XLI Annual ESAO Congress, 17-20 September 2014, Rome, Italy

Poster Sessions

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Poster Session 1 - Part 1

Renal Assist 1

P1

KIDNEY TRANSPLANTATION (KT) ALONE IN ESRD PATIENTS WITH HEPATITIS B (HBV) LIVER CIRRHOSIS (LC): A SINGLE CENTER EXPERIENCE

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Background: KT alone in ESRD patients with HBV-LC is controversial. This study compared outcomes of KT in HBsAg-positive patients with ESRD with (LC group) and without LC (Non-LC group).
Methods: Outcomes were analyzed in 101 HBsAg-positive patients with ESRD who underwent KT alone between 1997 and 2011. 89 were in the Non-LC group and 12 were in the LC group. Of the latter, eight were Child-Pugh (CP) class A and four were CP class B.
Results: Baseline AST and ALT levels were higher in the LC group. MELD scores were similar in patients with CP class A and B, serum albumin level was lower in CP class B. After KT, one CP class A patient showed an increase in the CP score from 5 to 10 points, MELD score from 22.3 to 44.1 points. The CP and MELD scores of the other 11 patients in the LC group did not increase. All four pre-KT CP class B patients were reclassified as class A after KT, because of elevated serum albumin levels after KT. Four patients in the LC group developed HCC at a median of 35 months (range: 20-57 months) after KT. The 5 year patient survival rate was similar in the LC and Non-LC groups (100% vs. 94%, p = 0.14). The incidence of pre-KT LC did not differ between survivors and non-survivors (11% vs. 20%, p = 0.34). Occurrence of HCC was significantly higher in non-survivors than in survivors.
Conclusions: KT alone may be safe in patients with compensated HBV-LC.

P2

CITRATE-DEPENDENT SECRETION OF CYTOKINES AND COMPLEMENT ACTIVATION IN WHOLE BLOOD

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Aim and Background: Regional citrate anticoagulation is a promising method for anticoagulation in extracorporeal blood purification because of less bleeding risk, longer filter lifetime as well as reduced complement activation, oxidative stress and blood cell activation. Despite there are some studies demonstrating reduced cytokine secretion, there is no systematic evaluation of different citrate and resulting Ca^{2+} concentrations on inflammation parameters. The aim of this study was the evaluation of the impact of citrate on cytokine secretion and complement activation.
Methods: Different trisodium citrate concentrations were added to heparinized fresh whole blood to adjust different Ca^{2+} concentrations. Immediately after blood donation, citrated whole blood was stimulated with LPS. After 15 minutes of incubation, samples were drawn for analysis of complement activation. Inflammation parameter analysis was conducted after 4 hours.
Results: Inflammation parameters could be reduced effectively by reducing Ca^{2+}. IL-1β dropped from 844 pg/ml at physiological Ca^{2+} to 170 pg/ml at 0.25 mmol Ca^{2+} and further decreased slightly to 145 pg/ml when Ca^{2+} was 0.12 mmol/l. Similar behavior showed IL-6 (13829 to 4456 and 3054 pg/ml), IL-8 (3423 to 641 and 538 pg/ml) and IL-10 (17.5 to 7.2 and 3.8 pg/ml). TNF-α and C3a-desArg were reduced to a lesser extent (8707 to 2805 and 3519 pg/ml and 842 to 448 and 405 ng/ml, respectively).
Conclusions: This study showed a dose dependent reduction in cytokine secretion and complement activation by addition of citrate and that a target Ca^{2+} concentration of ≤0.25 mmol/in extracorporeal blood purification might reduce cytokine secretion by more than 50 to about 80%.

P3

ADVANTAGE OF HIGH DOSE HEMODIALYSIS (HDD) WITH REGARDS TO LABORATORY TESTS

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Aim: A lot of usefulness of HDD was reported on the clinical advantages. We measured serum FGF-23, IL-6, inorganic phosphate, i-P, and Ca including routine laboratory tests and analyzed correlations between dialysis doses and the above serum parameters.
Methods: Subjects were 206 hemodialysis patients. We selected hemodialysis product, HDP, as the dialysis dose to divide the subjects in two groups. HDP was calculated as (hours/hemodialysis session) × (hemodialysis sessions/week)^2. HDD patients, whose HDP was higher than 54 such as 6 hours/hemodialysis session and 3 times weekly, consisted of 77 patients (27 women and 50 men) and Standard dose hemodialysis, SDD patients, whose HDP was lower than 54, did of 129 patients (53 women and 76 men). Their serum FGF-23, IL-6, i-P, Ca and routine laboratory tests were measured before hemodialysis. Statistical analysis was done using unpaired Student's test. Correlation coefficient between variables was estimated by the Pearson product moment correlation coefficient.
Results: FGF-23, IL-6, β_2-MG, and i-P were significantly lower in HDD patients than in SDD patients. Correlation coefficient between FGF-23 and i-P was moderate correlation in all patients (r = 0.553, P = 0.000) and that between i-PTH and Ca was little if any correlation in all patients (r = -0.270, P = 0.002).
Conclusions: HHD significantly decreased serum FGF-23, IL-6, β_2-MG, and i-P than SDD. The lower serum i-P significantly reduced serum FGF-23. Serum Ca and i-PTH were not correlated.

P4

HEALTH-RELATED QUALITY OF LIFE IN OUR HEMODIALYSIS PATIENTS WITH CARDIAC VALVE CALCIFICATION

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Aim: The aim of this study was to evaluate whether the presence of the cardiac valve calcification (CVC) may impact health-related quality of life (HRQoL) in hemodialysis (HD) patients.
Materials and Methods: In a cross-sectional study, baseline echocardiography was performed on 108 HD patients (66 male, mean age 54.6 ± 16.7 years) to screen for CVC. Patients were stratified in three groups: group I (n = 36) without CVC; group II (n = 44) with one calcified valve (either mitral or aortic); group III (n = 28) with calcification on two valves (both, mitral and aortic). The scales for mental component summary (MCS) and physical component summary (PCS), derived from eight different subscales (SF-36), were compared between the groups of patients.
Results: Patients with two calcified valves on echocardiography had significantly lower PCS (41.22 ± 25.15 vs 54.34 ± 26.71; p = 0.012) and MCS (43.37 ± 23.92 vs 51.84 ± 25.72; p = 0.024) score in comparison with the patients with absence of CVC. Patients with one calcified valve on echocardiography had only a significantly higher PCS (48.36 ± 26.19 vs. 41.53 ± 27.61; p = 0.037) score in comparison with group of patients without CVC. We did not find differences in both PCS and MCS scores among the group of patients with one and two calcified valves on their echocardiography. Also, there was no statistical difference in the MCS score between patients with one calcified valve and patients without CVC. The groups did not differ significantly in variables that may affect the HRQoL of HD patients, such as age, gender, dialysis doses, serum albumin and hemoglobin.
Conclusions: HD patients with CVC on echocardiography had lower HRQoL scores. This implies that clinical investigations aimed to preventing occurrence of CVC in HD patients are still needed to improve patient quality of life.

P5

DAILY PRESCRIBED DOSE OF CALCIUM CARBONATE AS A PREDICTOR OF THE CARDIAC VALVE CALCIFICATION PRESENCE IN OUR HEMODIALYSIS PATIENTS

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Aim: The aim of this study was to evaluate whether different daily doses of prescribed calcium carbonate ($CaCO_3$) may have an impact on cardiac valve calcification (CVC) occurrence in hemodialysis (HD) patients.
Materials and Methods: In a cross-sectional study, baseline echocardiography was performed on 108 HD patients (66 male, mean age 54.6 ± 16.7 years, mean duration of HD 98.7 ± 64.6 months) to screen for CVC. Patients were stratified according to the number of CVC in three groups: group I (n = 36) without CVC; group II (n = 44) with one calcified valve (either mitral or aortic); group III (n = 28) with calcification on two valves (both, mitral and aortic). The daily doses of prescribed $CaCO_3$ taken as an average of the last 24 months evaluations between the groups of patients were compared.
Results: There were no significant differences in serum calcium, serum phosphate and serum parathyroid hormone levels among the different groups of patients. Patients without CVC had significantly lower daily doses of

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prescribed $CaCO_3$ (1.37 ± 0.62 g) in comparison with the groups of patients having one (2.33 ± 0.59 g) and patients having two calcified valves (2.65 ± 0.72 g). There were no significant differences in the prescribed daily doses of $CaCO_3$ between the groups of patients having one and patients with both calcified valves. Multivariate adjusted logistic regression analyses (with group of patients without CVC as the reference value) identified daily doses of prescribed $CaCO_3$ as a factor independently and significantly associated with the occurrence of CVC [OR] = 1.04, CI (1.008-1.077), p = 0.02 for the group with one calcified valve/OR = 1.2, CI (1.054-1.446), p = 0.009 for the group with two calcified valves] in our HD patients.
Conclusions: This research showed significantly reduced CVC presence in our HD patients with lower daily prescription of $CaCO_3$.

P6
CARDIAC VALVE CALCIFICATION PRESENCE AND KDIGO SUGGESTIONS FOR MINERAL AND BONE DISORDER MARKERS ACHIEVEMENT IN HEMODIALYSIS PATIENTS
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Aim: The aim of this study was to evaluate the association between the attainment of the KDIGO suggestions for mineral and bone disorder (MBD) markers levels and cardiac valve calcification (CVC) occurrence in our hemodialysis (HD) patients.
Materials and Methods: In a cross-sectional study, baseline echocardiography was performed on 112 HD patients (68 male; mean age 54.8 ± 17.3 years) to screen for CVC. The patients ware stratified in three groups: group I (n-34) without CVC; group II (n-47) with one calcified valve (either mitral or aortic); group III (n-31) with calcification of two valves (both, mitral and aortic). The proportion of the KDIGO guideline achieved ranges for MBD markers of the last 12 months records between the groups of the patients were compared.
Results: Patients without CVC had significantly higher percentages of attained KDIGO recommended levels for serum calcium (Ca) (193/372; 55.2%), serum phosphate (P) (197/376; 52.4%) and serum intact parathyroid hormone (iPTH) (34/58; 58.6%) when compared with the other two groups of patients. There was no difference in the attainment of the recommended levels for serum Ca (157/524 vs 93/348), serum P (168/526 vs. 99/350) and serum iPTH (26/83 vs. 15/55) between the groups of patients having one and patients with both calcified valves. Multivariate adjusted logistic regression analyses identified serum P in KDIGO proposed ranges as a factor independently and significantly associated with the CVC occurrence [OR] = 1.24, CI (1.06-1.44), p = 0.007 for the group with one calcified valve/OR = 1.65, CI (1.20-2.26), p = 0.002 for the group with both calcified valves] in our HD patients.
Conclusions: A greater prevention of CVC development could be managed if a higher proportion of the suggested levels for the serum MBD markers, especially phosphate, are achieved in HD population.

P7
SURVIVAL AND PREDICTORS OF PERITONITIS IN PATIENTS ON PERITONEAL DIALYSIS
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Aim: The aim of the study was to determinate the survival of patients on peritoneal dialysis (PD) and the influence of the episodes of peritonitis on the survival of the study population.
Methods: Records of 33 patients undergoing PD from January 2000 to December 2013 were retrospectively studied. Demographic variables, education level, socioeconomic status and dialysis-related variables were included in the regression analysis for determination of the predictors of episodes of peritonitis in the study population. Patient survival was estimated by the Kaplan-Meier method. The log rank test was used to compare survival of the patients with and without experienced peritonitis.
Results: Peritonitis occurrence rate was 1 episode of peritonitis per 25.8 patient-months. The primary cure of peritonitis with antibiotic treatment only was given in 91.4% of episodes. The predictors associated with the episodes of peritonitis identified by simple regression analysis were: longer PD vintage (p = 0.004), lower residual diuresis (p = 0.036) and slower peritoneal membrane transport function (p = 0.043). The multiple regression analysis determined that the independent predictor of the episodes of peritonitis was longer PD vintage (OR = 1.45, 95% CI: 1.18-1.80, p = 0.001). All patient survival rate at 1, 3, 5 and 10 years was 97%, 90%, 77% and 46%, respectively. The causes of death were cardiovascular death (85.7%) and peritoneal infection (14.3%). There was no significant difference in survival between patients with experienced peritonitis and patients with no experienced peritonitis (log rank, p = 0.828).
Conclusions: Peritonitis was manageable complication and it was no leading cause for death in study population on peritoneal dialysis.

P8
SMALLER HOLLOW FIBER DIAMETER IS SUITABLE FOR FOULING-FREE HEMOFILTER
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Aim: The development of a fouling-free hemofilter is a key technology for wearable or implantable artificial kidneys. In the present study, the effects of the hollow fiber diameter and the operating conditions on membrane fouling were examined.
Methods: Porcine blood was circulated through hemofilters (membrane area: 0.5 m^2, hollow fiber diameter: 100 or 200 mL). The blood flow rate (QB) was set at 50, 100, or 200 mL/min. The filtration rate (QF) was set at 2.5% of the QB for one hour (baseline QF), increased by 2.5% to 5% of the QB for one hour, and then returned to baseline for 20 min. Next, the QF was increased by 2.5% to 7.5% of the QB for 1 hour, then returned to baseline for 20 min. This step was repeated until the QF reached 25% of the QB. The increases in the transmembrane pressure (TMP) at baseline QF from the baseline TMP (initial TMP at baseline QF) were measured. TMP changes were also measured for 72 h during hemofiltration under constant conditions.
Results: The QF value at which an increase in the TMP from the baseline value was observed was larger for the 100-μm hollow fiber hemofilter than for the 200-μm hollow fiber hemofilter. TMP did not change during hemofiltration for 72 h when the maximum local flux against the wall shear rate was set below 0.003 μm.

P9
FEEDBACK SYSTEMS IN HEMODIALYSIS: THE TARGET-RBV PROBLEM
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Aim: Operating a hemodialysis (HD) feedback system based on relative blood volume (RBV) monitoring requires to input in the machine a target RBV value which is known to depend upon total weight loss (TWL). Characterization of a patient with a RBV vs TWL (RBV/TWL) curve lacks a properly wide range of TWL that cannot be spontaneously observed in any single patient. A proper wide range, 0.5 to 6.5 Kg at least, may be better observed in a cohort of patients.
Methods: RBV/TWL values were observed (BVM system – 5008H machine – Fresenius M C) in three cohorts/centers: B (835 sessions), L (483 sessions) and S (214 sessions). TWL ranged from 0.4 to 6.3 Kg.
Results: Curve fitting to a power function gave RBV = f(TWL) equations: RBV = 94.078*TWL^-0.072 (B); RBV = 91.723*TWL^-0.070 (L); RBV = 92.133*TWL^-0.073 (S); Curve fitting of 20 RBV/TWL calculated by a model, gave RBV = 94.402*TWL^-0.076 (model). The concordance of those 4 curves is remarkable, since patient's data show a great dispersion, with a low probability to predict RBV for a given TWL (R^2 < = 0.35), while the model data have no dispersion and a very high R^2 (0.945). RBV outcome is the result of TWL minus plasma refilling rate (PRR). It has been reported in literature that PRR calculated with a time step of 1 minute, has a random behavior in both direction and greatness. That makes the RBV problem similar to the "random walk" problem and could therefore explain the low predictability of RBV outcome for a given TWL.
Conclusions: Searching for a predictable RBV outcome in a HD session might be a desperate quest. Equation RBV = k*TWL^-0.070 seems however reasonably acceptable for the target RBV calculation while routinely operating a feedback system.

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P10
INTERMITTENT CITRATE HEMODIALYSIS FOR MANAGING MASSIVE DABIGATRAN-ASSOCIATED BLEEDING
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Aim: We present a case of life-threatening bleeding in chronic kidney disease (CKD) patient with excessive dabigatran anticoagulation, in whom extracorporeal therapy was used in an attempt to remove dabigatran.

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Methods: A 82-year-old woman receiving dabigatran at 110 mg per os twice daily, with a history of chronic atrial fibrillation and CKD stage 4, was admitted with severely decreased hemoglobin of 21 g/L due to ongoing gastrointestinal bleeding. Multiple blood products were given and an intermittent citrate hemodialysis (HD) for 4 hours was started. High-flux dialyzer (Polyflux 210H, Gambro) was used, with blood flow 350 mL/min (2 femoral catheters) and dialysate flow 700 mL/min. Plasma dabigatran concentrations were calculated by Hemoclot Thrombin Inhibitors assay.
Results: Pre-dialysis dabigatran concentration was 447 µg/L and decreased to 170 µmol/L within 2 hours of HD. Dabigatran levels rebounded postdialysis, the activated partial thromboplastin time remained elevated, and the patient continued to actively bleed. A second HD for 4 hours was performed, reducing dabigatran concentration to 52 µg/L. The patient survived and became awake and alert.
Conclusions: In our case, HD successfully reduced dabigatran levels suggesting that HD may be an effective modality for rapid removal of dabigatran in the setting of acute bleeding. To avoid a post-dialysis rebound, serial monitoring of dabigatran plasma levels and coagulation parameters may help to optimize extracorporeal therapy.

P11

VASCULAR ACCESS PROBLEMS IN A LONG-TERM CHRONIC HEMODIALYSIS PATIENT WITH AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE AFTER LIVER TRANSPLANTATION

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Aim: Autosomal recessive polycystic kidney disease (ARPKD) classically presents with arterial hypertension and progression to end-stage renal disease by the age of 15. Our aim is to present a 34-year old patient with ARPKD, who needed a liver transplant after 19 years of hemodialysis.
Methods: The patient with histologically confirmed congenital hepatic fibrosis with Caroli's disease received a liver transplant after numerous septic episodes and prolonged antibiotic treatment. The origin of infections were liver cysts and/or intrahepatic bile ducts. During operation, his radiocephalic arteriovenous fistula (AVF) in right arm, that functioned for 15 years, trombosed. The reanastomosis of fistula vein was done 9 years ago. Before this, he had a typical AVF in the left forearm.
Results: Trombectomy of AVF was unsuccessful. Temporary his dialysis access was a single lumen jugular catheter until the construction of a Goretex AVF in left upper arm, after which a steel syndrome developed with dry necrosis of the tip of the 1st and 2nd finger. Angiographically, the occlusion of radial artery could be chronic, becoming symptomatic after the creation of AVF. The patient refused the reduction of blood flow through AVF.
Conclusions: Serious vascular access problems occurred after liver transplantation in a long-term hemodialysis patient with steel syndrome dominating, in the absence of diabetes. Urgent kidney transplantation may be the optimal solution of the problem.

P12

VITAMIN D DEFICIENCY IS PREDICTED BY AGE, GENDER AND CARDIAC FUNCTION IN DIALYSIS PATIENTS

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Aim: This study aimed to identify risk factors for nutritional vitamin D deficiency in the dialysis population.
Methods: We routinely measured clinical and demographic factors that could identify patients who are deficient in vitamin D in a study cohort of 80 dialysis patients. Using logistic regression modeling, with vitamin D deficiency as the dependent variable, we generated predictive models
Results: Vitamin D deficiency was present in 88% of the study population. In the univariate analysis, the younger age, female gender, lower albumin level, higher CRP, and lower Heart Ejection Fraction, were strongly associated with lower levels of Vitamin D. The higher required Erythropoietin dose was significantly associated to lower Vitamin D levels. In the final model as mightiest predictors of vitamin D deficiency remained female sex, gender and Cardiac function ($\beta = 0.426$, $p = 0.001$, $\beta = 0.278$, $p = 0.016$, $\beta = 0.301$, $p = 0.01$), respectively.
Conclusions: Clinical factors predict low Vitamin D levels. Further study is needed to prove the benefit of the deficiency correction. The nutrition, inflammation, and CVD comorbidities should be of a priority interest.

P13

IMPROVEMENT OF THE CLINICAL, NUTRITIONAL AND INFLAMMATORY PARAMETERS DURING HIGH FLUX HEMODIALYSIS

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Aim: To investigate the beneficial effect of high-flux (HFHD) *vs.* low flux (LFHD) dialysis on clinical findings in dialysis patients.
Methods: Comparative analysis on dialysis and laboratory data was done in one arm crossover study. 65 patients were dialyzed 2 years on Low Flux and then crossed on High Flux dialysis for 2 years.
Results: Urea Reduction ratio rose significantly ($p = 0.02$). In the HFHD the mean appetite score improved significantly from 3.66 to 4.17. The Hemoglobin level significantly rose from 115 to 118 g per liter in the HFHD. The level of total lipids significantly declined in the HFHD period from 7.92 to 7.43 g/L. The protective High-Density Lipids significantly rose from 0.96 to 1.16 and the Low-Density Lipids significantly declined from 2.61 to 2.38 mmol/L ($p<0.05$). The total calcium level significantly improved from 2.11 to 2.17 mmol/L. The phosphorous level did not change in spite the better appetite. We observed significant improvement in the leukocyte number and CRP level (6.82 ± 1.63 vs. 6.24 ± 1.62, $p = 0.0001$; 5.60 ± 5.14 vs. 4.40 ± 3.96, $p = 0.014$), respectively.
Conclusions: High Flux Dialysis had beneficial effects on the nutritional, clinical and inflammatory parameters in dialysis patients.

P14

HIGH CUT-OFF HDF FAILED TO REDUCE PROTEINURIA IN RECURRENT POST-TRANSPLANT FOCAL SEGMENTAL GLOMERULAR SCLEROSIS

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Background: Plasma exchange (PE) is used to prevent graft loss after failure of conservative therapy for recurrent post-transplant focal-segmental glomerular sclerosis (pTx-FSGS). Besides PE, dialysis with high cut-off (HCO) hemofilters can also remove the proposed middle-molecular permeability factors (PF's).
The Patient and The Methods: A 44-years old female patient received a kidney graft after 2 years of hemodialysis, but soon developed a resistant pTx-FSGS, with a moderate renal failure (creatinine 150-200 µmol/l) and persisting proteinuria (3-5 g/day). A partial response to PE was accompanied by exceedingly low immunoglobulin (Ig) blood level demanding regular i.v. substitution. A trial of HCO hemodiafiltration (HDF) was undertaken. The removal of PF's by HCO HDF or PE was assessed indirectly by two surrogate middle-molecular markers (pre-albumin, MW 26 kD; and α-1-anti-trypsin, MW 50 kD).
Results: Comparable decrease (47% vs 48%) of blood levels of the surrogate markers was achieved by both methods, whereas proteinuria decreased less by HCO HDF (32% vs. 46%). The patient was exhausted by intensive HCO HDF and was switched back to PE and regular Ig infusions. A transient remission was followed by a full-blown nephrotic syndrome and transplant failure within a year.
Conclusions: Despite comparable reduction of (surrogate markers for) permeability factors in blood, HCO HDF decreased proteinuria less than PE in our patient with resistant pTx-FSGS. However, either treatment failed to preserve the transplanted kidney.

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P16

GRANULOCYTE ACTIVATION IS REDUCED IN CITRATE-BASED COMPARED WITH ACETATE-BASED HEMODIALYSIS FLUID

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Aim: Citrate-based dialysis fluid was developed recently. Its use is increasing and studies suggest increased clearance and improved treatment tolerance. In the present study, complement and leukocyte activation of citrate-based dialysis fluid was investigated in human whole blood and compared with acetate-based fluid.
Methods: Whole human blood was mixed with acetate- and citrate-containing fluids at concentrations mimicking those in a dialyzer during a dialysis treatment session with 3 mM acetate and 1 mM citrate, respectively. Complement activation, i.e. C3a, C5a and terminal complement complex (TCC), and leukocyte activation, i.e. up-regulation of CD11b on granulocytes, were measured at different time points up to 1 hour of incubation at 37°C.
Results: Leukocyte activation was significantly reduced in the presence of citrate compared with acetate indicated by a 32% higher expression of CD11b on granulocytes exposed to acetate. Also, a reduction in C5a activation was observed after 15 min in citrate- compared with acetate-based fluid; however, this effect disappeared after one hour. No significant difference was seen in activation of C3a or TCC comparing the two fluids.
Conclusions: Our results indicate that substituting acetate for citrate in dialysis fluid contributes to a more biocompatible dialysis by reducing activation of the innate immune response.

