The core/shell microsphere as ICS was fabricated by an oil in water (o/w) type Pickering emulsion. The BMNCs with/without ICS were

intramuscularly implanted into mice ischemic hind-limbs for cell-based therapeutic angiogenesis.
**Results:** ICS showed spherical morphology and HAp fully coverd on the polymer surface with almost monolayer by SEM observation. The ICS size and PLCL/HAp weight ratio were successfully controlled by fabrication parameters. After co-injection of BMNCs and ICS, avoidance rate of limb necrosis statistically increased at three times than that of only BMNCs injection. The angiogenesis enhancement was explained increase of the proangiogenic factors secration and prevented apotosis, resulting in prolonged cell retention.
**Conclusions:** The novel core/shell microsphere as ICS potentiates cell-based therapeutic angiogenesis, which could be extermely useful for the treatment of severe ischemic disorders. (Acknowledgement) This research is partially supported by A-STEP from AMED.

## Session - Ventricular Assist Devices: The next Generation

### O157
### RELATIONSHIP BETWEEN FLUID FORCE FLUCTUATION AND IMPELLER DESIGN FOR MAGNETICALLY LEVITATED CENTRIFUGAL BLOOD PUMPS

*Masuzawa T[1], Ohno K[1], Satoh R[1], Osa M[1], Nishimura T[2], Kyo S[2,3]*
[1]Department of Mechanical Engineering, Ibaraki University, Ibaraki, Japan
[2]Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan
[3]The University of Tokyo, Tokyo, Japan

**Background:** Several types of the ventricular assist devices with rotary blood pumps are available in clinical usage. But, the blood compatibility at the bearing of the pump is not still perfect. The magnetic bearing is a key technology to enhance hemocompatibility of rotary blood pumps.
**Aim:** We have developed a magnetically levitated blood pump for extracorporeal use. The fluid force acting on a levitated impeller of the centrifugal blood pump is an important factor for device safety and energy consumption of the levitation control. In this paper, the relationships among the impeller design, the fluid force acting on the impeller and the levitation stability of a newly developed maglev blood pump are investigated.
**Methods:** The maglev centrifugal pump consists of an axial magnetic bearing, a synchronous motor and a levitated impeller set between the magnetic bearing and the motor. The axial position and inclination of the impeller are regulated actively, and the radial movement of the impeller is restricted by the passive stability. The radial fluid force acting on the impeller in centrifugal pumps fluctuates by the positional relationship between the impeller vane's edge and an outlet port on the pump casing. CFD analysis was performed to verify the effect of the vane number on the fluid force fluctuation. The six vanes and twelve vanes impellers were fabricated, and 3D movements of the levitated impellers during pumping were measured to study the stability of the levitated impellers.
**Results:** The magnitude of the fluid force and the impeller displacement from the center increase with increasing the number of the vanes even though the fluctuation of the fluid force and the radial movement of the impeller in a rotation decrease.
**Conclusions:** There is a trade-off relationship between the magnitude and fluctuation level of the fluid force due to the number of vanes. It is useful information for the development of levitated pumps.

### O158
### DEVELOPMENT OF A HYDRODYNAMICALLY LEVITATED CENTRIFUGAL BLOOD PUMP FOR LONG-TERM EXTRACORPOREAL MECHANICAL CIRCULATORY SUPPORT SYSTEMS

*Tsukiya T, Sumikura H, Mizuno T, Iizuka K, Akiyama D, Katagiri N, Takeshita D, Takewa Y, Tatsumi E, Taenaka Y*
Department of Artificial Organs, National Cerebral and Cardiovascular Center, Osaka, Japan

**Background:** A centrifugal blood pump with the novel hydrodynamically levitated impeller has been developed and the performance and the safety of the device have been evaluated in various mechanical circulatory support (MCS) systems.
**Aim:** The hydrodynamic levitation possesses significant advantages on mechanical endurance and antithrombogenicity. On the other hand, the system utilizes hydrodynamic pressure of blood in a very small gap to sustain the mechanical load, and it requires certain amount of rotating speed (RS) to have a stable levitation. The aim of the present study is to evaluate stability of the hydrodynamic levitation system.
**Methods:** Preclinical experiments carried out in our laboratory are 1) Endurance experiment using mock circulation loop under the pulsating flow 2) Hemolysis experiment using fresh bovine blood, and 3) 30-day chronic animal experiments of temporary LVAD.
**Results:** 1) The pump was installed onto the testing device (LaboHeart-NCVC) and was operated continuously for 60 days under the pulsating flow conditions with the average flow rate of 5.0 L/min. There was no mechanical or electrical failure. 2) Mechanical hemolysis was evaluated in the closed loop using fresh calf blood. The hemolysis after 4 hours of running at the flow rate of 5.0 L/min against the pressure of 100 mmHg was below lower limits of measurement. Additionally, hemolysis was evaluated under low speed conditions, and the results show that operating pump at speeds lower than 2000 rpm can possibly cause serious intolerable amount of hemolysis (NIH >0.01) 3) The centrifugal pump was installed for 30 days between the left apex and the descending aorta to make a left heart bypass using a calf. Three calves were used and the results were satisfactory with no trace of thrombus formation in the blood pump.
**Conclusions:** The centrifugal blood pump with the hydrodynamically levitated impeller demonstrated a sufficient potential to be used for a long-term temporary LVAD.