P17

PROTEIN-ENERGY WASTING (PEW) IS PRESENT IN HEMODIALYSIS PATIENTS ACROSS THE ALL BODY-MASS INDEX GROUPS AND INCREASES WITH DIALYSIS VINTAGE

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Aim: The aim of this study was to evaluate relationship between body mass index and serum albumins in hemodialysis population, and to investigate role of dialysis vintage in development of PEW.
Methods: 135 patients age ranging from 20 to 91 years were enrolled in the study. The median time spent on treatment was 34 (2-413) months. Laboratory and clinical data were obtained from the medical records and charts. The anthropometric measurements were performed after dialysis session. MIS was individually taken. Patients were divided into 5 groups regarding the body mass index (BMI) values: <20 kg/m^2 malnourished, 20-25 kg/m^2 properly nourished, 25.1-30 kg/m^2 overweight, and >30 kg/m^2 obese.
Results: 15.56% of our patients were nutritionally malnourished despite carefully provided renal replacement therapy. As time spent on maintenance hemodialysis was longer, BMI was lower and MIS had significantly increased – for patients undergoing HD less than 2 years median BMI was 25.35 (16.62-51.7) kg/m^2 and MIS 6.92 while after 10 years of treatment it was 23.06 (16.73-29.93) kg/m^2 and MIS 10.13 ($p<0.05$). Furthermore, median values of serum albumin were lower than 3.8 g/dl in all 5 analyzed groups. It was interesting to notice that serum albumin was the highest in the group of malnourished patients according to the BMI (3.71 g/dl). On the other hand, the lowest values were recorded in the group of overweight (3.54 g/dl). When divided into two groups due to albumin value (lower and higher than 4 g/dl), it could be seen that MIS was considerably higher in the group which measured lower albumin values (8.79 versus 5.79). There was no significant difference in time spent on HD (55 versus 54 months) regarding the serum albumin level.
Results: Our results demonstrated that PEW cannot be exclusively linked to malnourished patients - it is a major risk factor which extends to all patients, regardless of the BMI. PEW was more common in patients with longer dialysis vintage. Complex analysis like is MIS should be used to estimate malnutrition instead of the single parameter like is albumin or BMI.

P18

CONVECTIVE VOLUME (VC) CONTROL IN POSTDILUTIONAL HDF BY AUTOMATIC INTERMITTENT SCANNING OF TRANSMEMBRANE PRESSURE (TMP)

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Background and Aims: The VC may serve as an efficiency marker in HDF. Automatic VC optimization by the Gambro UltraControl® system is thus a tempting alternative to an a priori defined VC. The aim of this study was to investigate its feasibility and influence of its control parameter ΔQF_{min} upon the VC/VB (VB – blood volume processed) ratio value.
The UltraControl® Principle: In 60-minutes intervals, the Ultra-Control® system scans the TMP in 25 mmHg steps and checks the change in filtration rate (ΔQF). Scanning is stopped if the $\Delta QF < \Delta QF_{min}$ preset. The last TMP value resulting still in $\Delta QF > \Delta QF_{min}$, is preserved until the next scanning.
Materials and Methods: In 10 patients on postdilutional HDF, the conventional VC control was changed to UltraControl® with all treatment parameters unchanged. Three HDFs in that mode were performed in each patient with ΔQF_{min} = 0.3; 2 and 3 l/hour. Whenever the QF/QB exceeded 40% during HDF, manual TMP control was started. The VC/VB values reached at each HDF were recorded.
Preliminary Results: With ΔQF_{min} = 0.3, the UltraControl® mode had to be switched off in >90% sessions because of QF/QB >0,4 and manual TMP control used. HDF performed with ΔQF_{min} = 2.0 and 3.0 were all problem-free and resulted in VC/VB = 0.34,5 ± 0.040 and 0.312 ± 0.061, respectively. There was an apparent decreasing trend with increasing ΔQF_{min}.
Conclusions: The UltraControl® system can safely reach VC/VB values in the range of 0.33 to 0.35. However, to avoid alarms and operator´s interventions, the principal control parameter ΔQF_{min} had to be ≥2.0.

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PIV FLOW INVESTIGATIONS IN A ROTARY BLOOD PUMP FOR SPECIFIC BLADE POSITIONS

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Aim: Flow investigations on rotary blood pumps (RBP) are essential for their development. A common measurement technique is the Particle Image Velocimetry (PIV). We present an approach to perform PIV measurements on a RBP for specific blade positions, which is important for detailed flow investigations. In addition we compare flow data acquired with fluids of different properties.
Methods: The PIV was applied on a transparent RBP model made of PMMA (Plexiglas). A water glycerol sodium iodide mixture ($\eta \approx 4.9$ mPas, $\rho \approx 1.71$ g/cm^3) was used as a fluid to match the refractive index. An optical sensor was used to trigger the PIV acquisition system with the rotating part of the pump. This made recording of multiple images in specific blade positions possible. The same measurements were carried out with a water glycerol mixture ($\eta \approx 3.4$ mPas, $\rho \approx 1.12$ g/cm^3) resulting in lower image quality but bloodlike fluid properties. The results were compared to validate the laws of similarity of RBPs.
Results: The experimental setup allowed excellent measurements for different blade positions. In every position multiple images could be acquired. This allowed data averaging, which is necessary to separate laminar and turbulent effects. The comparison of flow data for two different fluid properties confirmed the laws of similarity.
Conclusions: An innovative setup for PIV measurements on RBPs is presented. The applied methods generated valuable flow data allowing detailed flow investigations. The laws of similarity of RPB and their application to PIV could be confirmed. The techniques will be applied in future studies.

P20

EXPERIMENTAL AND NUMERICAL INVESTIGATION OF FLOW FIELDS IN A LVAD AT DESIGN AND OFF-DESIGN OPERATION

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Aim: Current Left Ventricular Assist Devices (LVADs) exhibit a best-efficiency point defined by a rotational speed, flow und pressure head. They work in conjunction with the heart and thus operate within a wide range of operational points. The aim of this study is to investigate the flow in a centrifugal LVAD and to identify opportunities to improve the efficiency at all operational points.

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Methods: The flow was visualized with a Particle Image Velocimetry technique in a 1:1 model and predicted by Computational Fluid Dynamics (CFD). A water-glycerol-sodium-iodide mixture was used to match refractive indices of fluid and pump. Results were rendered non-dimensional to ensure similitude. The numerical prediction assumed a Newtonian blood model with a density of 1056 kg/m^3 and viscosity of 3,6 mPas.
Results: The numerical non-dimensional HQ-curve lies within the error margin of the experimental result. Moreover, an excellent agreement of the flow fields is found. The flow angle at the trailing edge increases with pump flow indicating a mismatch of the volute's tongue angle at the design point. Stagnation is found for low flows in the volute after the tongue and for high flows in the diffuser. The relative velocity shows a mismatch of the impeller/volute by an inhomogeneity in circumferential direction. It is also shifted to the suction side. The CFD results predict a drop of efficiency from 47,3% at 5 l/min to 29,4% at 1 l/min.
Conclusions: The results suggest a redesign of the volute to balance the flow. An adjustment to the blade angles reduces the shift within the passages and an increase in tongue angle reduces flow separation. Considering off-design operation, peak and mean efficiency and thus battery life can be increased leading to an improved quality of life for patients.

P21

THE CHANGES OF HEMODYNAMIC ENERGY CAUSED BY ISCHEMIC PRECONDITIONING

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Aim: The hemodynamic energy can be represented the blood flow pulsatility. Acute myocardial infarction (AMI) leads to changes of microcirculation in the myocardium and vascular tone which can affect to hemodynamic energy. The ischemic preconditioning might decrease the infarct area after AMI, but there have been a few studies which addressed the effect of preconditioning after AMI with using hemodynamic energy. We evaluated the effect of preconditioning after AMI by the concept of hemodynamic energy.
Methods: Twelve New Zealand rabbits were divided into 3 groups (C: coronary ischemia, P: ischemic preconditioning by clamp the coronary artery, R: remote preconditioning by clamp the right iliac artery). After preconditioning or without preconditioning, coronary ischemia for 30 minutes and reperfusion for 2 hours were done in all groups. The hemodynamic energy level and cardiac output (CO) were measured at several time points (baseline, coronary artery clamp, clamp off, reperfusion after 1 and 2 hours). The infarction area was measured.
Results: The levels of flow, mean arterial pressure, energy equivalent pressure, and surplus hemodynamic energy were not different in three groups at all time points. The CO of C were decreased depends on time point, but CO of P and R were not different as time went by. The infarction area of P was significantly smaller than other groups.
Conclusions: The hemodynamic energy levels were not affected by ischemic preconditioning before coronary artery ischemia and reperfusion.

P22

THE EFFECT OF LEFT VENTRICULAR ASSIST DEVICE SUPPORT ON CORONARY ARTERY BYPASS GRAFT USING COMPUTATIONAL STUDY

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Aim: In order to enhance the patency rate of coronary arteries bypass graft (CABG) in the heart failure patient who supported with left ventricular assist device (LVAD), local hemodynamic profile was considered. The effect from LVAD support might modulate local flow condition which related to progressive atherosclerosis and intimal hyperplasia. Therefore, flow pattern and endothelial shear stress should be analysis.
Methods: In this study, computational fluid dynamic was used to analyse three dimensional CABG (5:3 graft-to-host diameter ratios). Six end-to-side CABG configurations which consist of three patterns of the anastomotic angle (15, 30 and 45 degrees) and two patterns of the distance from a stenosis to the heel point of anastomosis (0 and 5 mm) were simulated. The flow measurements at diastolic phase of the acute animal experiment from the study of Y. Ootaki et al., 2005 during LVAD support at 2, 2.5 and 3 litre/min were used to impose at the proximal of graft and host vessels. The blood flow was assumed to be incompressible with Newtonian property at a viscosity of 0.004 kg m-s and a density of 1050 kg/m^3. In this study the steady flow simulation were performed.
Results: For increasing LVAD support, maximum shear stress at the toe of anastomosis were decrease and the area of low shear stress (<12 Dyne/cm^2) at proximal of graft region were increase at all graft configurations.
Conclusions: Low shear stress at the proximal area of graft may be the cause of graft occlusion or deformation.

P23

MITRAL REGURGITATION CHANGES AFTER LVAD IMPLANTATION: A NUMERICAL STUDY

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Aim: Although the left ventricular (LV) unloading due to LVAD, in some patients (PTs) with severe mitral regurgitation (MR) and severe LV and left atrium dilation, a suboptimal results of LVAD implantation, characterized by persistent relevant MR, elevated left atrial and pulmonary pressure and low cardiac output was observed. The aim of this work is the use of the numerical simulator of the cardiovascular system (NM) to simulate PTs candidate to LVAD implantation with severe MR to assess if NM can predict in advance which PTs will be responder to LVAD therapy and which PTs need a mitral valvuloplasty (MV).
Methods: Baseline and acute data after LVAD implantation of 5 PTs with severe MR were collected. PTs baseline were reproduced by the NM and then the effect of LVAD implantation was simulated with and without MV. Simulations results were compared to acute measured data.
Results: Comparing measured and simulated data, it can be deduced that the NM can well reproduce PTs baseline and predict the haemodynamic effects of LVAD implantation in all 5 PTs. Moreover the model was able to identify the PTs in which the LVAD implantation did not improve haemodynamic significantly due to severe MR and persistent high LV volumes. Finally the NM can predict the effect of LVAD implantation and MV performed in one of the 5 PTs.
Conclusions: NM could be useful to support clinicians in LVAD PTs selection and to optimize and personalize LVAD therapy.

P24

DEVELOPMENT OF AN IMPLANTABLE COMPLIANCE CHAMBER FOR A TOTAL ARTIFICIAL HEART

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Aim: A total artificial heart (TAH) is under development at the RWTH Aachen University. The TAH comprises a linear drive in between two ventricles, which are separated by a membrane. A compliance chamber (CC) is connected to the drive unit. It has to damp pressure peaks in the drive unit to avoid atrial suction and balance systemic and pulmonary output. In addition, the displaced volume of a single stroke has to be increased. This study focuses on the development of an implantable compliance chamber for the pulsatile TAH.
Methods: To reduce pressure peaks of the TAH a compensating volume is used. The pressure inside the CC is regulated internally. A negative pressure is generated inside the drive unit to support the passive movement of the membrane and thus to increase the displaced volume. An active mock circulation loop was used to analyse the size and elasticity of the CC. Clinical CT data was analysed to adapt the geometry of the CC to the human thorax.
Results: The pressure peaks inside the drive unit could be reduced up to 5 mmHg in the working area. The displaced volume was increased by up to 18.2% on the systemic side and 14.8% on the pulmonary side. An anatomical fit of the CC was achieved, which ensures implantibility into the pleural cavity.
Conclusions: An implantable device was developed, which is able to significantly reduce pressure peaks and to increase the flow output. Further tests in chronic animal trials are planned.

P25

SPECIAL TILTING DISC MECHANICAL VALVE FOR APPLICATION IN PNEUMATIC VAD RELIGAHEART

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Aim: Due to cease manufacturing tilting disc valves, confirmed as the efficient solution for pulsatile VADs and risk of thrombogenicity of soft leaflets

polyurethane valves, single disc valve was designed for new Polish pulsatile VAD ReligaHeart. The paper presents results of *in-vitro* and *in-vivo* study.
Methods: The valve consists of polymeric disc (PEEK Optima LT1) leaded by low profile catch elements of titanium ring (GRADE 2). To optimize the flow structure and avoid local turbulences, CAD project was examined with CFD simulations. Five valves size (Ø 14-24 mm) were manufactured. Following investigations were performed: hydrodynamics, local flow assessment, long-term durability, *in-vitro* haemolysis and acute thrombogenicity tests. Finally the valves were examined *in-vivo* on animals and human during heart assistance utilizing ReligaHeart EXT VAD.
Results: Static and dynamic backflows were comparable to the reference (Medtronic Hall valve). Durability test (200 days) revealed no damage of discs surfaces nor valves malfunction. Good haemolytic and athrombogenic features were confirmed *in-vitro*. The animal study (total about 250 days) revealed no serious thrombus adhered to the valves components. The human trials are pending (2 patients have been supported till the date).
Conclusions: Hemodynamic and athrombogenic features of developed valve were confirmed *in-vivo*. The valve is appropriate to be applied in pulsatile ReligaHeart VAD for adult and paediatric.

P26

PATHOLOGICAL FINDINGS IN CARDIAC APEX REMOVED DURING IMPLANTATION OF VENTRICULAR ASSIST DEVICES (VAD) ARE NON-SPECIFIC. A 13-YEAR-EXPERIENCE AT A GERMAN HEART CENTER

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Aim: Ventricular assist devices (VAD) have become an established therapy for patients with end-stage heart failure. The two main reasons for this development are the shortage of appropriate donor organs and the increasing number of patients waiting for heart transplantation (HTX). Furthermore, the enormous advances in the technical equipment and the rising clinical experience have improved the implantation technique, the durability and the long-term patient outcomes.
Methods: We reviewed all cases of left ventricular assist device (LVAD) implantation at our Erlangen Heart Center during January 2000 - July 2013. The main aim of this study was to analyze the underlying pathology from the cardiac apex removed during the implantation. From all patients, we created a follow-up, analyzed the pathological features with the clinical diagnoses and described the overall outcome.
Results: VAD implantation was performed in 266 cases at our center in the last 13 years (2.2% of the total of 12254 cardiac surgical operations in that period). From these patients 223 underwent LVAD or biventricular (BVAD) implantation; the remaining received a right (RVAD) implantation. The most frequent underlying clinical diagnoses were dilated (n = 84, 37.7%, DCM) or ischemic (n = 61, 27.4%, ICM) cardiomyopathy. The pathological findings in the apex biopsy were generally non-specific and showed variable interstitial myocardial fibrosis with evidence of fibre loss, fatty degeneration and variable irregular atrophy of muscle fibres, consistent with dilated and ischemic cardiomyopathies as the most frequent causes of heart failure in these patients. Only a few cases showed other specific features such as myocarditis and AL-amyloidosis.
Conclusions: Pathological findings in cardiac apex removed during LAVD implantation are rather non-specific and they generally reflect the late stage or consequences of chronic myocardial damage in cases of dilated or ischemic cardiomyopathies. Variable patchy chronic inflammatory changes may be observed in cardiomyopathies as a non-specific reaction caused by myocardial fiber damage and should not lead to misinterpretation as evidence of myocarditis or revision of original diagnosis.

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EFFECTS OF COLLOIDS ON MYOCARDIAL EDEMA IN ISOLATED HEARTS

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Aim: Recently, a large animal isolated-heart-setup was introduced to investigate the interaction between hearts and rotary blood pumps. These hearts were prone to myocardial edema formation, probably due to the low concentration of the expensive colloid albumin in the perfusates. Aim of this study was to compare the effects of albumin and the low-cost colloid hydroxyethyl-starch (HES) on edema formation in rodent isolated hearts.
Methods: Both colloids were added to standard crystalloid and erythrocyte-based perfusates. These solutions were compared in 4 groups of 7 isolated rat hearts (weight: 1.68 ± 0.20 g). The hearts were excised, resuscitated and then the setup was switched to working mode, for a total duration of 175 minutes. Myocardial water content and hemodynamics were measured and compared.
Results: Myocardial water content at the end of the experiment indicated edema formation in all hearts (84.3 ± 1.6%). No significant difference in water content was found between HES and albumin-based perfusate (84.5 ± 1.4 vs. 84.0 ± 1.7%). Erythrocyte-based solutions resulted in significant lower water content than crystalloid perfusate (83.3 ± 1.1 vs. 85.2 ± 1.4%). Hemodynamics were not significantly different between HES and albumin-based groups.
Conclusions: In this study myocardial edema formation seems inevitable in isolated hearts, independently of the colloid type. Although erythrocyte-based solutions resulted in lower myocardial water content, it was high compared to the physiological water content (74-76%).

P28

NEW BIOMATERIALS THROMBOGENICITY EVALUATION METHOD IN DYNAMIC BLOOD FLOW CONDITIONS

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Aim: Rotary blood pumps are the mostly used long-term heart support devices. However, shear stress induced platelets activation is still a problem. The work aim was development of physical model for blood rotating with different rotational velocity over a biomaterial surface, to evaluate *in vitro* biomaterial thrombogenicity and thrombocytes activity, at high shear stress.
Methods: Physical model was developed as chamber with rotating biomaterial disk (Ø 28 mm), simulating rotary pump rotor. Disk to chamber bottom distance is regulated from 0,05 to 0,30 mm. Disk rotation speed is varied from 500 to 5 k RPM. Controlled blood flow is provided through chamber: from 1 to 15 ml/min. The shear stress exposed thrombocytes activity is determined. The numerical analysis of flow conditions and e shear stress was performed.
Results: Blood particles motion trajectories in the chamber were determined. Boundary conditions of chamber crack, disk rotating velocity, blood cells exposure time for shear stress and shear stress modeled values were defined. Thrombogenicity test model was manufactured. Initial model tests, using water, blood substitute (viscosity 3,5cP) and blood, for different chamber crack size and rotational velocity, were confirmed ability to simulate wall level flow from 0,785 to 7,3 m/s.
Conclusions: The physical model for investigation of shear stress impact on blood in rotary blood pumps was developed. It will be used to examine thrombocytes exposed to shear stress and evaluate new biomaterials surface structure impact on the generated shear stress in rotary motion.

P29

ULTRASONIC DOPPLER SYSTEM FOR EVALUATION OF VAD OUTPUT AND DETECTION OF MICROEMBOLUS

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Aim: In spite of progress of material engineering and VADs construction, thromboembolism has still been the most fundamental problem of mechanical heart support. The aim of study was to apply the ultrasonic Doppler system to detect of microembolus and to VAD output measure.
Methods: The expected size of microembolus was assessed by means of flow cytometry (aggregates) and immune-histochemical examination of material filtered from the blood (40 um of filter porosity). Acute thrombogenicity method was applied to embolus generation. The multigate Doppler apparatus and ultrasonic transducers were constructed. Volumetric flow was calculated by integration of flow velocity at each gates. In order to detection of microembolus the following methods of echo analysis were developed: linear autoregression model, matching pursuit transformation and particle component analysis algorithm.
Results: Numerous small aggregates (up to 40 um) were found in blood. The filtered material consisted of larger fibric microthrombus (90-180 um) and intermittent filamentous embolus about 280 um. The accuracy of flow measurements was 20% in the range of 1-7LPM (pulsatile flow). Numerical algorithms were able to count the embolus and to distinguish it between air embolus and thrombus.
Conclusions: The developed system allows to measure the VAD output and to assess the number of microembolus. Further work will focus on improvement the accuracy of flow measurement and recognition of microembolus size.

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TOWARDS CLOSED-LOOP VAD CONTROL

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Aim: The quality of mechanical heart support strongly depends on the physician's individual experiences. To date, pump-operating parameters combined with clinical assessments from monitoring and laboratory values are the exclusive inputs for therapy decisions. Closed-loop control strategies of physiological parameters may overcome these clinical challenges.
Materials and Methods: The experimental setup consists of pressure measurements in the aorta, left ventricle, central vein and pulmonary artery. Cardiac output (CO) is measured with a perivascular ultrasonic flow probe on the pulmonary artery. These signals along with SpO2 and ECG are combined on a real-time computer that controls a rotary blood pump. A novel myocardial infarction model in sheep based on infusion of microspheres is used to identify a reduced cardiovascular system model and examine different model based control strategies.
Results: We are currently carrying out a study using the acute heart failure animal model in which we successfully tested controllers for mean arterial pressure and CO. First results indicate good controller performance in case certain boundary conditions such as sufficient blood volume are met.
Conclusions: We established a framework to assess closed-loop control strategies in animal models. Future work will consider identification of the degree of support.

P31

RESEARCH OF DYNAMIC AND POWER CHARACTERISTICS OF MECHATRONIC UNIT OF THE ARTIFICIAL HEART

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Aim: Important problem in creation of implanted systems of artificial heart based on the mechatronic units is definition of their dynamic and power characteristics.
Methods: The mathematical model of dynamics of the mechatronic unit of artificial heart which considers pulsing nature of movement of a membrane, elasticity of the chamber of the artificial ventricle of heart, parameters of the DC motor and the roller-screw executive mechanism is developed for the solution of this problem. Dynamics of the mechatronic unit of artificial heart is investigated on the basis of double-mass mathematical model. The first weight (entrance link of the executive mechanism) is rigidly connected with rotor of DC motor, and the second weight (an output link) progressively moves loading. For the solution of the differential equations the MATLAB complex was used.
Results: Dependences of change of the main dynamic and power characteristics of the mechatronic unit of the artificial heart, movements of the membrane of an artificial ventricle of heart considering pulsing character, elasticity of the camera of the artificial ventricle of heart, parameters of the DC motor and the roller-screw executive mechanism are received.
Conclusions: The researches of the developed mathematical model of dynamics of the mechatronic unit of artificial heart showed that for compliance technical requirements the mechatronic unit of artificial heart has to possess with a working power of 28 … 30 W at the power of thermal losses no more than 10 W.

P32

AUTOREGULATION UNIT FOR ADAPTIVE CONTROL OF VADS: EXPERIMENTAL SCENARIO ON A CARDIOVASCULAR HIBRID SIMULATOR

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Aim: The use of VAD as destination therapy points out the need of new therapy approaches of VAD control. In this work an innovative integrated autoregulation system for controlling a sensorized VAD is presented and tested by means of a hybrid cardiovascular simulator.
Methods: The ARU is an autonomous system able to automatically respond to physiological cardiac demand and to the dynamic evolution of patient's cardiovascular status. In the present work the ARU was connected to a cardiovascular simulator able to reproduce a wide range of pathologies and hemodynamic conditions. In this scenario, ARU autoregulation capabilities and remote control have been tested in order to show the feasibility of the approach.
Results: The capability of the ARU to control from remote the pump integrated in the hybrid simulator has been tested in dedicated experiments of speed control. Additional experiments permitted to test the autoregulation control while changing the hemodynamic conditions on the simulator.
Conclusions: The experiments show the ARU permits to control VAD speed settings both through a local controller and via wireless with response time below 1 s. When active, the autoregulation flow control detects the change of hemodynamic conditions and effectively reacts to keep VAD flow in a desired range within few seconds.
Acknowledgments: Work supported by SensorART (N. 248763) project.

P33

DEVELOPMENT OF A COMPACT DRIVE UNIT WITH HIGH CONTROLLABILITY FOR A PNEUMATIC TOTAL ARTIFICIAL HEART SYSTEM

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Aim: Downsizing of a driver for a pneumatic total artificial heart (PTAH) is one of key factors for improving the patient's QOL. However the controllability of the drive condition and the size of a device have a trade-off relation generally. The aim of this study is to develop a compact PTAH drive unit that can control the left and right pumps driving condition independently.
Methods: The core unit of the drive unit consists of a DC servo motor, a crankshaft, a cylinder-piston, pressure regulation valves and equipped with a relief valve in the diastole phase to avoid excessive negative pressure (the size and weight: 26 × 18 × 11 cm and 3 kg). The systolic ratio (SD) is generated by the speed control of the DC servo motor. The drive system consisting of 2 core units was examined in an overflow mock circuit (Preload: 10 mmHg, Afterload: 80, 100, 120 mmHg and 20, 30, 40 mmHg in the left and right pumps).
Results: The developed driver was able to regulate the SD, the HR and the pressure relief time independently in the left/right. The flow rates of the left and right pumps were 3.7-8.9 L/min and 4.1-9.5 L/min (SD: 30-50%, HR: 50-100 bpm). The driving pressures in the diastole phase were the left: -3.0-20.0 mmHg and the right: 3.9-8.2 mmHg.
Conclusions: These results indicated that the developed compact TAH drive unit had a sufficient performance and adjustability to drive PTAH pumps.

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RISK ANALYSIS TOOL APPLIED TO DEVELOPMENT OF VAD SAFETY CONTROL SYSTEM

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Aim: One of the challenges about bio-automation is the interpretation of biological requirements and consolidation of automated systems that perform the wish of a medical team. This ensues because of the difference of vocabulary and knowledge among engineers and doctors. This work proposes to apply mechatronic concepts and risk analysis tools to develop a VAD safety control systems.
Methods: Considers the nature of the fault signals, as well as the Discrete Event Systems theory and through the application of tools for risk analysis, and fault diagnostic and treatment techniques aiming the development of control models based on modular and distributed architectures. The diagnostic and treatment of faults are made according its severity and the control system performs the regeneration or degeneration of VAD system to a secure state.
Results: This study performed an effective risk analysis, considering the multidisciplinary context, through the use of the HAZOP (Hazard and Operability Studies). This tool simplifies to understand project requirements and support its consolidation making easier the integration with engineers and doctors. From the knowledge acquired about the system behavior during critical conditions, formal models are developed applying Bayesian Networks and Petri Nets to the diagnostic and treatment of faults.
Conclusions: The proposed procedure has been successfully applied on the VAD development, which was performed by a Brazilians researcher's team from the Escola Politécnica da USP and from the Instituto Dante Pazzanese de Cardiologia. Thus, is possible to achieve an autonomous and safe control system that complies with the applicable technical standards, as well as the strict project requirements for this class of system.

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Implants and Robots

P35

STUDY OF ESTIMATED FORCE FEEDBACK CONTROL FOR SURGICAL ROBOT

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Aim: In a surgical robot, haptic information including sense and force being delivered by hands is as importance as visual or aural information. This study focus is to quantify force information during robotic surgery.
Methods: Implementing force feedback systems in surgical robot requires three main steps: 1) Design of sensor amplification circuit; 2) Implementation of surgical dummy tool; 3) Device calibration and force feedback system test. Firstly, to develop a sensor module, the strain gauge of Linear S-series (AP-11-S15S-350) is used to compose bridge circuit and tension. Amplification circuit (INA118U) was designed to amplify a few mV of output signal from a force sensor. Secondly, a new surgical dummy tool was designed as follows: total length 430 mm, slave robot arm mount part 30 mm × 25 Φ. Finally, system calibration was tested by estimation of multi-axis force using the strain gauge. The sensor estimation detected force from 0 to 2N.
Results: Amplifying circuit augmented the output signal by 1000 times consistently (*p<.0001*). Optimal position (P-point) of string gauge was end-point for surgical instrument tool. Test results of the P-point are shown in Table 1.

P	10 mm	20 mm	30 mm	40 mm	50 mm
Voltage (V)	1.21	0.83	0.71	0.58	0.35
Force (N)	1	1	1	1	1

Conclusions: The realization of force sensing was successfully quantified. Further study is required to incorporate the force feedback system into *in-vivo* animal experiments as well as to develop compact component design and small size sensor for surgical robots.
Acknowledgments: Supported by a Korean Ministry of Health and Welfare (A121157).

P36

POSSIBILITY OF POTENTIAL RADIOLUCENT LINE OCCURRENCE INDUCED BY USING METAL BLOCK AUGMENTATION IN REVISION-TOTAL KNEE ARTHROPLASTY

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Aim: Rate of radiolucent lines beneath metal block augmentation has been reported. However, little information about the reasons of the occurrence of radiolucent lines is available. The aim of the current study is to identify the potential possibility of the occurrence of radiolucent lines induced by using metal block augmentation in revision-total knee arthroplasty (TKA).
Methods: Composite tibia finite element (FE) model was developed and revision-TKA FE model was integrated with the composite tibia FE model. Four metal block augmentations were then considered and integrated. A compressive load of 2000N through the femoral component was applied to the composite tibia FE model integrated with the tibial component, sharing by the medial and lateral condyles, simulating a stance phase before toe-off. Flexion positions from 0° to 140° were then considered with femoral rollback phenomenon.
Results: The stresses on the medial edge beneath metal block augmentations were 2.21 ± 0.37, 3.26 ± 0.34, 2.50 ± 0.43 and 2.24 ± 0.25 Mpa for 5, 10, 15, 20 mm metal block augmentations, respectively. These findings may indicate that 10 mm metal block augmentation is the most optimal for the prevention of the radiolucent lines because of the proper stress transfer into the medial edge region beneath metal block augmentations.
Conclusions: This study may be valuable by identifying for the first time the potential possibility of the occurrence of radiolucent lines possibility through evaluation of stress distribution beneath metal block augmentation in in revision-TKA.

P37

CHARACTERIZATION OF INFLAMMATORY POTENTIAL OF MODEL BIOMATERIALS USING NOVEL MACROPHAGE/FIBROBLAST CO-CULTURES

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Aim: Chronic inflammatory reactions are an undesired effect after implantation of biomaterials and lead to failure of implants. Here, we developed a novel *in vitro* macrophage/fibroblast co-culture model to evaluate the inflammatory potential of implants by using model biomaterials to detect how material surface properties affect the inflammatory response in the co-culture system.
Methods: The co-cultures were established using fence chambers having internal and external channels to establish separated and mixed co-cultures before and after removal of the chamber. SAMs with terminal methyl (CH_3), amine (NH_2), hydroxyl (OH) and carboxyl (COOH) groups were prepared by chemisorption of alkylsilanes onto glass. The physical properties of the SAMs were characterized by water contact angle and zeta-potential measurements. The inflammatory reactions of leukocytes on different SAMs were investigated in the presence of fibroblasts regarding THP-1 derived macrophage adhesion, foreign body giant cell (FBGC) formation, integrin β-1 expression and cytokine production.
Results: The physical characterization demonstrated the successful generation of model biomaterials ranging from hydrophilic to hydrophobic and from negatively to positively- charged surfaces. All inflammatory reactions studied were found to be highest on the hydrophobic CH_3 and lowest on hydrophilic anionic COOH surfaces.
Conclusions: The novel co-culture system we established can be used for testing the inflammatory potential of implants and shows how surface properties can affect the inflammatory responses.

P38

QUALITY OF BONE PLATES PRODUCED LOCALLY IN INDONESIA

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Aim: Osteosynthesis plates are clinically used to fix and position a fractured bone. They should have the ability to withstand cyclic loads produced by muscle contractions and total body weight. The very high demand for osteosynthesis plates in developing countries in general, and in Indonesia in particular, necessitates the utilization of local products.
Methods: We investigated the mechanical properties, i.e. proportional limit and fatigue strength, of Indonesian-made Narrow Dynamic Compression Plates (Narrow DCP) as one of the most frequently used osteosynthesis plates, in comparison to the European AO standard plate, and its relationship to geometry, micro structural features and surface defects of the plates.
Results: All Indonesian-made plates appeared to be weaker than the standard Narrow DCP because they consistently failed at lower stresses. Surface defects did not play a major role, although the polishing of the Indonesian Narrow DCP was found to be poor. The standard plate showed indications of cold deformation from the production process in contrast to the Indonesian plates, which might be the first reason for the differences in strength. This is confirmed by hardness measurements. A second reason could be the use of an inferior quality of stainless steel.
Conclusions: The Indonesian plates showed lower mechanical behaviour compared to the AO-plates. These findings could initiate the development of improved Indonesian manufactured DCP-plates with properties comparable to commonly used plates, such as the standard European AO-plates.

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NEW PEEK IMPLANTS FOR MANDIBLE RECONSTRUCTION

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Aim: Commonly, stabilization of mandible fractures is performed with titanium implants. Failure of implants occurs if microcracks are initiated by the surgeon during mechanical adaption to the bone shape. Successful replacement of titanium implants by polymeric implants made of PEEK (polyetheretherketone) requires a new design solution, mechanical modeling with the finite element method (FEM) as well as extensive mechanical long-term testing.
Methods: Starting from the design of the usual titanium mandibular reconstruction plates, new designs for PEEK implants were developed and optimized with FEM modeling. The manufactured implants were applied to a mandible model made by generative manufacturing. Both titanium and PEEK implants were tested mechanically using a specially designed test equipment with four actors (linear motion units) to simulate muscle behavior. Further, cyclic mechanical testing was performed to enable analysis of the chewing cycle and the chewing forces.
Results: The four actors simulate chewing based on a given chewing cycles up to 2.5 million times. Simultaneously, material deformation was observed by optical image analysis. Based on the mechanical data and morphological analysis of crack formation, fatigue and failure were analyzed and assessed.
Conclusions: Concerning mechanical properties, specially designed PEEK implants are able to replace titanium implants for mandibular reconstruction.

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NUTRITIONAL STATUS IN MAINTENANCE HEMODIALYSIS PATIENTS

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Aim: This study aims to evaluate the nutritional status of patients undergoing maintenance hemodialysis in University Hospital Center Zagreb.
Methods: 135 patients, age ranging from 20 to 91 years, were enrolled in the study. The median time spent on treatment was 34 (2-413) months. Laboratory and clinical data were obtained from the medical records and charts. The anthropometric measurements were performed after dialysis session. Malnutrition-inflammation score was individually taken. Patients were divided into 5 groups based on their body mass index (BMI), - <19 kg/m^2 severely, 19-21.9 kg/m^2 moderately and 22-24 kg/m^2 slightly malnourished, 24.1-30 kg/m^2 properly nourished, and >30 kg/m^2 overweight.
Results: 48.1% of our patients were nutritionally malnourished (8.9% severely, 18.5% moderately and 20.7% slightly) despite carefully provided renal replacement therapy. As the time spent on maintenance hemodialysis increased, malnourishment became more pronounced. Low serum concentrations of iron and total iron binding capacity indicate the existence of chronic anemia in all 5 groups. Levels of ferritin above normal range support this claim. As ferritin is one of the acute phase reactants this increase could also be the consequence of numerous comorbidities related to progressive loss of renal function. Furthermore, it was interesting to notice that serum albumin values were the highest in the group of severely malnourished (3.75 g/dl). On the other hand, the lowest values were recorded in the group of overweight (3.52 g/dl). Only 17 patients (5 severely malnourished) took oral dietary supplements. In all analyzed groups measured albumin values were lower than 3.8 g/dl.
Conclusions: This undoubtedly indicates the presence of comorbidity and inflammation, and accentuates the likelihood of poor treatment outcome. It also emphasizes that PEW cannot be exclusively linked to malnourished patients - it is a major risk factor which extends to all patients, regardless of BMI.

P42

THE USE OF CITRIC ACID DIALYSATE IN OUR DIALYSIS CENTER: PRELIMINARY EXPERIENCE

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Background: Citric acid dialysate (CD) is a dialysis acid concentrate for bicarbonate-based dialysis containing citrate instead of acetate as the primary acidifying agent. The aim of our study was to compare the impact of citrate- and acetate-based dialysates on acid-base status, rate of inflammation, calcium balance and dialysis efficiency.
Methods: We retrospectively evaluated 99 chronic hemodialysis patients treated during the months of Dec 2012 and Sept 2013. Before the switch to CD, all of the clinics used regular bicarbonate dialysate acidified with acetic acid. Regular pre-dialysis biochemical data were gathered a month before and after switching to CD.
Results: Subjects were 63% male, mean age was 62 ± 15 (range 26-92) years. After switching to CD, there was an increase in total CO_2 level from 22.9 ± 3 to 24.8 ± 3.7 mmol/l (p<0.001), CRP values decreased from 28 ± 36 to 16 ± 11 mg/l (p = 0.079), serum calcium remained unchanged (2.13 ± 0.2 pre-CD, 2.14 ± 0.2 mmol/l with CD, p = 0.74), troponin I levels were within normal parameters in both groups, concentration of phosphate was 1,56 ± 0.43 pre-CD, 1.6 ± 0.47 with CD (p = 0.54). iPTH levels were reduced from 342 ± 357 to 314 ± 375 pg/ml (p = 0.59). There was a minor decrease of serum creatinine and BUN concentrations after switching to CD (817 ± 243 to 793 ± 236 µmol/l, p = 0.48 and 27.2 ± 7.2 to 26.7 ± 6.9 mmol/l, p = 0.62), while the levels of potassium increased (5.44 ± 0.89 to 5.65 ± 0.95 mmol/l, p = 0.119).
Conclusions: Data suggest that the substitution of citrate for acetate in dialysis fluids may improve acid-base status and level of inflammation in maintenance hemodialysis patients.

P43

THE CHALLENGES AROUND POPULATION CHANGES IN RELATION TO PD USAGE IN EUROPE

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Aim: The usage of peritoneal dialysis (PD) varies across Europe and between different age groups with the trend of under-utilization of PD among elderly patients in all countries. The current projection of general population changes over 20-30 years could further impact the use of PD. The aim was to investigate if population structure and household composition can be considered as a direct limitation in PD usage.
Methods: The ERA-EDTA report was examined to understand differences in PD use related to patient age distribution in Europe. Statistics published by Eurostat, WHO and European Observatory were examined to investigate the population structure and living conditions in Europe along with projected trends.
Results: The number of people requiring renal replacement therapy is rising and dialysis incidence age increasing but usage of PD declines with age. Due to increasing life expectancy and decreasing fertility until 2050 number of people <65 will be doubled. In parallel the number of single households with elderly people living alone isolated from family support will grow. Nordic countries have the highest PD use in Europe and the highest number of single households. Currently Southern European countries have a much higher proportion of elderly people living with families, although this will trend down – and current PD use is already lower than in Nordic countries.
Conclusions: The number of elderly, single and multi-comorbid patients will be rising in Europe putting greater demand on the healthcare systems and challenging PD therapy usage. However, in this population setting, high PD usage is already possible as shown in Nordic countries.

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NEPHROLOGIST NUMBER AND GENDER AS FACTORS THAT MAY INFLUENCE PD CHOICE IN EUROPE

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Aim: The utilization of PD therapy varies in Europe. Common explanations for this variability include reimbursement, organization of health and social care system, centre structure, physicians' experience in clinical practice or general patients' characteristics. The aim was to investigate if nephrologist factors influence dialysis modality choice.
Methods: The ERA-EDTA report was examined to show differences in PD distribution across Europe. The analysis of publicly available nephrologist number/demographics was performed as well as literature searching to examine role of gender in decision process.
Results: There was no relationship between nephrologist number (controlling for population) and PD use with the exception of UK and IT that have 0.6 and 3.5 nephrologists/100000 population respectively. In US study female nephrologists were more likely to select PD as preferred option. A Canadian study found when the nephrologist is female the patients' chance of better outcomes increased. In a UK experimental study participants without CKD chose PD or HD based on video from female or male speakers and no significant influence of speakers' gender on modality choice was observed. Meta-analysis of non-dialysis studies revealed important effects of physician gender on communication during medical visit with females more active in partnership behaviours, positive talk, psychosocial discussion and emotionally focused talk.
Conclusions: It is not well investigated if gender of nephrologist or different configuration of nephrologist-patient gender may be factors that affect dialysis modality choice. There are gender differences in consultation behaviour which suggest this could play a role in modality choice.

P45

THIRTEEN YEARS OF NON-TUNNELED PRECURVED JUGULAR CATHETER WITH PERIPHERAL VEIN AS VASCULAR ACCESS IN A PATIENT WITH DIABETES TYPE 1 AND HEMODIALYSIS FOR 28 YEARS

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Aim: To present successful and uneventful hemodialysis for 13 years with nontunneled, precurved, single lumen catheter and peripheral vein as vascular access in a patient having been on hemodialysis (HD) for 28 years.
Materials: 59 years old woman with diabetes type 1 from the age of 12 began with chronic HD therapy in 1985. From 1985 and 1996 she had 3 unsuccessful creations of native AV fistula on both arms and 5 PTFE grafts on both upper arms, forearms and a thigh. Since then she had several femoral (11) and nontunneled and tunneled subclavian (4) catheters. From 2001 to 2014 a right jugular, single lumen, precurved nontunneled HD catheter was used together with right forearm basilic vein as vascular access.
Results: During the last 13 years the catheter was exchanged by guidewire for 11 times because of malfunction. It was removed only once because of Staph. aureus sepsis and reinserted after several weeks of antibiotic therapy. The right forearm basilic vein transformed in time into fistula-like vein, with thick wall and wide lumen, most probably because of high blood flow during HD. Although the attempt to create AV fistula from that particular vein was unsuccessful, the vein never thrombosed. Blood flow was 250 ml/minute. After each HD the catheter was primed with 30% citrate, with mupirocin at exit site and dressed with dry gauze.
Conclusions: 13 years, nearly half of 28 years of HD therapy time (46.4%) nontunneled jugular catheter and peripheral vein were excellent and uneventful vascular access.

P46

CHANGES IN OXIDATIVE STRESS DURING HEMODIALYSIS IN AN EXPERIMENTAL, SHEEP MODEL

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Aim: The aim of this study was to develop a new experimental, non-uremic and uremic sheep models of hemodialysis (HD) in relation to oxidative burst, which is one of the major factors leading to erythrocytes destruction during extracorporeal circulation.
Methods: Ten hemodialysis sessions were performed in nephrectomized rams, each day after the nephrectomy, and intact animals, which were dialysed three times a week. Changes of the thiobarbituric acid reactive substances (TBARS) concentration, total antioxidant capacity, morphology, osmotic fragility and LDH concentration during HD were determined. Dialysis efficiency was assessed with blood biochemical parameters correction.
Results: We observed a significant decrease of the absolute leukocyte number in peripheral blood in the first 15 minutes of the HD session. This effect was not permanent and the white blood cell count returned to pre-dialysis level at the end of the procedure. Decline of leukocyte was strong, negatively correlated with TBARS production. LDH concentration after dialysis session was significantly higher than before the treatment. Blood clots were formed in the area of the blood inlet and outlet of the dialyzer.
Conclusions: The model that we describe is the experimental step to understand biology and it will be a reference to evaluate methods preventing blood damage during hemodialysis.

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TWO-POOL VIRTUAL PHYSICAL SIMULATOR TO REPRODUCE FLUID AND MASS TRANSFER DURING DIALYSIS

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Aim: Hemodialysis (hd) induces fast changes of fluid volumes and electrolyte concentrations in patients' body compartments. The aim of this work is to develop a two-pool virtual patient physical simulator (tvps) reproducing intracorporeal transport phenomena during hd.
Methods: The main function of the tvps is to replicate the patient intra- and extra-vascular compartments (ivc and evc). ivc is reproduced by a rigid reservoir and a set of semi-permeable hollow fibers, representing the large arterial and venous vessels and the capillary system respectively; evc is simulated by rigid reservoirs, connected to a compliance. the hollow fibers are arranged in ad-hoc designed modular filters, placed in the ivc. test fluids reproduces rheological properties, oncotic pressure (by using polygelin and dextran), electrolytes and catabolites contents of an uremic patient.
A Gambro AK200 machine was used to test the TVPS, performing a 3.5 hours HD (average duration). Fluid samples were collected from TVPS at scheduled intervals to evaluate the IVC and EVC solutes concentrations, for comparison with clinical average data.
Results: All the electrolytes and urea concentrations showed good agreement with clinical data (dextran: max shift 10%, polygelin: 20%). Plasmatic volume profile showed good correlation with clinical patterns, also replicating the plasma-refilling phenomenon.
Conclusions: The tests proved the TVPS capable to reproduce fluid and mass transfer during HD. Such a system would be useful to characterize commercial or new dialyzers, accounting for the dynamic effects of mass transport induced by the patient-machine interaction.

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PLASMA REFILLING DURING HEMODIALYSIS

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Aim: Fluid removal by ultrafiltration (UF) during a hemodialysis (HD) session is balanced by vascular refilling from the interstitium, driven by the increase in plasma oncotic pressure. Our aim was to assess refilling rate (RR) during a weekly cycle of HD sessions with different pre-dialytic intervals and different degree of fluid overload.
Methods: Eighteen HD patients underwent three successive HD sessions, the first (HD1) with pre-dialytic interval of 3 days, and the remaining (HD2 and HD3) with pre-dialytic interval of 2 days. Session length was 240 min. Relative blood volume changes were measured on-line with Crit-Line. Bioimpedance was used to assess body fluid compartments. The refilling process was quantified calculating RR from on-line blood volume monitoring.
Results: Body weight (BW), extracellular water and fluid overload were higher before HD1 (BW 70.1 ± 17.7 vs. 69.0 ± 17.5 kg for HD2 and HD3, $p<0.05$). Ultrafiltration rate (13.1 ± 3.2 vs. 10.2 ± 3.3 mL/min for HD2 and HD3, $p<0.05$), changes in BW and total and extracellular fluid, the relative blood volume drop (HD1 0.14 ± 0.05 vs. HD3 0.10 ± 0.04, $p<0.05$), and the refilling rate during the

session were all higher for HD1. RR was also higher in HD1 during the whole session.
Conclusions: Because of the longer pre-dialytic period, patients were more fluid overloaded prior to HD1 than to other sessions and thus were treated with higher ultrafiltration rate. This caused a higher decrease in blood volume but also higher RR.

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COMPARING CHANGES IN PLASMA AND SKIN AUTOFLUORESCENCE IN LOW FLUX OR HIGH FLUX HAEMODIALYSIS
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Background: Tissue advanced glycation end products (AGE) are thought to contribute to the cardiovascular complications of hemodialysis patients. Skin autofluorescence (AF) is related to the accumulation of AGE, and is one of the strongest prognostic markers of mortality in these patients.
Aim: This interventional cross-over study was performed to investigate whether haemodialysis done by high flux dialysers could alter plasma or skin AF differently than using a low flux dialyzer.
Material and Methods: Hemodialysis was applied in 28 patients, using either a high flux or a low flux dialyser. Dialysis time was kept the same per participant during both types of dialyses. Plasma samples were taken and skin AF was measured non-invasively with an AGE Reader, both before and after hemodialysis. Fluorescence (370 nm/465 nm) of total plasma and the non-protein-bound fraction was determined for all samples. Paired and non paired statistical analyses were performed.
Results: There was no significant difference in the outcome of skin AF using low flux versus high flux dialysis. HD resulted in a more reduced ($p<0.001$) of total plasma fluorescence after HD with low flux membranes (reduction by 20%, $p<0.001$) than with high flux (red. by 5%, $p<0.001$).
Conclusions: The study showed that, in the dialysis settings used, there was no difference in the change of skin-AF using high flux versus low flux dialysers. Reduction was more prominent with LF dialyzers. The reason for the difference in plasma values may be due to greater recirculation in HF.