### O159
### A NOVEL, MINIATURIZED VAD CONFIGURED FOR RIGHT-HEART MCS

*Stanfield J[1,2], Snyder T[1,3], Wampler R[1,4], Long J[1,3]*
[1]Vadovations, Inc., Oklahoma City, USA
[2]Mechanical Engineering, University of Utah, Salt Lake City, USA
[3]Integris Health, Oklahoma City, USA
[4]Department of Surgery, Oregon Health and Science University, USA

**Background:** In the current clinical market, there exists no implantable and durable solution designed for right heart mechanical circulatory support (MCS). Here, we report the ongoing development of a device that will address the challenges unique to right ventricular support while incorporating considerations for affordability and hemocompatibility.
**Aim:** To demonstrate the hemodynamic performance, durability and hemocompatibility of a novel, miniaturized right ventricular assist device (RVAD).
**Methods:** The blood flow path of the pump includes a rotating impeller, vaned diffuser, and unique radial inlet configuration within a 7 mm hydraulic diameter. IACUC-approved animal studies were carried out with the RVAD configuration implanted in ovine models (50-80 kg) with the pump in the RV outflow tract (RVOT) and the outflow anastomosed to the pulmonary artery (PA). Flow rate was measured at the pump outflow and at the PA to assess total system flow. Studies were carried out to test the anatomic fit, biocompatibility of tissue interface, and hemocompatibility as assessed by complete blood counts, coagulation, organ function, hemolysis and von Willebrand Factor (VWF) function preservation.
**Results:** In vitro testing confirmed hemodynamic performance across a wide range of conditions representing clinical configurations. Anatomic positioning, hemocompatibility, and hydrodynamic performance of the RVAD were tested in over 20 acute and chronic ovine studies. Acute studies were <2 days, with chronic duration up to 90 days in continuous operation. In chronic studies, blood counts and coagulation parameters were normal, and organ function was preserved. Hemolysis was <5 mg/dL, and VWF function remained within the pre-op range with high molecular weight multimers preserved throughout.
**Conclusions:** In vivo tests of a novel RVAD have demonstrated optimal hemocompatibility through 90 days of continuous operation. While tests are ongoing, the first implantable RVAD may be nearing clinical use.

**O160**

**NOVEL PEDIATRIC AXIAL ROTARY BLOOD PUMP**

*Telyshev D, Denisov M, Selishchev S, Nesterenko I*
Biomedical Systems, National Research University of Electronic Technology, Moscow, Russian Federation

**Background:** Heart failure is one of the widespread reasons of death in the world. About one million new cases of heart failure are diagnosed among the adult and pediatric population annually. Rise of the heart failure incidents and limitation of the donor's hearts leads to increasing of VAD application among the adult and pediatric population. Due to the growing number of VAD implantation among a pediatric population and limitation of the pediatric VADs on the market, novel pediatric rotary blood pump is needed for the mechanical support of the heart. Our research team focused on the development and investigation of an axial pediatric pump, since axial pump have the high potential to the miniaturization.
**Aim:** Novel pediatric axial rotary blood pump development to ensure effective support of a blood circulation.
**Methods:** At the first stages of the study, 6 variants of an axial pump with different geometry of the flow section were designed. Mainly the pump includes a straightener, both impeller and diffuser with three blades. The geometry effects on the H-Q curves of the VAD were investigated. To determine the hydrodynamic characteristics a numerical simulation of the fluid flow was carried out.
**Results:** The modeling results demonstrated that VAD is able to deliver 5-85 mmHg of pressure rise for a flow range of 0.5-4 L/min and rotational speeds of 9000-15,000 RPM. The hydraulic efficiency of the pump was 32% at the operating point. The preload sensitivity is growing with increasing the blade's inlet angle of the impeller and the diffuser. The range of changing of the distribution of shear stresses over the pump's volume is less than 1%, depending on the geometry.
**Conclusions:** The designed VAD with a highest preload sensitivity was chosen as a basis for a manufacture. The weight of the first prototype is 102 g with length 60 mm and maximum diameter 26 mm.