P50
DIALYSIS CATHETER LEAKAGE CURRENT DISTRIBUTION
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Aim: Electrical leakage current (LC) during dialysis using central dialysis catheter (CDC) are regarded as a safety risk. The LC-limits for Cardiac applications in standard IEC60601-1 was established using the threshold for ventricular fibrillation when applying LC trough electrodes inserted in the heart tissue. The LC from a CDC to the heart tissue might depend on position and design of the CDC tip. The aim of this *in vitro* study was to investigate the effect of side holes on the percentage of LC shunted to the "vena cava" or to the "right atrium" related to the position of the CDC tip.
Methods: An *in-vitro* model was designed to measure the longitudinal LC distribution around CDC. An electrode chamber consisting of sixteen electrodes was made. The chamber and the CDC were primed with 4% saline, to mimic the conductivity of blood. Tests were done using 11 different CDC with the tip between electrodes E0 and E1. Current where applied in the luer of the CDC to simulate LC. The fraction of total LC flowing to electrode E0 was assumed to reflect the percentage of LC reaching the atrium if the CDC tip is positioned outside the atrium. The current from electrodes E0-E4 was used to calculate the percentage of LC reaching the atrium if the tip is positioned 20 mm. inside the atrium.
Results: The majority of the LC flows through the side hole closest to the CDC luer connection. With a CDC without side holes ~90% of the LC was going to the E0. None of the catheters with side holes delivered more than 5% of the LC to the E0. The sum of the current from electrodes E0 to E4 was 90% of the total LC.
Conclusions: Using a CDC with side holes and with the tip outside the atrium reduces the LC shunted to the atrium.

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HEPSIDINE LEVELS IN IRON DEFICIENT ANAEMIA IN PATIENTS ON HEMODIALYSIS
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Aim: Iron deficient anemia (IDA) is one of the serious problems in patients (pts.) with chronic kidney diseases (CKD). Recently a new regulatory protein, hepsidine (HPD), was discovered as an important marker of iron deficit. Higher serum levels of HPD in pts. with CKD suppress gastrointestinal absorption of the iron and the delivery of it from its body stores (cells and tissues). The result is a resistance to iron treatment. HPD could be used for diagnosis and treatment decisions of in iron deficient anemia in patients with CKD.
Materials and Methods: We measured quantitatively serum HPD by ELISA, using monoclonal antibodies, in 30 healthy controls and in 30 pts. on hemodialysis treatment (HDT) with IDA, treated by i.v. iron during the last 2 years.
Results: The mean levels of HPD in the healthy persons were 13.45 µg/l (6.1 µg/l - 18.22 µg/l), SD 3.5 and in the HD pts. with IDA the mean levels of HPD were significantly increased: 34.05 µg/l (25.31 µg/l - 68.06 µg/l); $p<0.05$.
Conclusions: Our results showed that quantitative measurement of HPD in blood is a reliable marker of IDA and especially for iron-resistant anemia in patients with CKD. The next step would be the discovery of a way for lowering serum HPD which could overcome the treatment's problem of iron resistant anemia in patients with CKD.

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HEMODYNAMICS OF SINGLE-NEEDLE DIALYSIS IN AN EXPERIMENTAL ARTERIOVENOUS FISTULA
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Background: Acceptance has grown of single-needle (SN) dialysis when a vascular access is not suited for the insertion of two needles. Most of the papers regarding SN dialysis investigated the efficiency of this method compared to double-needle dialysis. However, the impact of SN therapy on hemodynamics within the arteriovenous (AV) fistulas is unknown. This experimental study investigates the effects of SN dialysis on fluid dynamics using a simulated AV fistula.
Methods: We produced a transparent life-size model of AV fistula that we placed into a pulsatile flow system to examine flow characteristics during simulated dialysis cycles. For this purpose we injected dye, and recorded and analyzed the resulting flow patterns using suitable software tools.
Results: During the venous phase of SN mode, we found normal flow patterns in the AV fistula as described in the literature (vortex within the venous entry of the anastomosis). There is no retrograde flow at all. In contrast, there is a definite flow reversal during the arterial phases leading to flow oscillations.
Conclusions: Flow oscillations initiate subintimal hyperplasia favoring the development of stenoses and occlusions *in vivo*. Reversal of the arterial flow direction may also cause steal phenomena in the poorly perfused distal extremity. If possible SN dialysis should be therefore be avoided in a clinical setting not only because of its lack of efficiency.

P53
SAFETY AND COST-EFFECTIVENESS OF TANDEM HEMODIALYSIS AND IMMUNOADSORPTION TO DESENSITIZE KIDNEY-TRANSPLANT CANDIDATES
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Aim: Desensitization programs are mandatory to achieve good results in kidney-transplant patients that have a potential living donor to which they have donor-specific alloantibodies (DSA).
Methods: Desensitization at pretransplant is based on immunosuppressants (such as rituximab, tacrolimus, and mycophenolic acid) and apheresis to retrieve potentially detrimental DSAs from blood. In our center, in 2011, we implemented immunoadsorption (IA) instead of plasmapheresis as part of the desensitization protocol. Because IA is very tedious and time-consuming we decided to perform

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IA and hemodialysis (HD) in tandem instead of performing these methods sequentially. Herein, we report on 120 of these tandem procedures.
Results: The tandem process resulted in nursing time being cut by half: i.e. from almost 10 h/patient to 5 h/patient. Body-weight gain during the tandem session was -3 (0-4.3) kg compared with +1 ± 0.2 kg when IA is performed alone. In addition, there are no negative side-effects when IA and HD are performed simultaneously, with regards to natremia, bicarbonates, calcemia, protidemia, and hematological parameters. Ionic dialysance was good, i.e. 185 (102-238).
Conclusions: Tandem IA plus HD is a safe and cost-effective procedure.

P54

EXTRACORPOREAL Aβ REMOVAL SYSTEM FOR ALZHEIMER'S DISEASE THERAPY: MOST EFFECTIVE MATERIALS

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Aim and Background: Accumulation of amyloid beta (Aβ) protein in the brain is characteristic of Alzheimer's Disease and causes neuronal impairment. The rapid removal of blood Aβ by an extracorporeal system may act as a peripheral Aβ sink from the brain. We have reported that hemodialyzers remove Aβ effectively in renal failure patients. In this study, the materials for Aβ were investigated.
Methods: *In vitro*: hollow fibers sampled from dialyzers were cut into ca. 2 mm fragments, and incubated in Aβ/albumin solution in batch and in continuous column mode. In humans: the blood of patients was collected during hemodialysis sessions. This research was approved by the institutional review board at Fujita Health University and each institution. Aβ1-40 and Aβ1-42 were measured by ELISA.
Results: PolySulfone and PolyMethylMethAcrylate were most effective Aβ removers compared with hydrophilic Ethylene-Vinyl- Alcohol copolymer or CelluloseTriAcetate *in vitro*. Similar material dependence of Aβ removal rates were observed in hemodialysis patients. The blood Aβ levels before/after initiation of hemodialysis with polysulfone hemodialyzers will be discussed.
Conclusions: Medical materials were found to be suitable for Aβ removal *in vitro* and *in vivo*. The reduction of the blood Aβ may lead to development of therapeutic devices for Alzheimer's Disease.

P55

EFFICACY OF IMMUNOADSORPTION TO REDUCE DONOR-SPECIFIC ALLOANTIBODIES (DSA) IN KIDNEY-TRANSPLANT (KT) CANDIDATES

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Aim: We have implemented a desensitization program in our center to enable transplantation in KT candidates that have a living HLA incompatible (HLAi) donor.
Methods: To analyze i) the decrease in DSA across a pre-transplant desensitization program that relies on immunosuppressants and apheresis to remove detrimental antibodies, and ii) the post-transplant outcomes. We have chosen immunoadsorption (IA) as the apheresis technique, which is coupled with hemodialysis.
Results: 6 highly sensitized KT (5 females), waiting for their first (n = 1) or second (n = 5) KT with a living donor were enrolled in a desensitization program. They had one (2), two (1), three (2), or four (1) DSAs with mean fluorescence intensity (MFI) pre-desensitization ranging between 1200 to 19000. They underwent between 8 to 16 IA sessions. In 5 cases (B44, A24, DR3, DR11, DQ3) DSAs became negative; in 3 cases (DR3, DQ3 twice) DSAs decreased by >50%; finally in 6 cases (DQ5, DQ8, B50, Cw6, DR53, A11) DSAs remained unchanged, i.e. MFI between 5000 to 19000. Outcome: 3 patients had no rejection (1 with DSA elimination, 1 with DSA decrease 50%, and 1 with stable DSA at around 15000). One patient presented with acute antibody-mediated rejection (AMR) which required IA sessions and eculizumab therapy (DSAs between 5000 to 19000), and 2 patients presented with subacute AMR which was treated by plasmapheresis/rituximab therapy (DSAs between 6000 to 14000).
Conclusions: We conclude that HLA desensitization by IA procedure is efficient at reducing/eliminating DSAs in 57% of cases.

P56

ADVERSE EVENTS IN APHERESIS. UPDATE ANALYSIS OF WAA REGISTRY DATA

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Aim: Apheresis is used for a variety of indications with different procedures and devices. To increase safety it is important to know about side effects that may arise.
The aim of this study was to clarify the extent of various side effects and the possible reasons for their cause based on data from a multinational registry.
Materials and Methods: The WAA-apheresis registry data were entered electronically and analysed with focus on adverse events. A total of 50,167 procedures in 7142 patients (42% women) were included in the analyses. This is part of the safety assessment registry for apheresis approved by the ethical committee. Adverse events (AE) were graded as mild, moderate (need of medication), severe (interruption due to AE) or death (due to AE).
Results: More AEs were present during the first apheresis (8.4 vs 5.5%).
AEs were mild in 2.4% (of these access related 47% and device related 7%, hypotension 14%, tingeling in 7.5%). Moderate AEs were present in 3% (tingling 58%, urticarial 15%, hypotension 10%, nausea 3%). Severe AEs in 0.4% (syncope/hypotension 34%, urticaria 16%, chills and fever 7%, tingling 5%, asystolia 4,4%). Of the 160 severe cases, 5 had Quincke oedema, 5 bronchospasm, 2 anaphylaxia, 6 epilepsia and 2 had gastrointestinal bleedings. One case suffered from TRALI (replaced with albumin).
In general, hypotension was most common if albumin was used as replacement (48% if albumin only, 6% if albumin and plasma, 12% if plasma only was used). In 30% of the patients with hypotension neither plasma nor albumin was used. Urticaria was more often related to the use of plasma (76%). Arrhythmia more often occurred when using plasma or other solutions. In 80% of the cases with bronchospasm plasma was used as replacement.
Conclusions: Although severe adverse events are rare, especially hypotension and arrhythmia/asystolia may be critical for the patient. We suggest that safety is increased using regular blood pressure measurements, cardiac monitoring and an emergency equipment nearby.

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NEW HAEMODIALYSIS TREATMENTS FOR REMOVAL OF IMMUNOGLOBULIN FREE LIGHT CHAINS IN PATIENTS WITH MULTIPLE MYELOMA AND ACUTE RENAL FAILURE

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Aim: Acute renal failure (ARF) in multiple myeloma (MM) occurs in 12-20% of patients representing a poor prognostic factor for patients survival. It has been demonstrated that early reduction of immunoglobulin free light chains (sFLC) can lead to a higher proportion of patients recovering renal function with a better outcome, especially if high cut-off haemodialysis combined with chemotherapy is used. However, no data is available regarding other adsorption-based techniques, such as haemodiafiltration with ultrafiltrate regeneration by adsorption with resins (SUPRA-HFR). We evaluated the effectiveness of this technique in the reduction of sFLC.
Methods: We report five cases of MM (two IgG kappa, one IgA kappa, one IgA lambda, one kappa micromolecular myeloma). All patients were treated with chemotherapy and SUPRA-HFR. Levels of sFLC were assessed before and after dialysis and removal was calculated.
Results: The mean reduction rate of sFLC was 34%, 59%, 43% and 44% (MM kappa) and 67% (MM lambda).

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Conclusions: Our study suggests that SUPRA-HFR provides effective reduction of plasma sFLC. When combined with chemotherapy and an early treatment start, it may allows the recovery of renal function, as occurred in one case of our small series.

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BLOOD COMPATIBILITY CORRELATES WITH SURFACE ROUGHNESS OF ADSORBENT POLYMERS

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Aim: We studied the influence of the morphology of adsorbents for lipid apheresis, in particular surface roughness, on the release of microvesicles (MV) and on thrombocyte adhesion.
Methods: The surface roughness of DALI, Liposorber D, and the non-commercial polymer ReliSorb was studied by atomic force microscopy. To determine MV generation, freshly isolated thrombocytes (3×10^5/µl; total volume 50 ml) were circulated over adsorbent columns (3.5 × 1.8 cm; downscaled equivalent to clinical use) using anticoagulation with ACD-A (1:12). Thrombocytes were quantified in the flow-through using a blood cell counter. Flow cytometry was performed after calibration with fluorescent beads to cover the microvesicle (0.5 and 0.9 µm) and the thrombocyte size ranges (0.9 and 3 µm).
Results: Thrombocyte adhesion was significantly higher for the polymer with the highest surface roughness, ReliSorb, as compared to DALI and Liposorber D. Thrombocyte passage over ReliSorb resulted in significantly higher levels of MVs as compared to DALI, while Liposorber D and DALI showed comparable MV release. Activated thrombocytes were preferentially bound by the adsorbents, as shown by the preferential binding of $CD62^+$ and $PAC\text{-}1^+$ thrombocytes after activation with 50 µM TRAP-6.
Conclusions: The release of MVs and the adhesion of thrombocytes correlate with adsorbent surface roughness and can serve as markers of blood compatibility of adsorbent polymers.

P59

MODULATION OF INFLAMMATORY MEDIATORS FROM BLOOD BY POLYSTYRENE DIVINYLBENZENE-BASED POLYMERS REDUCES ENDOTHELIAL ACTIVATION

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Aim: In infection, endothelial cells are activated by pathogen-associated molecular patterns or by host-derived inflammatory mediators. We assessed the effect of adsorptive mediator modulation from whole blood on endothelial cell activation *in vitro*.
Methods: The polystyrene divinylbenzene (PS-DVB) copolymers Amberchrom CG161C and Amberchrom CG300M (Dow Chemical) were studied. Whole blood was stimulated with 100 ng/ml lipopolysaccharides from *E.coli* for 4 h. The stimulated blood was treated with 10 vol% of adsorbent for 1 h and the effect of mediator modulation on endothelial activation was assessed by incubating human umbilical vein endothelial cells (HUVEC) with 10% stimulated plasma in cell culture media. After 16 h the expression of cell adhesion molecules (ICAM-1, E-selectin) and the secretion of cytokines were measured.
Results: The PS-DVB copolymers exhibited excellent adsorption of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8 and IL-10. TNF-α, an important stimulator for HUVEC, was reduced to 12% and 8% of the initial concentration by CG161C and CG300M, respectively. Treatment of stimulated whole blood with both adsorbents, CG161C and CG300M, resulted in a subsequent significant reduction of IL-6 and IL-8 secretion from HUVEC and in a significant decrease in the expression of ICAM-1 and E-selectin.
Conclusions: The adsorptive modulation of mediators by PS-DVB copolymers reduced endothelial activation significantly and may thus represent a promising supportive treatment of sepsis.

P60

MICROVESICLE RELEASE AND CYTOKINE INDUCTION BY WHOLE BLOOD ADSORBENTS FOR LIPID APHERESIS

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Aim: We studied the release of microvesicles (MV) of different cellular origin induced by whole blood adsorbents for lipid apheresis, as well as their contribution to thrombin generation.
Methods: Freshly isolated blood anticoagulated with ACD-A 1:20 and 0.8 IU/ml heparin was circulated over adsorbent columns (3.5 × 1.8 cm, downscaled equivalent to clinical use) containing DALI or ReliSorb. Blood cells in the flow-through were quantified using a blood cell counter, and MVs were detected by flow cytometry after calibration with fluorescent beads to cover the MV (0.5 and 0.9 µm) and the cell size ranges (0.9 and 3 µm). Cell specific markers were used to differentiate MVs according to their cellular origin, and Annexin V staining was used to discriminate MVs of cellular origin from debris.
Results: Passage of whole blood over the adsorbents resulted in increased levels of MVs derived from erythrocytes and thrombocytes. MV generation increased with increasing surface roughness of the adsorbents and was highest for ReliSorb, while there was no significant difference with respect to leukocyte, thrombocyte and erythrocyte adhesion. Thrombin generation was significantly higher for ReliSorb than DALI.
Conclusions: Blood contact with adsorbents induces MV release and correlates with the morphology of the adsorbents, in particular their surface roughness. MV quantification and differentiation may by a valuable marker for the blood compatibility of whole blood adsorbents.

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IMPROVEMENT OF HEMODYNAMIC PARAMETERS BY COMBINED CYTOKINE ADSORPTION AND CONTINUOUS RENAL REPLACEMENT THERAPY IN SEPTIC MULTI ORGAN FAILURE-AN OPEN LABEL CLINICAL CASE SERIES

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Aim: Sepsis multi-organ failure (MOF) still carries very high mortality rates despite being given full intensive care consideration. This study aimed at investigating hemodynamic effects of a direct hemoperfusion treatment for the reduction of circulating cytokines added to regular continuous renal replacement therapy in patients with septic shock with septic acute kidney injury (AKI).
Methods: Nine patients with septic shock and septic AKI were treated for 24 hours with a combination of continuous veno-venous hemodiafiltration (CVVHDF, Multifiltrate, FMC Germany) and direct hemoperfusion (CytoSorb, Cytosorbents Germany). Laboratory (e.g. serum-Interleukin 6) and clinical parameters (e.g. mean arterial pressure (MAP), Noradrenalin (NA)-dosage) were followed throughout the treatment phase.
Results: The patients (age 67 ± 11,5 years, 7 males, mean SAPS II 53 ± 12,2) had sepsis due to pneumonia (n = 5), peritonitis (n = 2), urosepsis (n = 1), and soft tissue infection (n = 1). Two patients died within the first 24 hours post treatment. Serum IL6 decreased significantly (-72 ± 27,1%). Median MAP pre, during, post treatment was 58, 63, and 65 mmHg. Accordingly, mean NA-dosage was 1,0; 1,2; 0,7 µg/kg/min. ICU-mortality was six of nine patients (67%). No complications of the treatment were observed.
Conclusions: Combined cytokine adsorption/CVVHDF appeared safe and effective in septic shock with septic AKI. We suggest further clinical evaluation of this extracorporeal treatment approach.

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INFLUENCE OF THE BULGING SINUS SIZE OF THE SIMULATED EPTFE VALVE AND VALVE LEAFLET SHAPE ON THE FLOW AND LEAFLET MOVEMENT OF THE SIMULATED VALVE CONDUIT

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Aim: Contegra and expanded polytetrafluoroethylene (ePTFE) valve conduits may be a good choice for treating right ventricular outflow tract (RVOT) reconstruction in congenital heart defects. ePTFE valve with bulging sinus seem to show good clinical record, however, fluid mechanical research proving the effect of bulging sinus has been limited. In the previous experimental study, similar shaped simulated aorta was utilized to see the effect of bulging sinus size on the flow field and results showed that the valve with normal and 50% enlarged bulging sinus shows strong vortex close to the leaflet location and resulted in wider valve opening area. This paper aims to study the effect of the bulging sinus size

of the simulated ePTFE valve and valve leaflet shape on a flow phenomenon inside the conduit.
Methods: Five simulated ePTFE valves with different bulging sinus sizes and fan- and non-fan-shaped leaflets were used. Effect on a flow field inside the simulated ePTFE valve was experimentally analyzed using Dynamic PIV system running at 1900 frames/s and valve opening and closing mechanism were directly observed and compared using high speed digital camera running at 300 frames/s.
Results and Discussions: Result showed bulging sinus size and leaflet shape greatly influence on flow inside the conduit. Closer proximity of vortex location seems to act favorably on valve opening area. Valve opened wider with 25% reduced, normal and 50% enlarged bulging sinus compared to straight and 50% reduced bulging sinus with non-fan-shaped leaflet. Valve opening area was less sensitive for bulging sinus size with fan-shaped leaflet.
Conclusions: Bulging sinus size and leaflet shape greatly influence on flow inside the conduit. Closer proximity of vortex location seems to act favorably on valve opening area.

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BIOINSPIRED ANISOTROPIC MICROSTRUCTURE IN POLYMERIC PROSTHETIC HEART VALVES

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Aim: Anisotropic orientation of collagen contributes to the high cycle durability of the native heart valve. Polymer prosthetic heart valves show potential to overcome the limited lifetime of biological prostheses. Certain styrenic block copolymers exhibit a cylindrical morphology, whose domains can be aligned to yield anisotropic properties. Controlling anisotropic orientation is a tool to achieving the collateral goals of increased valve lifetime and improved hemodynamic characteristics.
Methods: Hemocompatible polystyrene-*block*-polyisoprene-*block*-polystyrene (30 wt% styrene) was injection moulded at 160°C to form a tri-leaflet prosthetic heart valve. Various injection points were used to obtain 3 flow fields. A computational model was developed to predict polystyrene hard block cylinder orientation from the modelled flow field in the cavity. The cylinder orientation was mapped using small angle X-ray scattering.
Results: Both injection point and flow rate could be used to control orientation within the leaflet. The experimental data validated the numerical model for the 3 tested flow fields. Injection at the centre of the free edge of the leaflet at flow rates <5 mm^3/s brought most success in fabricating orientation comparable to the native valve. Higher flow rates also allow the production of a layered biaxial arrangement of styrene cylinders.
Conclusions: Specification of flow rate and injection positions allows polymer prostheses to harness the anisotropic mechanical properties resulting from microstructure orientation in block copolymers.

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TOWARDS A NOVEL SPATIAL-RESOLVED HEMOLYSIS DETECTION METHOD USING FLUORESCENT LOADED GHOST-CELLS

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Aim: The determination of device-induced hemolysis is crucial in the development of artificial implants, such as heart valve prostheses or blood-pumps. So far, hemolysis is often measured by photometric techniques giving one value for the complete test-setup. A detection of the location where the hemolysis takes place was not possible yet. We develop an optical method to detect hemolysis of ghost-cells spatially resolved.
Methods: Citrate bound Calcium is loaded into ghost-cells produced in a hypotonic solution. After resealing of the ghost-cells, a fluorescent calcium indicator (Assante Calcium Green) is put extra-cellular in a 44% ghost-cell suspension. The fluid volume is illuminated by a laser-light sheet at the excitation wave-length of the indicator. By induced hemolysis of the cells via tenside (Triton X), indicator and calcium get in contact with each other and emit a fluorescent signal which can be recorded by a high-speed camera through an optical long-pass filter.
Results: First experiments show promising results indicating that a fluorescent signal can be recorded in the moment of ghost-cell lysis.
Conclusions: Further experiments are performed to confirm the first results. The method would allow for a spatial-resolved hemolysis detection using a slightly modified standard PIV-setup. In this way devices can be more efficiently optimized with respect to low hemolysis.

P65

EXPERIMENTAL CHARACTERIZATION OF CORROSION PROPERTIES OF ANNULOPLASTY RINGS

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Aim: Mitral valve regurgitation occurs when the mitral valve, located between the left atrium and left ventricle, does not close properly during systole, thereby allowing a certain amount of oxygenated blood to leak back into the left atrium. This condition is treated either by mitral valve replacement or mitral valve repair; when possible, the latter is preferable to the former, because of its efficacy, durability, and freedom from long-term anticoagulant drug therapy. Annuloplasty rings (ARs) are commonly implanted during mitral valve repair procedures. They are available in many shapes, sizes and materials. The present study addresses the characterization of the corrosion properties of commercially available ARs, of rigid and semi-rigid type.
Methods: The metallic core, extracted from each device, was subjected to corrosion testing by means of the potentiodynamic system PARSTAT 2273, equipped with a temperature-controlled corrosion cell, in accordance with the relevant ASTM standards (in particular, ASTM F2129).
Results: Potentiodynamic (current-potential) curves were obtained for the devices under test. The curves of the device type whose core was made of titanium were characterized by an hysteresis-type behaviour, with the reverse-scan track almost crossing over the forward-scan track, indicating that the passive/oxide layer was being reformed after the potential-induced breakdown. Instead, the potentiodynamic curves of Ni-Ti cores showed no evidence of hysteresis upon scan reversal, indicating no substantial local oxide damage.
Conclusions: The potentiodynamic technique is a powerful tool to evaluate the corrosion properties of medical devices assembled with metal components. All the commercial annuloplasty rings subjected to test showed an acceptable resistance to corrosion.