**O161**

**DEVELOPMENT OF A MINIATURE, HEMOCOMPATIBLE CONTINUOUS FLOW PEDIATRIC VENTRICULAR ASSIST DEVICE**

*Snyder T[1,2], Stanfield J[1,3], Coghill P[1], Wearden P[4], Wagner W[5], Kameneva M[5], Olia S[5], Ye S[5], Crompton D[5], Long J[1,2]*
[1]Vadovations, Inc., Oklahoma City, USA
[2]Integris Health, Oklahoma City, USA
[3]Department of Mechanical Engineering, University of Utah, Salt Lake City, USA
[4]Nemours Children´s Hospital, Orlando FL, USA
[5]Department of Regenerative Medicine, McGowan-Inst., University of Pittsburgh, Pittsburgh, USA

**Background:** There is a substantial need for ventricular assist devices (VAD) with reduced adverse event rates for use in small children and especially infants.
**Aim:** To demonstrate the hydrodynamic and hemocompatibility performance of a miniature VAD for use in children and infants
**Methods:** The pump is implanted into the left ventricular apex with outflow connected to the aorta by a vascular graft using custom developed implant tools. Initial testing of the pump using a rotating impeller and vaned-diffuser designed for an adult RVAD were promising, but hemodynamic performance in hypertensive conditions could be improved. Thus, a hydraulic design specific for children (1-4 L/min) was developed and evaluated computationally. Each hydraulic design can be used without changes to other system components: pump housing, cables, etc. Hydraulic designs were evaluated in vitro and via implant in juvenile sheep. Hemocompatibility was assessed by blood chemistry, coagulation parameters, plasma free hemoglobin (PFH), flow cytometric assays of platelet and leukocyte activation, aggregation, and microparticles, and by von Willebrand Factor (VWF) function and multimer distribution.
**Results:** In vitro testing confirmed low hemolysis (NIH < 0.05 g/100L). During implant, flow rates of 0.8-4.0 L/min were generated for study durations up to 3 months with low hemolysis (average PFH <12 mg/dL), low platelet activation, and preservation of VWF function and high molecular weight multimers, in spite of no post-op anticoagulation. No renal infarcts were observed in 9 of 10 chronic implants with only superficial infarcts observed in 1 study with severe hypertension and outflow graft thrombus. There have been no controller failures and the pump has functioned properly during defibrillator and cautery tool use. Six month in vitro durability tests have been completed successfully and one year tests are ongoing.
**Conclusions:** A versatile, miniature VAD for children has been developed and demonstrated exceptional performance and hemocompatibility.

**O162**

**NEXT GENERATION ULTRACOMPACT CENTRIFUGAL PEDIATRIC VAD WITH FULL AXIS CONTROLLED MAGLEV MOTOR**

*Osa M[1], Masuzawa T[1], Tatsumi E[2]*
[1]Mechanical Engineering Department, Ibaraki University, Ibaraki, Japan
[2]Department of Artificial Organs, National Cerebral and Cardiovascular Center, Osaka, Japan

**Background:** Due to the lack of device options in mechanical circulatory support (MCS) for infants, the research interest in the pediatric VAD development is increased in recent years. However, technical difficulties such as miniature device size, wide operational range according to patient age, device durability and blood compatibility are inhibiting progress of the pediatric VAD development. A next generation ultracompact maglev pediatric VAD has been developed in our institute.
**Aim:** This paper is an initial report to investigate the feasibility of the maglev VAD for pediatric MCS. Design strategy is completing following requirements: 1) fully implantable in infants and 2) continuous support of infants 1-6 years of age.
**Methods:** The developing VAD consists of two motor stators, levitated impeller and centrifugal pump. Impeller full axis active control is developed to achieve device simplicity and enhance magnetic suspension stability. The maglev motor and a centrifugal blood pump were developed based on numerical simulation to satisfy target pump performances of a head pressure of 100 mmHg and a flow rate range of 0.5-2.5 L/min. The pediatric VAD, which has diameter of 31 mm, height of 36 mm and total volume of 18 cc, was constructed. performances of H-Q curve, energy consumption and magnetic suspension stability of the developed pediatric VAD were evaluated with a closed loop circulation circuit.
**Results:** The developed pediatric VAD indicates the target pump performances at a rotating speed of 4000-5000 rpm. The power consumption of the motor is 8-15 W over the driving conditions. Oscillation amplitude of the levitated impeller is sufficiently suppressed less than 30% of the blood clearance. In the future, energy consumption will be decreased by 5-10 W by design optimization of motor geometry and material. Further downsizing toward 10 cc in volume will also be conducted.
**Conclusions:** The hydraulic and magnetic performances of the developed next generation pediatric VAD are sufficiently suitable for pediatric MCS.