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HYDRODYNAMIC ASSESSMENT OF NEW POLYMERIC HEART VALVES UNDER CONTINUOUS AND PULSATILE FLOW

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Aim: In order to combine the hemodynamic properties of biological valves with the durability of mechanical valves a new prosthetic heart valve (PHV) made of styrenic block co-polymers was developed. Aim of this work was to evaluate the haemodynamic performances (regurgitation and pressure drop) of the developed PHV.
Methods: Two groups each one comprising 8 PHVs prototypes differing in polystyrene fraction (19% and 30%) were tested under continuous and pulsatile flow conditions. The continuous tests were carried out at flow rates from 0 to 10 l/min (step 0.5 l/min) to evaluate pressure drops. Static regurgitation was assessed by applying backpressures from 30 to 130 mmHg. A test bench was specifically built according to the ISO5840 guidelines. Each valve was tested at different cardiac output, frequency and backpressure. Regurgitation, pressure drops and effective orifice area (EOA) were evaluated. Unpaired *t*-Test was used to evaluate the statistical difference ($p<0.01$) between the two groups.
Results: All 16 PHVs met the minimum requirements of ISO5840. The PHVs made up of 30% polystyrene showed higher pressure drops than the other group under both pulsatile and steady flow conditions, while no statistical differences was present in static and dynamic regurgitation between the two groups in both tests.
Conclusions: The results of this study demonstrate the effectiveness of the newly developed PHVs, encouraging further improvements to minimise regurgitation and maximise EOA.

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A COMPUTATIONAL TOOL FOR THE OPTIMIZATION OF A NEW POLYMERIC HEART VALVE PROSTHESIS

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Aim: A new polymer prosthetic heart valve (PHV) made of styrenic block copolymers was developed. Regions of stress concentration on heart valves leaflets have been suggested as a factor leading to structural failure. The aim of this work was the development of a computational tool to optimize the PHV design and structure, minimizing stress concentration on the valve leaflets.

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Methods: A geometrical model representing 1/3 of the PHV which allowed the control of the valve design parameters (e.g. leaflet thickness and curvature) was developed. The polymer mechanical behaviour was described by a hyperelastic anisotropic constitutive law which includes the material microstructural description. The material parameters were optimized on experimental data. A routine was implemented to optimize the polymer chains orientation in the PHV leaflet; the routine defined the orientation along the maximum principal stress direction by an iterative procedure. Suitable kinematic constraints were applied to the structure, while a uniform pressure up to 180 mmHg was defined on the leaflet to simulate the valve closure.
Results: The valve leaflet was subjected to lower stress if the polymer chains orientation was optimized. The model also allowed the evaluation of the stress distribution among different valve designs, giving fundamental information for manufacturing.
Conclusions: The developed computational model represents a sound tool to optimize the PHV design and structure.

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ANALYSIS OF ARTIFICIAL HEART VALVE BY HEMODYNAMIC ENERGY
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Aim: Artificial heart valves can be divided largely into two groups, mechanical and biological, and differ greatly in material and structure. The difference in construction inevitably affects hemodynamic characteristics including flow pattern, flow rate, and pressure. Because the choice of valve prostheses can affect tissue perfusion or side effects, hemodynamic analysis of heart valve prostheses is of great interest in the field of cardiac surgery. In this study, we analyzed the HE changes depending on valve type.
Methods: Two artificial heart valve prostheses were compared in terms of HE: a mechanical valve (BiCarbon 21 mm, Sorin Group, Milano) and a tissue valve (Edwards 3000 Perimount Magna 21 mm, Edwards Lifesciences, Irvine). Pulsatile flow was generated by a Korean external ventricular assist device (KH-VAD, KAOC, Seoul), and the mock system was primed with 40/60 glycerin/water solution. Real-time flow rates and pressures were recorded at 50, 60, 70, 80, and 90 pulse rates per minute for five minutes. HE markers were surplus hemodynamic energy (SHE) and energy equivalent pressure.
Results: Under the same diameter, the mechanical vs. tissue valve was found to have different impact on HE. The tissue valve showed higher hemodynamic energy performance (SHE, SHE retention, %EEP, %EEP retention) overall except EEP retention.
Conclusions: It suggests that a tissue valve is likely to retain more hemodynamic energy and flow pulsatility generated by the heart, which in turn leads to higher tissue perfusion.

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STEREO-PIV MEASUREMENTS OF PROSTHETIC HEART VALVES: THE ROLE OF PULSE DUPLICATOR TYPE
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Aim: Prosthetic heart valves (PHVs) impart mechanical loading on blood, causing potential complications (hemolysis, thrombogenicity), which call for strict safety requirements. In order to test PHVs, pulse duplicators (PDs) have been designed and built, following different concepts. This study addresses the comparison of anemometric measurements made on the same PHV, with two widely used PDs.
Methods: The valve (a 27-mm bileaflet valve) was mounted in the aortic section of the selected pulse duplicator (Sheffield University PD and RWTH Aachen PD). A glassblown aorta, realized according to the anatomical data of healthy individuals, was positioned downstream of the valve, obtaining 1:1 geometric similarity conditions; also kinematic similarity applied. The flow field downstream of the valve was measured by means of the stereo-PIV technique, providing the 3D velocity field as well as the entire Reynolds stress tensor.
Results: The expected three-jet profile in the plane crossing the leaflets was found with both experimental series. The extent of the typical recirculation zone in the Valsalva sinus was much larger in the RWTH PD, on account of the different duration of the swirling motion in the ventricular chamber, caused in turn by both the elasticity of the ventricle and its geometry.
Conclusions: The comparison of the hemodynamic behaviors of the same bileaflet valve tested in two PDs clearly demonstrated the impact of the PD type on the findings. An earlier inception of recirculation downstream of the valve was observed in the valve mounted on the PD with an elastic ventricular chamber, highlighting the role of the local compliance, as well as the geometric disposition of the upstream chamber with respect to the valve axis, in determining the fluid dynamics associated to the valve.

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REGURGITANT FLOW JETS IN MECHANICAL HEART VALVES: FLUID STRESSES AND SPATIAL CORRELATION
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Aim: Regurgitant flow in mechanical heart valves (MHVs) is known to be a possible cause of blood trauma (hemolysis, platelet activation). Regurgitant-flow jets can generate mechanical stresses in blood. In the present study, regurgitant flow in MHVs is studied with noninvasive velocimetry, addressing fluid stresses and self-similarity of the velocity field.
Methods: A suitably designed physical model of the regurgitant flow was used for the measurements. The prosthetic valve under test was seated coaxially with a 12-face prism, enabling easy optical access. This model was inserted in a closed flow loop, with regurgitant steady flow, which allowed to avoid the effect of leaflet repositioning in successive cycles. 80 mmHg transvalvular pressure was chosen, as representative of the mean aortic pressure during diastole. A Particle Image Velocimetry (PIV) investigation was carried out on currently marketed MHVs, by measuring the 2D flow field at several planes parallel to the hinges' plane. Average velocities, maximum turbulence shear stresses (TSSmax) and normalized autocorrelation function (AF) of the jet velocity along both parallel and perpendicular direction (with respect to the jet axis) were calculated.
Results: The distribution of the jets exiting the valve, mainly from the hinge corners, was observed. Low peak TSSmax and viscous stress values were found. Different self-similarity properties of the flow field were found, with regard to the direction of the vector distance defining the argument of the AF. Moreover, the distance from the jet origin was also found to be important: at increasing distance, a slower convergence of the AF to low plateau values was found, suggesting a higher coherence of the velocity fluctuations at increasing distance from the valve.
Conclusions: MHVs' flow field in leakage phase was accurately characterized, thanks to a set-up optimized for PIV measurements.

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***IN-VITRO* OBSERVATION OF FLOW AND PRESSURE CHANGES ACROSS THE MECHANICAL HEART VALVE PROSTHESIS**
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Aim: Changes of pulsatile pump rate might influence the pattern of flow as well as pressure across the mechanical heart valve. This study was designed to evaluate this hypothesis by using *in-vitro* MOCK system.
Methods: 40% glycerin/water solution was used to match the blood viscosity. A bi-leaflet mechanical heart valve (BiCarbon 21 mm®, Sorin, Milano) was placed in a mock circulation with a pulsatile ventricular assist device (KH-VAD, Korea Artificial Organ Center, Seoul). Pressure and flow were recorded at 20 cm proximal and distal to the valve. Data were collected at every 5 min using pressure transducers (PS9030, Sensortechnics, Puchheim) and flow meters (TS410 flow meter, Transonic, Ithaca). Pump rate was changed to 50, 60, 70, 80, and 90 beats per minute.
Results: Changes of pump rates induced minimal impact on pressure while sigmoidal increment of flow ($p = NS$). Pressure difference across the mechanical valve was 49.9 mmHg on average, and average increase of flow was 0.41 L/min. Diastolic flow pattern showed irregular and abrupt changes, while systolic flow patterns were similar to the native heart.
Conclusions: During diastole, the natural aortic valve closes properly to prevent reflux of blood. Unlikely, mechanical valve leaflets lack elasticity which combined with the hinge movements of the prosthesis, may cause irregular and abrupt changes in flow pattern. Further study is required to compare with tissue or polymer valves.
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DEVELOPMENT OF A NOVEL AUTOLOGOUS HEART VALVE (BIOVALVE STENT) FOR TRANSCATHETER IMPLANTATION

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Aim: A novel autologous aortic valve with a metallic stent (Biovalve Stent) was developed, using simple, safe and economical in-body tissue engineering. In this study, the long-term evaluation of the Biovalve Stent for transcatheter implantation was investigated in a goat model.
Methods: Biovalve Stents were prepared by 2-month embedding of the molds, assembled using plastic rods and a metallic stent, in the subcutaneous spaces of goats. After extracting the molds and removing the plastic rods only, Biovalve Stents with tri-leaflets similar to those of the native aortic valves were constituted from completely autologous connective tissues. Fourteen out of nineteen Biovalve Stents were implanted in the aorta in situ and other five Biovalve Stents were implanted in the pulmonary artery (PA) in situ with transcatheter technique.
Results: In both aortic and PA cases, the Biovalve Stents were successfully implanted. Angiography showed smooth movement of the leaflets with a little regurgitation under the systemic and pulmonary circulation. The Biovalve Stents were extracted 1, 2 or 5 months after implantation. The leaflets of the Biovalve kept their shape and elasticity even after 5 months, and neither calcification nor thrombi were observed. Histological examination showed the cell populations inside the valves and endothelial cells covering the laminar surface of the valve leaflets.
Conclusions: The Biovalve Stent satisfied the higher requirements of systemic and pulmonary circulation in goats for 5 months with the potential for transcatheter implantation.

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OUTCOME OF REDO AORTIC VALVE REPLACEMENT AFTER PRIOR CORONARY ARTERY BYPASS SURGERY: RESULTS OF A MULTICENTER REGISTRY IN THE TAVI ERA

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Aim: The outcome of patients undergoing first-time isolated surgical aortic valve replacement (AVR) after prior coronary artery bypass grafting (CABG) has not been thoroughly investigated. Despite this, these patients are increasingly treated by transcatheter aortic valve replacement (TAVR).
Methods: 113 consecutive patients (mean EuroSCORE II, 10.3 ± 7.7%, median 8.0%) who underwent first-time isolated AVR after CABG were the subjects of this multicenter study. The procedure was performed through full sternotomy in 95.7% of cases, a patent internal mammary artery graft was clamped in 76.6% of patients. Temperature of cardioplegia was ≤12°C in 62.8% of patients and systemic temperature was <32°C in 23.9% of patients.
Results: 30-day mortality 4.4%. Stroke was observed in 8.0% of patients, low cardiac output syndrome in 14.1%, prolonged tracheal intubation in 20.8% and intensive care unit stay was longer than 5 days in 19.5% of patients. Among patients with patent internal mammary graft (91 patients), clamping of this graft (5.7% vs. 0%, p = 0.57) was associated with a non-significant trend toward increased 30-day mortality. One-, 3- and 5-year survival rates were 91.5%, 90.4% and 88.4%, respectively.
Conclusions: Patients undergoing isolated AVR after prior CABG have an excellent immediate and late survival. According to these findings, history of prior CABG should not be considered an absolute indication to TAVR.

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A VASCULAR MODEL WITH VARIABLE ELASTICITY

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Aim: Continuous non-invasive blood pressure measurement for long-term application is an unsolved technical challenge. Pulse transit times (PTTs) correlate with blood pressure, but repeated recalibration is needed. The correlation depends on the elastic properties of the arteries. To enhance the correlation with a model-based time series analysis, an experimental model with variable elasticity was developed.
Methods: The bifurcation of the brachial into ulnar and radial arteries is modelled using polyurethane foil. Physiologic flow and pressure curves were generated using a piston pump. The elastic properties of the three arteries can be changed separately during the experiments. This was done by increasing the force on the vessel which changes its cross-sectional shape. Pulse waves were measured by detecting the movement of the vessel wall with a magnet and a Hall sensor. PTTs and pulse wave velocities (PWVs) were calculated from both the pressure and the pulse wave signals with Matlab® using the base points of the curves.
Results: The volume elasticity coefficient $E' = \Delta p/\Delta V$ increases from 40.4-53.7 mmHg/ml (at 100 mmHg vessel pressure) with decreasing force on the vessel. The PWVs of the pressure and the pulse wave signals vary between 6.2 and 7.7 m/s and 5.4-9.2 m/s in comparison to 412 m/s in the human body.
Conclusions: Measurements were performed in a vascular model with physiological flow, pressure, pulse waves, flow distribution and variable elasticity. PTT changes in the model are mainly realized through changes in the elasticity and not variations in fluid pressure.

P75

UNSTEADY BLOOD FLOW THROUGH THE ARTERIO-VENOUS FISTULA FOR HAEMODIALYSIS - NUMERICAL INVESTIGATIONS

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Aim: The arterio-venous (a-v) fistula is a connection between an artery and a vein of the patient and it is a widely accepted vascular access for haemodialysis. It is thought that a significant number of complications is related to abnormal hemodynamics. The aim of this study was to carry out the simulation of the blood flow in the a-v fistula, taking into account its pulsating nature and complicated geometry of blood vessels. Computational fluid dynamics methods (CFD) were used for an analysis of the flow in the patient's specific geometry.
Methods: DICOM images of the a-v fistula, obtained from the angio-computed tomography, was a source of data used for the development of a 3D geometrical CAD model of the fistula. The model was imported and meshed in ANSYS CFX v. 14.0, in which the simulation was performed. The velocity profile at the inlet cross-section (feeding artery) and static pressure at the outlet cross-sections (veins) were introduced as boundary conditions. The non-Newtonian rheological model of blood was employed and the Shear Stress Transport model of turbulence was used. Blood vessel walls were assumed to be rigid.
Results: The simulated pulsating blood flow was observed in 3D animations. Flow patterns, velocity fields, the wall shear stress propagation on blood vessel walls were shown as functions of time. The maximum abnormal value of the blood flow was identified in the anastomosis - the place where the artery is connected to the vein. The flow rate was calculated for all veins receiving blood.
Conclusions: A high and oscillating value of the WSS was obtained at the anastomosis. It may be a reason of dysfunctions of the a-v fistula. CFD methods may help predict the usability of the a-v fistula.

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VIRTUAL IMPLANTATION OF A PAEDIATRIC BIODEGRADABLE STENT

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Aim: Early restoration of normal blood flow in infants suffering from congenital or acquired constrictions in the great arteries is essential for their vascular development. Considering the contra-indications of balloon angioplasty or conventional stenting in such a young population, this study addresses the development of a biodegradable paediatric stent serving as a temporary scaffold without any obstruction for somatic growth or future interventions.
Methods: In order to shorten the development cycle and decrease the amount of *in-vitro* and animal testing of the new transcatheter device, a complete virtual

simulation framework is being developed. First, *in-vitro* degradation studies and mechanical tests were performed on a polymeric bioresorbable braided wire stent. Based on these experiments, a calibrated and validated finite element model (FEM) was set up. The FEM captures the mechanical behaviour of the stent throughout the degradation process. A patient-specific FEM of congenital constricted pulmonary arteries served as a first virtual anatomy to deploy the stent.
Results: Both FEMs combined with a virtual stent deployment simulation formed a first preliminary virtual simulation framework of bioresorbable stent implantation in a paediatric setting. The constructed tool allows us to investigate the influence of a specific biodegradable stent design and a patient-specific vessel geometry on successfully opening constricted branches.
Conclusions: A first important step to assess the success rate of biodegradable paediatric implants has been taken. The simulation framework will be further elaborated with other stent designs and generic 3D models of both the pulmonary arteries and the aorta. This tool will allow engineers and clinicians to respectively develop and anticipate the ideal biodegradable implant for each patient specifically.

P77

THE EFFECT OF ANASTOMOTIC ANGLE ON CORONARY ARTERY BYPASS DURING PARTIAL MECHANICAL CIRCULATORY SUPPORT: A COMPUTATIONAL STUDY

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Aim: Recovery of the myocardium function in heart failure patients supported with a left ventricular assist device (LVAD) is one of the interesting topic for current treatment purpose. Coronary blood flow (CBF) is the main factor that relates to myocardial work especially in heart failure patients who were previously treated with bypass surgery. Therefore the configuration of anastomosis is considerable.
Methods: In this study, computational fluid dynamics was used to analyze the coronary arteries bypass graft (5:3 graft-to-host diameter ratios). Blood was assumed to be incompressible. The properties were set as Newtonian fluid, viscosity (0.004 kg m-s) and density (1050 kg/m^3). Six configurations of end-to-side CABG were simulated (3 anastomotic angles at 15, 30 and 45 degrees and 2 distance from a stenosis to the heel point of anastomosis at 10 and 15 mm. from the inlet of host vessel). They were performed with steady flow simulation. The CBF of acute animal experiments during partial LVAD support at 2, 2.5 and 3 litre/min from the study of Y. Ootaki et al. 2005 were used at the proximal of graft and host vessels. The blood flow and shear stress during diastole was simulated.
Results: For increasing anastomotic angles, the area of non-uniform blood flow at the toe of anastomosis was wider. In addition, maximum shear stress at the toe of anastomosis were increased.
Conclusions: Anastomotic angle is the considerable factor which affects both flow pattern and shear stress level, particularly at the heel, toe and bed of anastomosis region.

P78

A COMPUTATIONAL CARDIOVASCULAR SIMULATOR FOR VAD TRAINING

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Aim: VAD management training is a relevant issue involving all medical professionals deputed to advanced heart failure treatment. The aim of this work is the development of a computational cardiovascular simulator (CCS) to support learning of VAD management, focusing on VAD and circulatory system interactions.
Methods: The CCS is a component of a comprehensive platform aimed at VAD management training. The lumped parameter computational circulatory model includes heart, systemic and pulmonary circulations and baroreflex. The CCS includes sub-models of continuous flow VADs, for both atrio-aortic and apical connections and of iv drug infusion. The CCS is able to simulate patients' specific conditions or to generate preset or random pathologies offering to the trainee the possibility to manage the VAD and the related therapeutic actions such as drug or liquid administration. Further, the CCS can be used locally or remotely to enhance its training possibilities merged into a Learning Management System.
Results: The whole model was verified with clinical and experimental data. It was used for training of medical professionals on specific clinical cases and on predefined hemodynamic pathological conditions.
Conclusions: The CCS is flexible enough to be applied to different training needs. Its further development will include new autonomic controls and the respiratory system.
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A MODEL TOOL TO STUDY THE COMBINED EFFECTS OF DRUG ADMINISTRATION AND LVAD ASSISTANCE IN PATHOPHYSIOLOGICAL CIRCULATORY CONDITIONS

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Aim: To develop a numerical tool to study the joint effect of Sodium Nitroprusside (SNP), baroreflex and left ventricular assist device (LVAD) on hemodynamics.
Methods: A numerical model of the pharmaco-dynamic effect of SNP was developed and inserted into a lumped parameter circulatory model integrated with baroreflex and continuous flow LVAD (with atrio-aortic connection sub-models). The experiments were carried out in two steps.
First step: the model was verified by comparing simulations with experimental data acquired from previous studies on Mongrel dogs in terms of mean arterial pressure (MAP), cardiac output (CO), heart rate (HR), total peripheral resistance and left ventricular properties.
Second step: the combined action of SNP and LVAD was studied. Data were measured at LVAD off and at LVAD on (20000 and 24000 rpm).
Results: At LVAD off, with a 2.5 μg/kg/min SNP infusion under heart failure condition, the MAP reduced approximately 8%, CO and HR increased about 16% and 18%, respectively. In contrast, during assistance (24000 rpm) the changes in MAP, CO and HR were -9%, +12% and +20%, respectively. The effects of drug on hemodynamic parameters at different heart conditions were significantly different.
Conclusions: The model provides insight into the complex interaction among baroreflex, drug infusion and LVAD and could be a support to clinical decision-making in cardiovascular pathologies.
Acknowledgements: This work was supported by EU project SensorART (Grant number: 248763) and by Erasmus Mundus Masters Program (CEMACUBE).

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A HYBRID CARDIOVASCULAR SIMULATOR FOR VAD TRAINING

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Aim: The use of VAD training is a relevant issue involving physicians, care givers and, to some extent, patients. The aim of this work is the development of a hybrid (hydro-computational) cardiovascular simulator (HCS) as a support to learning of VAD control and of VAD-circulatory system interactions.
Methods: The model is a component of a comprehensive platform aimed at VAD training. It consists of the lumped parameter computational circulatory model and the hybrid (hydro-computational) interface based on the impedance transforming idea. The latter enables the atrio-aortic and apical connections of real VADs to the computational circulatory model to train various VAD-HCS interaction scenarios for specific patients' conditions. Furthermore, the HCS can be used locally or remotely to enhance its training possibilities merged into a Learning Management System.
Results: The computational circulatory model was verified with clinical and experimental data, then HCS was used for training of care givers and physicians both on specific clinical cases and on predefined hemodynamic pathological conditions.
Conclusions: The HCS is flexible enough to be applied to different training needs. Its further development will include the connection with the hybrid respiratory simulator to obtain cardio-respiratory interaction.
Acknowledgments: This work was supported by SensorART (N. 248763) EU project.

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RESEARCH OF THERMAL CHARACTERISTICS OF AN IMPLANTABLE SYSTEM OF ARTIFICIAL HEART

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Aim: Important problem in creation of implantable electromechanical systems of artificial heart is ensuring continuous work for a long time, under conditions

of limited heat transfer. Temperature of the body of electromechanical systems should not exceed 40°C, and overheating to 42°C is admissible only in short-time modes.
Methods: For the solution of this problem, numerical analysis of the thermal condition of an implantable electromechanical system of artificial heart, based on results of the solution of a stationary task of heat conductivity, was carried out by the finite elements method. Geometrical modeling of the body of electromechanical system of artificial heart was carried out in CAD-system Pro/Engineer WF 5. The solution of stationary heat transfer was approached by the finite elements method using the CAE-system by Ansys. Owing to symmetry of the design, only ¼ of the system (including all constructive elements) was considered that influences its thermal state. The model consisted of 642263 nodes and 363231 elements. The average size of edges of finite elements is 1 mm. Modeling was carried out for various power of thermal losses 5, 8, 10 W for density of a thermal stream of 1500, 2400 and 3000 W/m^2 respectively.
Results: Images of temperature fields on the surface of the body of electromechanical system of artificial heart were obtained.
Conclusions: The analysis of the thermal state at various power of thermal losses showed lack of overheating of the surface of the body of electromechanical system above critical temperature during the continuous work for a long time, and the possibility of application of the developed design as an implantable system.

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ACTUAL LENGTH OF ENDURANT LIMBS IS SMALLER THAN THEIR NOMINAL LENGTH
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Objective: Endurant stent graft system is one of the popular devices for EVAR (endovascular aneurysm repair). Major advantages of Endurant are secure fitting to the short angulated proximal neck and suitability for the torsion of iliac arteries. It is said that Endurant is the most frequently used device in the world. On the other hand, at the clinical use, we often recognize that the actual length of Endurant limbs is smaller than their nominal length. When we select the legs by their nominal length equivalent to the measured sizes at DSA (digital subtraction angiography), deployed limbs do not cover the expected length. In this study, we measured actual lengths of Endurant limbs to compare their nominal length.
Methods: We measured the lengths of the Endurant limbs in their sheaths before deployment under the fluoroscope and the length after deployment. Five kinds of contra lateral limbs (82 mm, 93 mm, 124 mm, 156 mm and 199 mm of the standard value) and 82 mm iliac extensions were measured (n = 63). The values were compared to their nominal length and analyzed statistically.
Results: The actual lengths of all the limbs in their sheaths were smaller than their nominal length (93.1%; 82 mm, 92.7%; 93 mm, 93.6%; 124 mm and 92.7; 156 mm. Averagely, actual limb lengths were 93% of their nominal length. In addition, the actual lengths of all the deployed limbs were about 5% shorter than their nominal length.
Conclusions: Nominal length is defined as the length of the graft fabric before stent flames are sutured. By suturing the stents, the actual length shortened by 5%. Furthermore, the Endurant limbs have 2 mm gaps between the stents. We suspected that theses gaps easily wrinkle and shorten when they are lorded into the delivery sheathes. Even after the deployment, the shortened limbs could hardly extend to their nominal length. This could be the reason why their actual length of the Endurant limbs is 93% that of the designed size. As a result, we recommend selecting 10% longer limbs by nominal length than the measured lengths under the angiography.

Poster Session 2 – Part 1

Computer Modeling

P83
INFLUENCE OF RENAL DENERVATION ON RENAL ARTERY HAEMODYNAMICS
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Aim: Catheter-based denervation of renal sympathetic nerves is a novel method for treatment of resistant hypertension. In recent clinical trials, a blood pressure (BP) reduction of more than 30 mmHg could be observed in patients with severe hypertension (BP >160 mmHg) which was resistant to conventional medical treatment. Although regrowth of sympathetic efferent nerves is possible, no recovery of renal sympathetic function and therefore no increase in BP could be observed over a period of two years. The aim of the current study was to determine this effect of renal denervation on renal arterial haemodynamics.
Methods: 4D VENC MRI of ten patients were acquired before and six months after renal denervation. These data were used to create three dimensional vessel geometries and assess flow rates, which in turn allowed calculation of the blood flow within the renal arteries with the aid of computational fluid dynamics.
Results: The renal denervation led to a significant increase in renal arterial diameter (0.27 $\pm$ 0.35 mm, $p<.05$) as well as renal blood flow after treatment (1.24 $\pm$ 1.81 ml/s, $p<.001$). The change in vessel diameter and flow due to renal denervation resulted in a significant reduction in the surface averaged wall shear stress (WSS) (0.48 + 0.91 Pa, $p<.05$).
Conclusions: The clinical meaning of this WSS reduction is unclear. Reduced WSS values are potentially dangerous, as lower WSS promotes thrombus formation and atherosclerosis Further investigation of patients treated via renal denervation seems warranted.

P84
A MULTISCALE MODEL TO ASSESS THE PERFUSION IN HUMAN CIRRHOSIS
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Aim: Liver cirrhosis is a chronic liver disease affecting both liver architecture and perfusion by the formation of fibrosis, regenerative nodules, shunt vessels etc. This process impairs the hepatic circulation and may elevate the intrahepatic vascular resistance (IVR). To gain more insight in the hemodynamic consequences of cirrhosis, multiscale models were developed.
Methods: Vascular corrosion casting and multi-level micro-CT imaging (up to a 1.7 µm resolution) were applied to an excised human cirrhotic liver. Image processing enabled 3D reconstructions of the cirrhotic microcirculation which formed the basis for computational fluid dynamics (CFD) simulations. In addition, a simplified 3D CFD model of the cirrhotic macrocirculation was constructed to analyze the effect of the presence of regenerative nodules (lacking sufficient perfusion) on IVR.
Results: The macrocirculation model indicates that regenerative nodules may severely increase the IVR, with a low (x1.5), moderate (x2.9) and high (x17) increase corresponding to a nodular volume percentage of 30%, 60% and 83%. In contrast, the micromodels suggest that local compensation mechanisms are present to counteract the macroscopic IVR effect. For example, shunt vessels and dilated sinusoids decreased the IVR by a factor 30 and 5.5 respectively, compared to normal liver tissue.
Conclusions: Numerical modeling allows quantifying the perfusion characteristics of the cirrhotic macro- and microcirculation, i.e. the effect of regenerative nodules and compensation mechanisms.

P85
EFFECTS OF MORPHOLOGICAL VARIARIONS IN HEARING-SUPPORT DEVICE: SIMULATION STUDY
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Aim: In most situations, algorithms for hearing-support devices are developed considering ideal and standardized structures. However, in actual cases, the morphology and part arrangement of the device with each other is different due to various factors such as size, type, and design, which deteriorates the performance of the algorithm. In this study, we evaluated the variations of the frequency response of a hearing aid due to the morphological variations of the device using 3-D acoustic simulation.
Methods: A standard human body model was 3-D scanned and hearing aid models with various morphological variations were modeled. These models were loaded into COMSOL simulator, various environmental factors, such as temperature, pressure, reverberation, were exerted to the models, and the effects of the morphological variations in the device were investigated using computer simulation.
Results: The frequency response in the audible range was different as the morphological factors – variations in cover shape – of the device varied.
Conclusions: The acoustic characteristics of the real hearing aid can be different from the ideal case, which can affect the performance of the implemented algorithms. Therefore, it is necessary to design the algorithms to fit to the morphology of the applied device to improve its acoustic performance.

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APPLICATION OF OUR ARTIFICIAL PATIENT TO INTERPRETATION AND CONTROL OF THORACENTESIS.

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Aim: Too big a fall of intrapleural pressure and increase in its breathing amplitude during thoracentesis may: make breathing more difficult, cause pulmonary edema, and disturb circulation. An electronic mano-meter constructed previously by the authors enabled to measure instantaneous intrapleural pressure during thoracentesis. Significant differences among patients in the pressure fall and amplitude increase were observed. Their interpretation was the study aim.
Methods: Previously developed artificial cardiopulmonary patient was modified to enable simulation of fluid inside the pleural cavity. The intrapleural pressure course was observed for various combination of values of pulmonary parameters and the rate of fluid removal.
Results: Most of events observed in patients could be simulated. In particular, the pressure fall was more significant for low thorax compliances; and the amplitude was bigger for low lung compliance and slow depended lung regions opening.
Conclusions: Our modified artificial patient is profitable in interpretation of phenomena during thoracentesis. It may also be useful in tests of simple models for the particular clinical use that is control of thoracentesis performance.
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A NEW CORONARY CIRCULATION MODEL FOR HYBRID APPLICATIONS

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Aim: The Waterfall model of the coronary circulation in a whole computational circulatory model used in hybrid cardiovascular simulator (HCS) has several limitations. The aim of this study is to develop a new computational coronary circulation model (CCM) useful for HCS applications.
Methods: The new CCM is based on a time-varying normalized impedance, whose resistive component is strongly nonlinear and depends on the phase of the cardiac cycle. The CCM was integrated in the HCS together with the base computational circulatory model, where the left and right ventricles are represented by time-varying elastance and systemic and pulmonary circulation are lumped Windkessel models. Starting from the HCS reproducing the same patho-physiological conditions, two groups of simulations were performed: one with the Waterfall and one with the new CCM. Then, a comparison between the two groups of results was performed.
Results: Using the HCS in real-time modality, time courses of coronary flow, aortic, left ventricular and right atrial pressures were collected. Results show that in comparison to the simple CCM, the new CCM better reproduces nonlinear coronary flow pattern, according to the reference data from literature.
Conclusions: The presented new CCM is able to reproduce the proper coronary flow pattern and is useful for HCS applications related especially to intra-aortic balloon pump assistance investigations.

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ORAL AND NASAL PAEDIATRIC ENDOTRACHEAL TUBES TESTED USING RESPIRATORY SYSTEM MODEL

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Aim: Paediatric respiratory system model (PRSM) is a hybrid (numerical-physical) simulator designed in IBIB PAN to study various lungs pathologies and questions of ventilation therapy.
The main aim of the paper was to test which of the two ways of an endotracheal intubation: via nose or oral cavity, is better, and should be recommended due to a ventilation quality of paediatric patient.
Methods: Numerical model in PRSM was adopted for airways of premature baby and 3-month-old baby. Next, the PRMS was connected via endotracheal tube (ETT) to Puritan Bennet Ventilator. Standard and reinforced ETT of 2.5 and 3 mm ID (internal diameter), placed in specially made polymer form with carved channel, shaped like a profile of: trachea, larynx, throat and oral/nasal cavity, and were examined during volume-controlled (VC) ventilation. Patient-ETT inspiratory and expiratory resistance (Ri, Re) and work of breathing done by ventilator (WOBvt) were measured.
Results: There were no significant differences in the Ri, Re and WOBvt between endotracheal intubation via nose and oral cavity, and between standard and reinforced ETTs of the same ID ($p>0.05$). But, the Ri, Re, WOBvt values obtained using ETTs of 2.5 mm ID were significantly higher than using ETTs of 3.0 mm ID ($p<0.05$).
Conclusions: Endotracheal intubation via nose and oral cavity had similar influence on ventilation parameters during VC ventilation of artificial infant.

P89

PATIENT-SPECIFIC MODELLING OF THE AORTIC CIRCULATION AFTER MUSTARD PROCEDURE

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Aim: The transposition of the great arteries (aorta and main pulmonary artery) is a congenital malformation, leading to death in the very first years if left untreated. In such a condition, the normal position of the arteries is reversed: blood enters the aorta from the right ventricle (RV), instead of the left one (LV), and the pulmonary artery is connected to the outlet of the left ventricle. The Mustard procedure enables to restore a more physiological situation, by means of surgical redirection of blood flow to appropriate atria: then, pulmonary and systemic circulation are driven by the left and right ventricle, respectively. The present study aims to characterize the aortic hemodynamics associated with the Mustard procedure.
Methods: MRI images of a patient after Mustard procedure were used to build a 3D model of the aorta, from the aortic root downstream to the abdominal aorta, including the supra-aortic arteries. The meshed model was then imported in Ansys Fluent 12.1, a computational fluid dynamics (CFD) software package.
Results: A remarkable recirculating secondary flow was observed in a section downstream of the left subclavian artery (LSA), whereas a lower level of recirculation was found in the abdominal aorta, similarly to what has been found in physiological aortic circulation. A zone of separated flow was not observed, contrary to, e.g., Kilner et al. (1993) and Wood et al. (2001). This may be explained by the steady flow regime (peak systole) in this study, with its minimal inertial effects.
Conclusions: The Mustard hemodynamics was found to share the characteristic patterns of physiological aortic flow, notwithstanding the fact that the native connection of the aorta to the RV entails a higher curvature of the aorta, with respect to the physiological case of aorta-LV connection. The findings support the effectiveness of the procedure in terms of hemodynamics.

P90

THE MECHANICAL ROLE OF CARDIAC TRABECULAE

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Aim: A significant percentage of left ventricular mass (12%-17%) is represented by cardiac trabeculae, cylindrical structures which cover the inner surfaces of both ventricles preferably oriented along the apico-basal direction. The aim of the work was to study the role of trabeculae on heart performance by comparing different FE models of the left ventricle (with or without trabeculae).
Methods: The ventricle was simplified as a truncated ellipsoid and the trabeculae as cylindrical strands oriented along the ventricular axis. Different trabeculae diameters and mass were implemented. The total muscular mass and the intraventricular volume were kept constant in all models. The myocardium mechanical behaviour was modeled with an anisotropic law. The material parameters were optimized to fit the physiological pressure-volume relationship. Cardiac fibres were oriented helically in the ventricular wall and along the axial direction in the trabeculae, according to the literature. The muscular contraction was simulated by increasing the material stiffness according to the contraction curve of a myocyte. Kinematic constraints were applied at the ventricular base. Physiological atrial pressure was set during diastole; an RCR model was coupled to the ventricle to simulate the systemic circulation.
Results: The trabeculated vs. the non trabeculated ventricle displays: higher compliance and higher cardiac output at 75 bpm (5 l/min vs. 4 l/min). The end-diastolic volume increases with the trabecular mass, while the trabeculae size influences the fibre stress.

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Conclusions: This study highlighted a significant role of the trabeculae on ventricular performances.

P91

MODELLING OF ADDITIONAL PULMONARY BLOOD FLOW IN THE BIDIRECTIONAL CAVOPULMONARY ANASTOMOSIS

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Aim: Since the pioneering contributions of Fontan, patients with congenital malformations leading to a circulation driven only by one functional ventricle (i.e., the univentricular patients), have been subjected to surgical operations meant to create a more favourable haemodynamics. The bidirectional cavopulmonary anastomosis (BCPA) is one of such operations, meant to adapt the body to a future total cavopulmonary connection. Since the circulation associated to the BCPA is given by two parallel circuits, the upper and the lower circulation, with the latter not directly contributing to the lung perfusion, there is a potential problem of low oxygen saturation. It has been proposed that an additional pulmonary blood flow could increase the oxygen saturation, with respect to the classical BCPA (Caspi et al. 2003). This study aims to verify this hypothesis in quantitative terms.
Methods: The role of additional pulmonary blood flow (e.g., a modified Blalock-Taussig shunt) was investigated by means of a lumped parameter model, considering different degrees of shunting. The model generalizes the one previously proposed by Santamore et al. (1998).
Results: The results support the view that an additional source of blood flow can actually increase the saturation level in pediatric patients operated on with a BCPA. A marked improvement (>16%) was observed for IVC oxygen saturation, especially for the minimum physiological value of the flow ratio in the caval veins, $r = Q_{IVC}/Q_{SVC}$.
Conclusions: Mathematical modeling of the circulation after BCPA and of an additional source of pulmonary blood flow demonstrated clear advantages of this surgical option over simple BCPA, in terms of systemic blood oxygen saturation, especially in the lower circulation.

P92

SURGICAL PLANNING WITH 3D PRINTING FOR A PATIENT WITH HUGE CARDIAC MASS

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Aim: Surgical planning with 3 D printing is useful in the medical field. We report a case of huge mediastinal sarcoma which we had used 3D printing for surgical resection planning.
Methods: A 43 years old female admitted with huge mediastinal mass. The mass size was 10 by 8 cm, and it attached with the heart from right atrium to pulmonary arteries. Because the mass was huge, we should plan how to approach to the mass for a surgery. For this planning, we converted the computer tomography image to 3D image using Mimics Basic (Materialize, Belgium) and printed 3D structure with uPrint (Stratasys Ltd, US).
Results: Before surgery, we used the prototype of patient's rib cage, heart, lung, and mass for surgical planning. The prototype was almost same with the real patient's anatomy when we confirmed it in the real surgical field.
Conclusions: 3D printing in a patient with huge mediastinal mass was very helpful to make a surgical plan. Especially in this patient, we can check the mass margin with the heart before surgery.

Biomaterials 1

P93

INFLUENCE OF MICROSTRUCTURE ON THE ANTIBACTERIAL ACTIVITY OF AG DOPED HYDROXYAPATITE BASED BIOMATERIALS

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Background: To reduce the risk of infection in bone surgery local antimicrobial treatment may be applied. Silver is commonly known for its broad spectrum of activity against bacteria, fungi and some viruses. The incorporation of silver ions into the structure of hydroxyapatite may lead to the fabrication of materials with high biocompatibility and antibacterial properties.
Methods: Three materials based on silver-doped hydroxyapatite (AgHA) were tested. AgHA with 1.0 wt.% of Ag additive was synthesized by the wet chemical method. The dried precipitate (A), calcinated above 700°C (B) and sintered over 1100°C (C) materials were studied. Phase composition, water absorbability, microstructure and porosity were examined. The antibacterial activity of the products was tested against *Staphylococcus aureus* and *Escherichia coli*.
Results: XRD studies confirmed that developed materials contain hydroxyapatite as the only crystalline phase. Microporous materials A and B (~60 vol.% of open pores in the range of 0.020 - 0.065 μm) revealed very high antibacterial activity. After 24 h, amount of viable bacterial cells was reduced to 0, both in the case of *S. epidermidis* and *E.coli*. Dense sintered AgHA ceramics (C) with water absorbability below 0.5 wt.% did not show any antibacterial activity.
Conclusions: Microstructure of the Ag doped HA materials resulting from the preparation method influence their antibacterial character.
Acknowledgements: The work has been supported by the Polish National Science Centre (DEC-2013/09/N/ST8/04171).

P94

EVALUATION OF CELL DAMAGE BY FE IONS RELEASED AS DEGRADATION PRODUCTS OF BIOMATERIALS. INFLUENCE OF PH CHANGES

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Background: Fe and some of its alloys have been proposed for the manufacture of temporary stents because they are susceptible to fast corrosion in biological media. However, their degradation products may cause side effects like oxidative stress and inflammation. In this work, the effects of Fe^{2+} and Fe^{3+} ions and pH changes on CHO-K1 cell cultures were evaluated.
Methods: CHO-K1 cells were exposed to Fe^{2+}, Fe^{3+} salts (1 mM-5 mM) and different pH. Mitochondrial activity, generation of oxidative stress products and total Fe content within the cells were determined. The effects of pH changes were also evaluated.
Results and Discussion: After any treatment ("*pH*", "*pH+*Fe^{2+}" and "*pH+*Fe^{3+}") the cellular mitochondrial activity was lower than the control. Fe^{2+} effect in the 1 to 3 mM range was owed to decrease in pH. Meanwhile in the 4 to 5 mM Fe^{2+} range, the detrimental effect was higher than the observed in similar pH solutions. The effect of Fe^{3+} at 3 to 4 mM was greater than that caused by the pH alone. However, in the presence of Fe ions, higher oxidative stress was found, independently of the pH value.
Conclusions: Cytotoxicity and oxidative stress occurring at the biomaterial/biological medium interface during the degradation of Fe may markedly affect the viability of cells in the vicinity of the stent.

P95

HEPARIN IMMOBILIZED ON ACTIVATED CHARCOAL BINDS DNA ANTIBODIES

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Aim: Heparin (Hp), administered as an anticoagulant during hemosorption procedure, may have additional therapeutic effect due to its interaction with diverse biologically active substances like cytokines, growth factors, etc., taking part in the process of acute and chronic inflammation. The aim of this study is to show that Hp immobilized on carbon adsorbents can bind n- DNA (native deoxyribonucleic acid) and ss-DNA (single stranded deoxyribonucleic acid) antibodies (AT) from diluted pool of patient's sera with immunodependent diseases.
Methods: Modified ELISA method was used for measurement of anti-n-DNA, anti-ss-DNA AT and Phadia kits for measurement of anti-n-DNA AT in diluted with 4% BSA 20-25 times pool of patient's sera before and after incubation "*in vitro*" with 0.5 ml of Hp-coated or uncoated (control) granulated carbonic hemosorbents. Selectivity of adsorbent was calculated as the relation of adsorbed AT –DNA to adsorbed total protein. Two factor analysis and the Scheffe's test were performed using SAS software
Results: Selectivity of heparin containing charcoal to anti-ss-DNA AT 1.5 ± 0.2 (n = 19) is significantly higher than those of uncoated charcoal 1.1 ± 0.2 (n = 31), idem for anti-n-DNA AT 1.6 ± 0.18 (n = 6) and 1.0 ± 0.18 (n = 6).
Conclusions: Hp-coated hemosorbents exhibit the augmentation of selectivity to anti-ss-DNA and anti-n-DNA AT in experiments "*in vitro*". These preliminary results confirm the possible role of injected heparin in the long-lasting therapeutic effects of hemosorption procedure.

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BIODEGRADABLE INTERCONNECTED POROUS NERVE GUIDE CONDUITS FABRICATED BY PHASE SEPARATION METHOD

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Aim: Restoration with sufficient functional recovery after peripheral nerve injury has attracted a great deal of attention as a new clinical challenge. Artificial nerve guide conduit (NGC) to bridge the gap between severed peripheral nerve stumps is widely accepted as a useful alternative that creates a favorable microenvironment for nerve regeneration. There are many requirements for desirable NGCs including permeability, mechanical strength, immunological inertness and biodegradability. In this study, we developed a novel method to fabricate three dimensionally interconnected porous NGC.
Methods: Biodegradable porous NGC was fabricated by thermally induced phase separation method. PLGA, g-PGA and Fluronic L64 were dissolved in DMSO at 80°C. This mixture was injected into a PTFE tube and cooled to 40, 50 or 60°C, respectively. Then this mixture was cross-linked with diisocyanate for preparing rod type NGC. The characterization and cytocompatibility assay of NGC were carried out in detail.
Results: Biodegradable porous NGCs consisted of PLGA and g-PGA were successfully prepared by phase separation method. These NGCs showed double porous structure which was deeply affected by the cooling temperature. Among them, NGC cooled to 40°C exhibited uniformed porous structure and excellent cytocompatibility.
Conclusions: We fabricated porous NGCs with cytocompatibility and hydrophilicity by thermally induced phase separation. This is very simple and effective method for the fabrication of biocompatible NGCs.

P97

EVALUATION OF PREPOLYMERIZED ALLYL 2-CYANOACRYL(PACA) AS A BIO-ADHESIVE

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Aim: Bio-adhesives are generally used to reduce wounds or scarring after surgery. We have developed a new type of bio-adhesive prepolymerized allyl 2-cyanoacryl (PACA). To evaluate effectiveness of PACA as a bio-adhesive, we compare PACA with/without epidermal growth factor (EGF) with octyl-cyanoacrylate (Dermabond®), and 2-Butyl-cyanoacrylate (Histoacryl®) with a physical tensile strength test and histopathological examination.
Methods: PACA was compared to the controls, PACA with EGF, Dermabond, and Histoacryl. Twenty-eight SD rat were used, and each animal underwent 4 skin incisions (20 mm in length) on the back. The wounds were glued with the tested adhesives and observed on the 4th and 7th day after the incision. The physical tensile strength test was performed with the Crosshead Speed 40 mm/min using Universal testing machine. The degree of inflammation, and the collagen distribution were determined by histopathological examination.
Results: Dermabond showed the strongest tensile strength on the 4th day. However, PACA adhesive with EGF exhibited the strongest tensile strength on the 7th day in physical tensile strength tests. The inflammation reduced in Dermabond, Histoacryl, and PACA with EGF at the 7th day compare with the 4th day. PACA with EGF showed collagen regeneration were increased rapidly after the 4th day than other groups.
Conclusions: PACA with EGF bio-adhesive showed good physical tensile strength and collagen regeneration on the 7th day.

P98

EVALUATION OF THE FREEZING TECHNOLOGY BY QUANTITATIVE PHYSICAL EVALUATION FOR HOMOGRAFT

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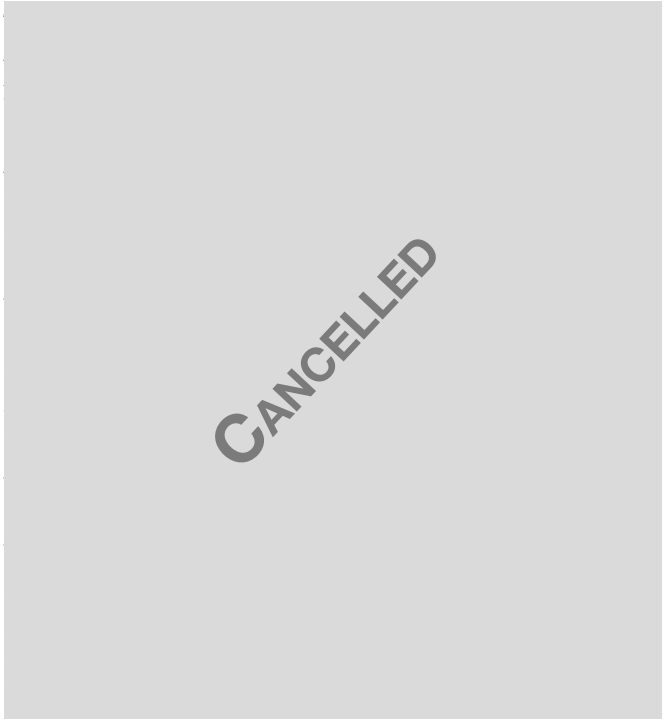
Aim: Homograft technology is important not only in cardiovascular surgery, but also in the field of artificial organs, because complex surgery combined with artificial organs and transplantation technology will increase in near future. However, there had been no report comparing the physical properties change of cardiovascular homograft after various freezing methods. In this study, physical properties after various freezing methods were compared in animal experiments after animal ethical committee allowance.
Methods: Aortic tissue of the goats was frozen with the ethanol-type freezing method, the liquid nitrogen freezing method, and by freezing in the gas tank type freezer method, and compared with tissue before freezing. Such a paper reporting the quantitative comparison of physical characteristics is the first such report in the world. Focusing on the first weight change, weight change of the ethanol freezing method was minimal in the frozen group. This is assumed to be due to differences in dewatering efficiency. Quantitative evaluation of physical properties including the total system, as the anatomical structure, were performed using a precision measuring biological tissue.
Results: Considering tissue as an elastic material, it was possible to quantify the measurement for each element, the variation of physical properties. By observing decay over time of tissue elasticity, a precise evaluation of physical properties can be achieved. For example, in the samples frozen with the gas tank refrigeration, phenomenon showing the non-linearity limit in the smallest stretch power were observed. This presents the limits of the maintenance of tissue by this freezing method. On the other hand, there was no significant difference between the non-frozen group and the ethanol-type freezing method.
Conclusions: By this precise quantitative evaluation, it is expected that better and gentler systems for storing human tissue will be developed in near future.



P100

TOWARDS A CORRECT RISK ASSESSMENT OF MEDICAL DEVICES CONTAINING NANOMATERIALS

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Aim: The increasing diffusion of medical devices (MDs) containing nanomaterials witnesses the great benefits given by the nanoscale unique properties. At the same time, it is necessary to define the associated risks. This study addresses the current status of risks assessment of MDs containing nanomaterials.
Methods: This work starts form the risk assessment for common medical devices, adding the modifications to be included if they contain nanomaterials. Every substance can generate inappropriate reactions even when used according to the desired aims. The possible harm is given by the combined effect of product toxicity and exposure level (quantity, kind and time of the contact).
A full assessment of the effects of exposure to nanomaterials would require a wealth of knowledge, currently not available. Current guidelines for risk management of medical devices are generally accepted also when they contain nanomaterials but, before standard testing, it is necessary to perform an adequate physical-chemical characterization of the nanomaterials (intentional and incidental) involved in the entire life cycle of the MD. Actually, the toxicity

of the same nanomaterial may vary in different locations and forms (airborne, surface bound, suspended…), and also in different points of the product's cycle of life.
Results: The guidelines for risk evaluation of MDs containing nanomaterials are still in a very preliminary phase. In absence of proper guidelines for such MDs, the laws regulating chemical products should be taken as the reference for nanomaterials.
Conclusions: Current testing procedures are just a good start in view of attaining the level required for a correct risk management. A coordinated, international and multidisciplinary work is needed to improve knowledge, innovation and safety of MDs with nanomaterials.

Biomaterials 2

P101
MECHANICAL AND BIOLOGICAL PROPERTIES ASSESSMENT OF NANO-CARBON LAYER ON PEEK
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Aim: Moll type mechanic valves with disc made of PEEK, for pulsatile VADs were developed, and used in humans. Study aim was to evaluate DLC carbon layer fabricated on PEEK base and applied to Moll valve disc. *In-vitro* biocompatibility, mechanical strength, fatigue and animal blood thrombogenicity tests were performed.
Methods: Material thrombogenic proprieties were evaluated in shear stress conditions, utilizing IMPACT-R test. After the test, activation of blood plates in cytometric examination of selected receptors CD62P, and CD45, plus adhesion of morphotic component on DLC surface, was assessed. Structural proprieties of carbon layer were characterized by scanning microscopy: SEM and AFM. Valve disk with DLC layer were subjected to fatigue tests and carbon layer degradation was evaluated, after specific valve work time intervals (from 2 to 30 months). *In-vitro* experiment of acute thrombogenicity on valve was conducted.
Results: It was observed that DLC carbon coating formed on PEEK works protective and they don't generate increased activation of blood. In addition, DLC surface coating cause rise of hardness of disc and better abrasion resistance. After blood test no presence of thrombus within valve and other parts of system were observed.
Conclusions: Use of DLC coating on PEEK substrate seems to be proper direction in obtaining right material combination which is resistant to long-term performance in heart valve for VADs.

P102
'CORE-SHELL' TYPE HYDROGEL MICROFIBER FOR TISSUE ENGINEERING
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Aim: We have developed broadly applicable three-dimensional (3D) 'core-shell' type hydrogel microfiber to apply functional scaffold as a tissue block that could be used for tissue or organ regeneration. To generate 'core-shell' hydrogel 3D microfiber, the coaxial flow-based microfluidic device was assessed for manipulation of cell behaviour in controllable 3D microenvironments.
Methods: To synthesize cell-laden microfiber, the polydimethylsiloxane (PDMS) block and micro-pulled glass pipettes were assembled as a coaxial flow device. The collagen type I, Naalginate solution and $CaCl_2$ solution were generated in microfluidic device as a 'core-shell' type. While the coaxial flow is generated, the solidification and cross-linking process occur at the interface between the core and shell wall, simultaneously. During the process, the HepG2/A549 cells and microparticles could be immobilized in fibers, respectively. Also, the 'shellalginate' outer layer could be removed with sodium citrate solution.
Results: The collagen type I and Na-alginate mixture in coaxial flow device, the alginate was cross-linked by $CaCl_2$ solution and collagen type I solution was solidified by warmed $CaCl_2$ solution-cell medium mixture, respectively. In this case, we assumed the 'shell-alginate' outer wall could support the solidification of 'core-collagen' microfiber. In different cell-laden structure, we could manipulate the cell behaviours within 3D microenvironments.
Conclusions: In this study, we suggest a 'core-shell' type cell-laden hydrogel microfiber with 3D culture system. We generated 'core; HepG2 cell-laden collagen type I' and 'shell; A549 cellladen alginate' 3D microfibers. This approach could be used for creating 3D scaffolds needed for tissue engineering.

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P103
SYNTHESIS AND CHARACTERIZATION OF HYDROLYZED PAN FOR NUCLEUS PULPOSUS REPLACEMENT
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Aim: Disc degeneration is the result of damage to or dehydration of the nucleus pulposus, which reduces its hydrostatic pressure on the internal surface of the annulus fibrosis. In this work, hydrolyzed polyacrylonitrile (HPAN) hydrogel was synthesized in order to replace nucleus pulposus in a degenerated intevertebral disc without surgical excision and implantation of prosthesis.
Methods: Hydrogels were prepared by reacting different molar ratio of polyacrylonitrile and NaOH, dissolving in 55% NaSCN solution. ^{13}C NMR spectra of the HPAN polymers were recorded using 55% NaSCN/D_2O solvent in 10 wt%. The water contents of HPAN polymer was calculated by measuring the weight in dry and swollen state. Also *in vitro* degradation tests were performed and compression modulus was evaluated in mechanical tests.
Results: We successfully synthesized HPAN polymer. The HPAN hydrogel has similar water binding capabilities to nucleus and the elasticity of the hydrogel can also be controlled by adjusting the chemistry and the water content, allowing the material to be used in replacement of the nucleus pulposus. In degradation tests and compression tests, the hydrogel maintains its shape.
Conclusions: The results of this study demonstrate that HPAN hydrogels may be feasible as nucleus pulposus implants.

P104
DEVELOPMENT OF MICRO-POROUS TITANIUM SCAFFOLD FOR PROMOTING THE EARLY NEOINTIMAL GROWTHS
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Aim: Thromboembolism event around the cannula is one of the critical problems after implanting a ventricular assist device (VAD). We have developed the surface modification based on the titanium (Ti) micro-porous structure for promoting early neointimal growth. The purpose of this study is the evaluation of our micro-porous structure as scaffold material of the vascular prosthesis.
Methods and Methods: A Ti powders, sifted about 150 micro-meters, were mixed with 10 wt% of thermoplastic wax. The mixture was warmed up to 50°C and injected into a mold. Green specimens were sintered in argon gas for 1.5 h. These specimens were studied in mechanical strength tests and cell adhesion evaluated. Specimens were also implanted around connective and muscular tissues in rat for evaluating the specimens interaction.
Results: The theoretically predicted micro-porous specimens showed similar strength compared to bovine femoral bone. Cells invasions and collagen rich structure were observed inside the microporous structure. Organ adhesion tests showed higher strength as compared to bulk Ti specimens.
Conclusions: Our micro-porous scaffold is based on Ti that is known as a biocompatible materials. By modifying it as a cell scaffold, the possibility of critical events after VAD implantations was studied. The results indicated the advantages of modified micro-porous surface structure as the blood contacting surface of vascular prostheses.

P105
CHITOSAN BASED BIOMATERIALS: THE EFFECT OF CROSS-LINKING AGENTS
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Aim: Chitosan, the well-known natural biopolymer, is non-toxic, biodegradable and biocompatible in nature. The advantages of this biomaterial are such that they can be easily processed into different forms and have a variety of biomedical applications such as wound healing, drug delivery and tissue engineering. Apart from all these advantages, chitosan has a limitation of being unstable in aqueous media due to salt formation between ammonium ions, along the chitosan chains, and the carboxylate ions of acetic acid, which is a solvent of chitosan. Therefore, cross-linking is required to improve mechanical strength and degradation properties of chitosan-based biomaterials. Various stabilizers

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in the form of cross-linkers are used by different research groups, namely glutaraldehyde (GA) but there are few works on using other cross-linking agents or any comparison between them in the literature.
Methods: In the present study, the effect of adipic, oxalic & sebacic acid and adipoyl chloride on the properties of the cross-linked chitosan was evaluated using mechanical and weight loss experiments. Actually, chitosan films were obtained from 1% wt chitosan solution in acetic acid to which the above mentioned materials were added.
Results: It was found that GA, oxalic, sebacic and adipic acid resulted in films with most promising physical and mechanical properties meanwhile adipoyl chloride did not show any cross-linking effect on chitosan.
Conclusions: Based on our study, oxalic, sebacic and adipic acid which have less cytotoxicity in compare with GA are recommended for biomedical application of cross-linked chitosan.

P106
COMPARATIVE STUDY OF THE LONG-TERM ALTERATIONS OF ELASTICITY OF SOME HERNIA MESHES AND HUMAN ABDOMINAL FASCIA
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Aim: Synthetic meshes have many applications in surgery. Usually they remain in abdominal cavity for years. The aim of this study is to investigate the long-term alterations to elasticity of some hernia meshes and to compare them with human fascia's elasticity.
Materials and Methods: Long-term behavior of polypropylene meshes Surgimesh (SM), Tecnomesh (TM) and Surgipro (SP) were revealed using tensile experiments. The samples were cut along the rows of loops and parallel to the column of loops and were tested before their expiration date (ED) and between two months and four years after (ED). The fascia samples were taken from 13 donors aged 45-87 years and divided into three groups: up to 64 years (group A), 65-80 years (group B) and 81-90 years (group C). Tensile tests of 84 samples cut along the fibers and perpendicular to them were performed. The secant modulus at 5% deformation (E) was calculated for meshes and fascia samples and the obtained values were compared.
Results: The secant modulus of SM increases and after one year approaches the mechanical properties of the fascia in the direction parallel to collagen fibers. Elastic properties of SP are the same 4 years after ED and are close to those of group B, while elastic properties of TM decrease between 30 and 50% in both directions and approach fascia's elasticity of group A and B in one direction only.
Conclusions: The elasticity of the investigated hernia meshes is not close to the elasticity of human fascia and needs to be improved.

P107
COMPARISON OF ARTIFICIAL SCAFFOLD TRANSPORT PROPERTIES TO NATURAL TISSUE
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Aim: The performance of tissue engineering scaffolds for cell growth is influenced by their physical properties. Their morphology is described in terms of porosity, pore size and pore distribution. The architecture of tissue engineering porous scaffolds is a crucial actor in effectively guiding tissue regeneration. For this reason, the characterization of scaffold architecture is essential to better understand to what extent scaffold texture does mimic the natural tissue structure, does influence the cell-substrate system and, eventually, to give detailed information for designing and building up effective functional substitutes. The aim of the present study is to characterize the microstructure of an artificial porous hydroxyapatite biomaterial and to compare it to the natural tissue.
Methods: We selected (a) a commercial porous hydroxyapatite scaffold produced by sinterization and (b) we harvested cancellous bone from sheep. Cylindrical samples (10 mm diameter, 10 mm height) were cut from the raw materials using a core cutter. Starting from realistic 3D models of the scaffolds reconstructed from micro-CT images, the scaffold architecture of both artificial scaffold and natural tissue is evaluated in term of porosity, pore size and pore distribution.
Results: The results demonstrate that the commercial porous hydroxyapatite scaffold selected not only reproduces macroscopic features such as porosity, but mainly scaffold microarchitecture giving rise to structural heterogeneity, in terms of pore size and pore distribution, which could have an impact on the local cell-scaffold interaction and scaffold performances.
Conclusions: The adopted approach allows to investigate the scale-dependent pore distribution within the scaffold and the related structural heterogeneity features, providing a comprehensive characterization of the scaffold texture in comparison to natural tissue.
Acknowledgments: Study co-funded by the Italian Ministry of Instruction and University (MIUR) (Project PRIN 2010, MIND).

P108
AUTOMATED FABRICATION OF ELECTROSPUN SCAFFOLD STRUCTURES
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Background: The demand for replacement of damaged tissue increases constantly due to the increasing life expectancy. The demand cannot be satisfied by donated tissue and organs. To provide patient specific tissue tissue engineering is an option. For tissue engineering purposes, scaffolds may be produced via electrospinning. Electrospinning is not jet integrated into a production line which leads to possible damage to the scaffold.
Methods: In this study, various concepts have been developed for integration of an electrospinning device into a production line, taking the production of a heart valve scaffold as an example. The concepts are based on an existing spinning device and concentrate on the transport mechanism in between the production steps. The production line consists of five manufacturing steps: (i) electrospinning of cusps, (ii) laser cutting, (iii) electrospinning of cylinders, (iv) laser welding and (v) packing.
Results: The cusps are manually positioned in the cylinder collector prior to spinning the cylinder. The user feeds the prepared cylinder into the process via a transfer tray. The collector is picked up by a robot, which rotates the collector during spinning and puts it onto a round magazine afterwards. The collector is then picked up by the next robot in the laser welding process room. The cusps are welded to the cylinder and the collector is placed on another transfer tray. The scaffold is manually removed from the collector and packed for transport.
Conclusions: A concept for an automated production line with integrated electrospinning was developed.

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P109
SEEDING OF OVINE ENDOTHELIAL CELLS ON BIOFUNCTIONALIZED ARTIFICIAL MEMBRANES AS MODEL FOR AN ENDOTHELIALISED OXYGENATOR
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Background: Extracorporeal membrane oxygenation (ECMO) supports patients with chronic lung diseases. Commercially available systems consist of hollow fiber membranes, made of polypropylene (PP), silicone (PDMS) or polymethylpentene (PMP). Long-term application is limited by a gas transfer reduction due to unspecific protein adsorption and side effects like activation of the coagulation and complement system. Better biocompatibility would allow for long-term application and can be obtained by endothelialisation of flat membrane oxygenators.
Materials and Methods: Ovine Endothelial cells were seeded on PP, PMP and PDMS slides, biofunctionalized with the peptide sequence RGD by star-shaped polyethylene glycol (starPEG) linkers. Then cell proliferation was performed starting under static and changing to dynamic conditions in a custom-made bioreactor. Shear stress was increased daily, starting from 0.20 dyn/cm^2.
Results: After 4 days of static cultivation a confluent cell layer was obtained on RGD-functionalized PMP. Under dynamic cultivation this cell layer remained stable until a shear stress of 0.71 dyn/cm^2, which was reached on day 3. Cell morphology changed from cobblestone pattern to a physiologic spindle-shape.
Conclusions: A confluent layer of endothelial cells is stable under shear stress conditions, which is an essential requirement for the development of a biohybrid lung.

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P110

CULTIVATION OF ENDOTHELIAL CELLS USING TWO-TYPES OF NANOFIBROUS MEMBRANES AND VARIOUS LEVELS OF HYDROGEL CONCENTRATION

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Aim: The blood vessels are part of the circulatory system that transport oxygen, nutrients, and drugs to the tissues and organs of the body, and also provide a route for metastasizing cancer cells to other organs. Therefore, *in-vitro* microfluidic chips, that mimic the microenvironment of blood vessels, have great potential to be a platform for developing a cure for various diseases including cancer. The purpose of this study was to investigate the effect of woven and non-woven nanofibrous membrane and various levels of hydrogel concentration on the monolayer formation.
Methods: In this study, we tested the effect of alignment of nanofiber and various levels of hydrogel concentration on the monolayer formation using endothelial cells and compared between woven and non-woven nanofiber. In order to obtain random and aligned nanofibers, we exploited two-types of electrospinning collectors which are rotating drum and 2D plate.
Results: After 7 days of cultivation, the elongation factor of cells was higher on the woven nanofibrous membrane than non-woven membrane. Also, the cells formed more densely on the woven nanofibrous membrane with high concentration of hydrogel.
Conclusions: We expect that the endothelial cells cultured with the nanofibrous membrane and hydrogel can be applied to develop blood vessels that mimic microfluidics chip.

P111

TISSUE-SPECIFIC SMALL-DISPERSED MATRIX–AS A TECHNOLOGICAL BASIS FOR PRODUCING IMPLANTS CELL-ENGINEERING DESIGNS

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Aim: To develop a technology for producing tissue specific small-dispersed matrices (TSSDM), suitable for cell-sowing and using in the form of cell-engineering designs implanted into corresponding damaged organ.
Methods: The technology for making TSSDM was tested on Wistar rats (n = 40). Organs (liver, kidney) were decellularized and detergents washed out by generally accepted methods. Then, matrices of decellularized organs were ground according to our original method and sterilized. Tissue-specificity of matrix particles (MP) was evaluated by adhesion of cells: liver cells, cells of renal epithelium, MSC of BM and HepG2. Viability and proliferative activity of these cells were evaluated by using Mossman method. Cytodex-3 was used as a control matrix.
Results: TSSDM, produced from decellularized liver and kidneys and also Cytodex-3 possessed adhesion properties for all cell types. Adhesion activity of liver cells and HepG2-cells was more expressed to liver MP and that of renal epithelium cells was more expressed to kidney MP.
Conclusions: The offered technology for producing TSSDM provided increased reliability of cell-attachment on MP; preservation of tissue specificity of MP and possibility of using TSSDM for producing implantable cell-engineering designs.

P112

MICRO RIDGES CAN CONTROL ORIENTATION OF CULTURED CELLS

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Aim: The acceleration technique for orientation of cells would be applied to regenerative tissue technology. In previous studies, the orientation of cells was controlled by sandwiching the cells between walls in grooves, or in capillaries. Cells, on the other hand, might sense the direction of micromorphology of the scaffold. In the present study, cells have been cultured on the surface with micro linear ridges, and the effect of ridges on the orientation of cultured cells has been studied *in vitro*.
Methods: Several patterns of micro ridges have been fabricated on a transparent polydimethylsiloxane disk with the photo lithography technique. The ridges consist of several lines of rectangular column: width of 0.003 mm, interval of 0.007 mm. Variation has been made on the height of the ridge between 0.0003 mm and 0.0035 mm. C2C12 cells (mouse myoblast cell line originated with cross-striated muscle of C3H mouse) were cultured on the disk with the micro ridges for one week and were observed with an inverted phase contrast microscope.
Results: Cells adsorb on the top of the ridge, extend pseudopodium along the longitudinal direction of the ridge, and align along the longitudinal direction of the micro ridges with height between 0.0015 mm and 0.0025 mm.
Conclusions: The experimental results show that cells sense micro morphology of the ridge and that the optimum size of micro ridges can control orientation of cells.

P113

EFFECT OF MECHANICAL FORCE FIELD ON CULTURED CELLS

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Aim: Mechanical stress is one of the interesting factors in the environment of cells, which may be subjected to mechanical forces *in vivo*. The mechanical stress on cells might induce various responses: deformation, migration, proliferation, and differentiation. In the present study, the effect of the mechanical force field on cultured cells has been studied *in vitro*.
Methods: Cells were cultured on a polystyrene plate coated with collagen for three days in the mechanical force field. To apply the mechanical force field to the cells on the plate, the plate was inserted into a centrifugal tube. The tube was placed in a conventional centrifugal machine, and the surface of the culture plate was set in parallel position to the centrifugal field. Three kinds of cells were alternatively used in the test: L929 (fibroblast-like, mouse connective tissue), HUVEC (normal human umbilical vein endothelial cells), or C2C12 (mouse myoblast cell line originated with cross-striated muscle of C3H mouse). Shape and orientation of the cells were observed with a phase contrast microscope during cell culture.
Results: C2C12 cells proliferate to confluence even at centrifugal forces 100 times the gravitational force. The mechanical force field accelerates extension of pseudopodia of C2C12 cells to the perpendicular direction against the mechanical force field and differentiation of the C2C12 cells.
Conclusions: The mechanical force field can accelerate extension of pseudopodium and differentiation of C2C12 cells.

P114

ARTIFICIAL MATRICES FOR GENERATING HUMAN THYMIC ORGANOIDS

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Aim: Development of conditions supporting enhanced self-renewal of TESC *in vitro* and to enable development of transplantable human thymic organoids, generated by seeding human thymic epithelial stem cells onto bio-active scaffolds that are capable of supporting sustained thymopoiesis in human patients. The research work is conducted under an FP7 project ThymiStem (602587).
Methods: Electrospinning was used to prepare a 3D nanofibrous scaffold similar to natural ECM, using synthetic or natural biodegradable polymers. Nanofibrous layers serve as ideal substrates to grow soft tissue, such as thymus, in that they provide a unique structure characterized by a high surface area to volume ratio and 3D interconnected pore network, both of which enhance cell attachment and proliferation.
Results: As our starting point, we focused on the scaffolds development for the generation of an OP9-DL1-based organoid, which have been extensively modified to optimally support the output of committed T cell progenitors.
Conclusions: Cell growth, viability, and morphology of cells seeded on scaffolds were monitored using confocal microscopy of live cells, cell viability staining, and MTT assays.

P115

DEVELOPMENT OF CARTILAGE TISSUE ANALOGUES HIGHLY MATURE BY A NOVEL IN-BODY INCUBATION TECHNOLOGY

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Objective: Although several cultured cartilage grafts have been commercialized, their preparation needs a series of complicated culture procedure including growth, re-differentiation and maturation of chondrocytes using very expensive culture reagents under strictly sterile condition. In the last ESAO congress, we reported the development of in-body incubation technology for vessel fabrication, in which native-like vascular tissues were automatically

obtained by subcutaneous placing of porous cell-diffusing molds filled with vascular-constitutes cells. In this study, we attempt to apply this technology to prepare cartilage tissues.
Methods: Dedifferentiated costal chondrocytes (DeCCs) prepared by 2 weeks expansion culturing of their primary were used in this study. The autologous DeCCs were suspended in 0.8% atelocollagen solution (3.2×10^7 cells/ml) and poured into plastic disc-shaped case molds that have multiple pores on both sides (d: 10 mmΦ, h: 1~4 mm, pore size: 0.5 mm, pore number: 0~100). The molds were placed into dorsal subcutaneous pouches of rats for 4 weeks.
Results: Although DeCCs formed brittle tissue without any cartilage formation when they were filled in molds having relatively low pore numbers (less than 30), robust cartilage tissue analogues formed when they were filled in the molds having more than 60 pores. Interestingly, very mature hyaline cartilage tissue having abundant cartilage matrix like that of native cartilage formed in the molds more than 2 mm height, while fibrocartilage tissue with poor cartilage matrix formed in the molds less than 1 mm height.
Conclusions: To regulate pore number and height of the molds for in-body incubation of chondrocytes, we could firstly obtain mature cartilage tissue analogues even from dedifferentiated chondrocytes without using any expensive reagent.

P116
BIOMIMETIC POLYURETHANE SCAFFOLDS AS CARDIAC MODEL
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Aim: The aim was to use Tissue Engineering (TE) approach to build *in vitro* models of cardiac tissue. Polyurethanes scaffolds were produced by Thermally Induced Phase Separation (TIPS), in order to obtain oriented fibers texture, like muscle tissue topography. Scaffolds were further surface-functionalized with fibronectin, mimicking the ECM composition of native tissue.
Methods: Polyurethane (PUR) was synthesized starting from poly(ε-caprolactone) diol, 1,4-budandiisocyanate and L-lysine ethyl ester. PUR scaffolds were fabricated by TIPS. Briefly, the polyurethane was first dissolved at 60°C in dimethyl sulfoxide and the solution was poured in a stainless steel mould and cooled. Quenching occurred by application of a thermal cooling gradient. The scaffold was placed for seven days in a water/ethanol solution and refreshed twice a day. Functionalization was performed by plasma treatment with acrylic acid, followed by the activation of carboxylic groups and coupling with fibronectin. The constructs were characterized by SEM, DSC, Tensile Test and DMA Analysis. The functionalization steps were studied by Contact Angle and X-ray photoelectron spectroscopy (XPS). Alamar tests were conducted to estimate cell viability. Primary cultures of cardiac cells were prepared from neonatal Sprague-Dawley rats.
Results: TIPS allowed fabrication of PUR scaffolds with suitable mechanical properties for Cardiac TE (Young modulus of about 1/1.2 MPa in the dry state, and in the range of 0.3/0.5 MPa in wet conditions; strain at break values were higher than the typical deformation of the heart during cardiac cycle). XPS analysis confirmed the surface immobilization of ECM protein. Three-dimensional confocal laser scanning microscopy (CLSM) time-lapse imaging was performed on PUR scaffolds seeded with Neonatal rat cardiomyocytes, showing high cell viability. Synchronized beating of cardiomyocytes was observed after few days and for over 40 days.
Conclusions: The functionalized PUR scaffolds described in this work can be used as myocardial tissue models, since they showed mechanical properties and morphology similar to native tissue, and maintain long-term cardiomyocyte viability, showing spontaneously beating cells.
Acknowledgments: The study was co-funded by the Italian Ministry of Education, University & Research (MIUR) (Project PRIN 2010, MIND).

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P117
NANOFIBERS BASED ON NATIVE FIBRINOGEN FOR GUIDED ENDOTHELIAL CELLS BEHAVIOR
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Aim: This study describes the biological consequences of presenting electrospun nanofibers [NFs] based on native fibrinogen [FBG] to endothelial cells providing them spatially organized cues, resembling the natural extracellular matrix.
Methods: Random and aligned NFs consisting of native FBG (bovine, Sigma-Aldrich) or of FBG/poly-L,D-lactic acid [PLA] blend were produced with a custom-made electrospinning setup. The electrophoretic profile confirmed that FBG retains its native configuration during electrospinning.
Results: Fluorescent tracing via FITC-FBG showed that pure FBG NFs are stable in physiological media for several days, but present poor mechanical properties. Here we report on the development of novel biomechanically improved composite FBG/PLDLA NFs. Both types of NFs are very well recognized by HUVEC. The spatial organization of NFs however provides further opportunity for guiding endothelial cells behavior in a way not possible when the protein is in an adsorbed form: a rapid orientation along the fibers and increased cellular motility were observed on aligned NFs while a stellate-like morphology and local immobilization of cells were typically found on random ones, accompanied with improved cell functionality marked by NO secretion. NFs orientation significantly influenced also the organization of secreted fibronectin matrix.
Conclusions: Collectively, we demonstrate that NFs based on FBG have potential for different tissue engineering applications.

P118
USE OF AN ACOUSTIC METHOD FOR THE EVALUATION OF SCAFFOLD TRANSPORT PROPERTIES IN BONE TISSUE ENGINEERING
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Aim: Transport phenomena characterize the effectiveness of scaffolds for tissue engineering (TE), because transport properties are strictly related to, e.g., uptake of oxygen and nutrients in depth, scaffold colonization by cultured cells. An important feature affecting transport in a scaffold is permeability. In fact, permeability is an effective parameter in (a) estimating mass and species transport through the scaffold and (b) describing its topological features, thus allowing a better evaluation of the scaffold biological performance. Artificial scaffolds should be designed in order to have transport properties similar to the natural tissue they are supposed to mimic.
Methods: To support the design of bone TE scaffolds, here we use an ad hoc test bench to measure the intrinsic permeability of an artificial scaffold for bone tissue engineering and we compare it to a natural sample of cancellous bone of animal origin. The test bench allows for intrinsic permeability measurement using a slow alternating airflow as a fluid medium and a calibrated low-frequency pressure field capacitive microphone. For this study we used: (a) an artificial ceramic scaffold, and (b) a natural cancellous bone sample.
Results: The intrinsic permeability of the scaffold was effectively measured with a confidence level of 95%.
Conclusions: The application of the airflow-based system proposed could lead to reproducible, repeatable and accurate experimental data, thus producing an improvement of the structural/architectural characterization of the bone tissue-engineering scaffolds under investigation.
Acknowledgments: Study co-funded by the Italian Ministry of Instruction and University (MIUR) (Project PRIN 2010, MIND).

P119
PULSATILE BIOREACTOR FOR CONDITIONING AND EVALUATION OF TISSUE-ENGINEERED HEART VALVES
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Aim: Proper mechanical conditioning of tissue-engineered heart valves (TEHVs) is crucial to achieve the desired tissue properties by stimulating and guiding cellular deposition of extracellular matrix. To this end, we have developed a pulsatile system that allows for controlled mechanical stimulation and monitoring of the valve performance by optical and ultrasound imaging.
Material and Methods: The flow-loop system is driven by computer-controlled pneumatic pulses that result in physiological pressures ranging from the pulmonary to the aortic conditions. The TEHV inside the bioreactor can be visualized from the top by means of an optical camera and laterally by means of a linear ultrasound probe.
Results: Highly adjustable and progressive mechanical conditioning through reproducible physiological pressure waveforms was obtained. Easy-to-handle fixation of cultivated valves is allowed. Non-invasive and non-contact assessment of proper valve kinetics and function is performed by means of ultrasound. Ultrasound measurements enabled evaluation of leaflets' co-aptation, flow patterns and functionality of the TEHV.

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Conclusions: A new bioreactor for the biomechanical stimulation of TEHVs was designed, built and characterized. Monitoring of the dynamic performance of the TEHV is crucial for the optimization of the conditioning protocol.

P120

PILOT STUDY OF BIOVALVE WITH STENT AS SURGICAL AORTIC VALVE REPLACEMENT IN A GOAT MODEL

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Aim: We have developed Biovalve as an aortic valvular tissue by collagenous encapsulation using in-body tissue architecture technology. After implantation, native vascular cells including endothelial cells infiltrated into the Biovalve for its in situ maturation. In this study, two types of Biovalves with a stent were developed and animal implantation study was firstly performed in a goat model for the evaluation of surgical aortic valve replacement (AVR) procedure.
Materials and Results: Two types of Biovalves were designed as a conventional (C-AVR) valve or a sutureless (SU-AVR) valve. The Biovalves were prepared by 2-month embedding of the plastic molds combined with different kinds of stainless stents with or without balloon expandability in the subcutaneous space of goats. In both Biovalves three leaflet tissue was strongly connected with stent strut. These valves were successfully implanted into the aortic valve annulus (AVA) of goats through aortotomy under cardiopulmonary bypass. The SU-AVR valve was implanted more smoothly than that the C-AVR was.
Conclusions: Both types of Biovalves with stent were firstly implanted by surgical AVR procedure. Size-matching between native and Biovalve's annulus was a key to proper implantation. Implantation results will be reported during this presentation.

P121

IMPACT OF MESENCHYMAL STROMAL CELLS ON THE FUNCTION OF ENDOTHELIAL CELLS UNDER FLOW CONDITIONS

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Aim: Mesenchymal stromal cells (MSC) are known to support endothelial cells (EC) in revascularization and influence vessel formation in engineered tissue constructs. Aim of this study was to assess the effect of MSCs on endothelial function in vascular prosthesis in a bioreactor simulating low and high flow conditions.
Methods: A PTFE prosthesis was used to culture ECs and MSCs in a 3D tissue culture model. ECs attached to the inner graft surface and a constant low (0.0015 Pa) or high flow (0.092 Pa) was applied by a perfusion system. ECs were supported by MSCs attached to the outer graft surface. The effect of MSCs on ECs viability under low flow and high flow conditions was determined using LDH and viability assays. Additionally, the expression of 43 angiogenic factors was analyzed using angiogenesis arrays.
Results: Compared to single cell culture viability of ECs, in MSCs-ECs co-culture under low flow was improved by 13.5%. In addition, necrosis and apoptosis could be reduced by 1.9% and 5.7%, respectively. Co-culture of MSC-EC decreased LDH activity by 18% and 47% under low and high flow conditions, respectively. Furthermore, MSCs influenced the angiogenic expression profile of ECs under low and high flow conditions. ECs showed an increased expression of 18 and a decreased expression of 17 out of 43 measured pro- and anti-angiogenic proteins in MSC-EC co-culture applied to low flow, such as angiopoietin, endostatin, and MCP-1. High flow induced an increase of 17 and a decrease of 22 angiogenic factors.
Conclusions: In conclusion, MSC-EC co-culture in a flow culture model enhances viability of ECs. MSCs induced differences in the angiogenic expression of ECs that were further modulated by low and high flow conditions.

P122

TRANSPORT MODEL OF RADIAL-FLOW PACKED-BED BIOREACTORS SIMULATING NATURAL BONE VASCULAR AND INTERSTITIAL FLUID NUTRIENTS DELIVERY

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Aim: Radial flow perfusion of osteogenic cells seeded in 3D annular porous scaffolds in radial flow packed-bed bioreactors (rPBB) may resemble the pattern of natural nutrients delivery in large engineered bone constructs. So far, little attention has been paid to optimize rPBB design to minimize transport resistance and ensure physiologic nutrients delivery to cells in constructs. In this work, a transport model of rPBBs is proposed aimed to optimize rPBB geometry and operation and simulate the nutrients delivery pattern to cells enabled by bone vascular and interstitial fluids in natural bone.
Methods: A pseudo-homogeneous model was used to describe steady-state transport of momentum and dissolved solutes across rPBB compartments according to Navier-Stokes and Brinkman equations and convection-dispersion-reaction equation, respectively. The effect of external transport resistance from bulk fluid to cell surface was accounted for. Solute concentration profiles were predicted with a FEM code for varying values of dimensionless groups determining rPBB behavior.
Results: The model permitted to adjust rPBB geometry and minimize flow maldistribution. Transport resistance significantly hindered nutrients delivery to cells. Similar to natural bone in exercise, high radial perfusion velocities could balance transport resistance as cell metabolic requirements increase and yielded smooth radial and axial solutes concentration profiles in the construct.
Conclusions: Model results may help optimize rPBB design and allow for physiological nutrients delivery in large bone constructs.
Acknowledgments: Study co-funded by the Italian Ministry of Instruction and University (MIUR) (Project PRIN 2010, MIND).

P123

NOVEL APPROACH TO MAGNETICALLY GUIDED DELIVERY OF MICRO-RNA TO ENDOTHELIAL CELLS

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Aim: Genetic manipulation of angiogenesis is recognized as a potential therapeutic tool for multiple disorders (e.g. peripheral artery disease, myocardial infarction, cancer). Nevertheless, the lack of clinically applicable vectors for gene delivery is matter of considerable concern. Recently, a great amount of competing advanced strategies for gene delivery has been developed. Application of nanoparticle-based non-viral carriers for targeted delivery of nucleic acids is among the most promising of them.
Methods: In this paper, we assessed *in vitro* the possibility of magnetically guided local delivery of microRNA (miR) into endothelial cells with polyethyleneimine magnetic nanoparticles-based vector (PEI-MNP) produced in our group.
Human umbilical vein endothelial cells (HUVECs) were tested for transfection with Cy-3 labeled miR (Cy3-miR) (for different patients separately). Evaluation of miR uptake efficiency and cytotoxicity under different conditions (miR amount, NP ratio, amount of MNP, incubation time) was carried out using flow cytometry. Additionally, the results of confocal laser scanning microscopy (LSM) z stacks were used to confirm cytoplasmic localization of introduced Cy3-miR. The optimal range of transfection conditions was selected for targeting experiments (magnets are placed locally under the culture plates). In this case, conclusions about Cy3-miR uptake and cytotoxicity were based on the results of LSM.
Results: High cell viability (85-90%) and efficient uptake of Cy3-miR by HUVECs (80-95%) were observed under following conditions: 5-15 pmol miR/cm^2; NP ratio 2.5-7.5; MNP amount up to 0.5 µg/pmol miR. Furthermore, targeting experiments demonstrated specific uptake of Cy3-miR in the area of magnetic field application for all these conditions. Using certain complex formations the amount of transfection complexes could be reduced to ~30% resulting in efficient uptake of Cy3-miR in the localized area with increased total cell viability.
Conclusions: To reduce side-effects of nucleic acid-based therapeutics, targeted delivery can be applied. We showed that magnetically driven delivery of miR with nanoparticle-based vector allows guided uptake of introduced molecule by endothelial cells, reduced amount of transfection complexes and decreased cellular toxicity.

Poster Session 2 – Part 2

ECMO and Instrumentation

P124

REQUIRED GAS EXCHANGE AREA AND SETUP OF DEOXYGENATORS IN AN *IN-VIVO* LIKE TEST CIRCUIT

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Aim: Normative *in-vitro* testing of oxygenators for gas exchange efficiency can be done with a simple circuit containing one oxygenator for both, testing and

setting of blood parameters. Advanced *in-vitro* testing in a clinical setup requires a test setup including two parallel, cross-linked circuits. We investigated the required relation of membrane areas and a setup that would allow continuous testing to improve scientific findings prior to *in-vivo* testing and to reduce the number of animal tests.
Methods: Our circuit contains a custom-made reservoir with two chambers, one blood line for testing and one blood line to mimic the patient. This circuit serves three purposes: it ensures venous blood at the inlet of the oxygenator, it simulates the blood gases of critically ill patients, and it investigates the dynamics of a test oxygenator challenged with different O_2 and CO_2 levels in the blood. Different blood flows within the test oxygenator and the two de-oxygenators (all three: Medos Hilite 7000 LT) were investigated. Different flow rates and ratios of N_2, CO_2, and O_2 for de-oxygenators were tested.
Results: Results show that one de-oxygenator is able to reduce the O_2 to a venous value in approx.1 L/min oxygenated blood, two de-oxygenators in approx. 2 L/min, respectively. There were no differences between the parallel and the serial setup of the de-oxygenators. We found the removal of O_2 is only related to the membrane area of the de-oxygenators. The loading with CO_2 is independent from the membrane area.
Conclusions: An advanced test circuit is possible, but requires approx. 2 m^2 of de-oxygenator membrane per 1 L/min test flow.

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SINGLE-CENTER STUDY WITH PROLONGEDEXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) IN 231 PATIENTS AFTER DIFFERENT INDICATIONS WITH LOW CARDIAC OUTPUT

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Aim: For ventricular and pulmonary support the extracorporeal membrane oxygenation (ECMO) system using the Bio-Medicus centrifugal pump (Medtronic®, Minneapolis, MN, USA) was used in 231 patients with low cardiac output for a prolonged period of several days.
Methods: From December 1996 to May 2011 the ECMO was implanted in 231 patients (180 adult, mean age: 52,5 ± 17,5 years and 51 children, mean age: 1.6 ± 3.1 years) with mostly postcardiotomy low cardiac output. The surgical procedures included congenital heart surgery (n = 38, 16.5%), heart transplantation (HTx) (n = 38, 16.5%), coronary artery bypass operation (CABG) and/or valvular operation (n = 67, 29.0%), other operations (n = 26, 11.3%) and 62 (26.8%) patients with ECMO support for bridge-to-recovery.
Results: In contrast to other studies the mean supporting time was 4.7 ± 4.5 days. Overall, 30-day-survival was 42.6%. Best survival rates were seen after congenital heart surgery (29 from 38, 76.3%) and after HTx (20/38, 52.6%); the worst rates were in the group of CABG and/or valvular operations (19/67, 28.4%), only ECMO support (24/62, 38.7%) and other operations (6/26, 23.1%). Altogether 96 patients died while supported by ECMO, 46 were weaned from ECMO but died in hospital, Overall 82 patients were weaned and survived, 7 patients were lost to follow up. Causes of death were multi-organ-failure (35.3%), persistent low cardiac output (21.8%), bleeding (10.9%), sepsis (7.1%), allograft failure (3.8%), others (12.2%) and not exactly known (9.0%).
Conclusions: Prolonged ECMO support showed best results in pediatric patients after congenital heart surgery and in patients after HTx in contrast to multi-morbid, older patients with often irreversible myocardial damage.

P126

A LONG-TERM DURABILITY AND ANTITHROMBOGENICITY FOR A NOVEL ECMO SYSTEM CONSISTING OF BIOCUBE OXYGENATOR AND SOFTLINE COATED ROTAFLOW PUMP

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Aim: Heparin coating is usually applied to ECMO system for providing antithrombogenicity. Some of heparin-coated ECMO systems have demonstrated capability of more than a few weeks use. On the other hand, biogenous substance such as heparin requires high cost and complicated handling process. The polymer coating SOFTLINE® was developed to avoid these issues. In this study, we applied a SOFTLINE coated centrifugal pump (ROTAFLOW®) to our durable thrombo-resistant ECMO circuit with a compact oxygenator (BIOCUBE™ 6000), and evaluated its durability and antithrombogenicity in a series of chronic animal experiments.
Methods: The BIOCUBE was made of polymethylpentene membrane to prevent plasma leakage, and was coated with a heparin bonding material (T-NCVC®). Veno-arterial bypass ECMO was conducted for 5 weeks using 2 goats. Systemic anticoagulation was not conducted, except for one-shot heparin injection at cannulation. Bypass flow rate was set at 2.5 L/min by adjusting pump rotational speed.
Results: Heparin-free ECMO could run for 5 weeks without device exchange in all cases. Bypass flow rate could be maintained stably. There were no significant changes in free hemoglobin (12.2 and 12.8 mg/dL, respectively at 5 weeks). O_2 and CO_2 transfer rates were kept at sufficient levels. After the experiments, a small amount of thrombi was found around the pivot of impeller and the bifurcation of the outlet port in the 1st pump, while no thrombi were observed in the 2nd pump. Pieces of thrombi were stuck on the inlet side of the bundle of hollow fiber membranes in each oxygenator.
Conclusions: The ECMO system has sufficient durability and thrombo-resistant property for 5 weeks heparin-free cardiopulmonary support.

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OUTCOME OF ARDS PATIENTS WITHOUT AND WITH EXTRACORPOREAL LUNG ASSIST DEVICES (ELAD)

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Aim: To investigate frequency of ELAD usage and associated outcome at a national ARDS referral centre specialized on treatment of patients in severe respiratory failure.
Methods: Single centre retrospective analysis at a university hospital in Germany between 2007 and 2013.
Results: In total, 442 patients were analyzed. On the day of admission, patients without and with ELAD presented significant differences for PaO2 (109 [85;139] vs. 89 [70;121]) and PaCO2 (50 [42/59] vs. 53 [43/66]); Ppeak (35 [31;38] vs. 35 [32;396]) and PEEP (17 [15;20] vs. 17 [15;20]) were equal in both groups. In multivariate logistic regression adjusted for SOFA and PaO2/FiO2*Pmean, age (OR 1.02 [1.01-1.04], p = 0.002) and ELAD (OR 2.8 [1.8-4.3], p<0.001) were independent predictors for mortality.
Conclusions: ELAD was used in more than half of the study population. Patients on ELAD were associated with higher mortality, longer length of stay and mechanical ventilation.

TABLE I - OUTCOME PARAMETERS

	No ECMO N = 186	ECMO N = 256	p
Type of discharge			<0.001
Deceased	56 (30.1%)	146 (57.0%)	
Discharged to home	39 (21.0%)	21 (8.20%)	
Transfer to other hospital	51 (27.4%)	44 (17.2%)	
Transfer to rehab. facility	40 (21.5%)	45 (17.6%)	
Length of stay (ICU) [d]	31.0 [22.0; 50.0]	46.0 [28.0; 63.0]	0.001
Length of stay (hospital) [d]	38.0 [25.0; 61.8]	49.0 [32.2; 70.5]	0.013
Mechanical ventilation [h]	407 [252; 611]	740 [475; 1129]	<0.001

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EFFECTS OF PORE SIZE AND PORE SIZE DISTRIBUTION ON PLASMA BREAKTHROUGH IN ECMO

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Aim: Extracorporeal membrane oxygenation (ECMO) has become routine treatment of respiratory or cardiac failure patients. Plasma leakage (or wetting) through microporous capillary membranes is a known complication during prolonged ECMO. The occurrence of plasma leakage has been associated to water vapor condensation in the gas compartment, the presence of larger-than-normal pores or pinholes in membrane wall, the adsorption of surfactants in the blood on membrane wall, and the presence of very high trans membrane pressures. In this study the attention was focused on the actual membrane pore size and pore size distribution in the presence of surfactant molecules.
Methods: Lab-scale oxygenators (ca.0.16 sq.m surface area) were prepared which were equipped with microporous polypropylene membranes prepared

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on purpose and featuring varying average pore size and pore size distribution. Mean membrane pore size and pore size distribution was characterized by differential liquid permeametry. Membrane capacity to withstand plasma leakage was assessed in terms of the time-to-leakage in experiments in which a solution containing varying concentrations of phosphatidylcholine was re-circulated outside the membrane bundle into the oxygenator shell at ca. 120 ml/min, while a dry gaseous stream was flown through the membrane lumen in single pass mode at 1.5 L/min. Vapor and liquid water crossing the membrane wall into the gas stream was captured in a trap kept at 0°C with an ice bath. Water flow rate across the membrane was estimated by weighing water collected over a set time interval. Penetration of liquid water into the membrane wall was investigated by checking for the presence of phosphatidylcholine by SEM elemental analysis of membrane cross-sections at end of experiments.
Results: As a result of the actual membrane pore size distribution plasma leakage never occurred at a clear-cut time. Plasma leakage occurred significantly earlier at higher phosphatidylcholine concentrations and with membranes with a broader pore size distribution and greater average pore size. Occasionally, the presence of phosphatidylcholine was found inside the membrane wall suggesting that the liquid solution was able to get deep into the pores.
Conclusions: The results suggest that adsorption of a surfactant present in the liquid may indeed promote plasma leakage by changing the surface hydrophobicity of the membrane. Occurrence of plasma leakage was facilitated not only by a larger maximal pore size, but also by a broader pore size distribution.

P130

EFFICIENCY OF TWO SYSTEMS OF AUTOMATIC SPEECH RECOGNITION IN EXPERT SYSTEM FOR INSULIN DOSE CALCULATION

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Aim: Diabetes may lead to serious complications when blood glucose levels are not maintained in safe ranges. Proper insulin dosing is crucial in good metabolic control, however it is not easy for all patients. There are some computer applications supporting insulin bolus calculation based on the meal composition, but they may be difficult to use for some patients. Our team decided to develop a simple interface (voice-driven) system for insulin meal compensation. The aim of the present study is to test the efficiency of automatic speech recognition (ASR) of two systems used in the project.
Materials and Methods: A server version of ASR system and a SDK version for Android were used in the efficiency tests. Fifteen adults were recruited for the tests and voice descriptions of meals were recorded using Samsung Galaxy S4 smartphone and saved in WAV format (44.1 kHz, 16 bit, mono). Totally, 241 files with voice descriptions of meals lasting from 2 to 120 seconds were analyzed. Recognized texts from sound files by both ASR systems were compared with text descriptions of meals and the efficiency were calculated as ratio of number of proper recognized words and number of all words in text descriptions of meals. Blurred portions of sound recordings were excluded from the efficiency analysis.
Results: Efficiencies of the tested ASR systems were 97.0% and 92.8% for the server and the SDK versions, respectively. Lower efficiency of the SDK version is probably due to less accurate algorithm used for speech recognition.
Conclusions: Both values of efficiency were higher than necessary minimum values for the project and thus they will be accepted for the project.

P132

EXPERIENCE WITH VENO-VENOUS ECMO IN PATIENTS WITH SEVERE ARDS

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Aim: Extracorporeal membrane oxygenation (ECMO) is often the last resort for serious acute respiratory distress syndrome (ARDS) when all non-invasive treatment options have failed to improve the patient's pulmonary condition.
Methods: We retrospectively evaluated all patients who underwent veno-venous ECMO in the observation period between June 2009 and June 2012 at our university hospital. Our main attention was in particular turned to the indication, the runtime, the weaning protocol and the outcome.
Results: Veno-venous ECMO was performed in 25 cases at our center in the last 3 years. 15 patients were men with a mean age of 53.4 ± 16.4 years (range 26.5-75.0 years) at the time of ECMO implantation. The mean age for the 10 females was 43.9 ± 13.2 years (range 29.9-69.7 years). The main reason for ECMO support was severe pneumonia (n = 20; 80%), in 5 cases multiple traumas were the implantation causes. The middle runtime of the ECMO lay with 20.5 ± 23.7 days (range 3-118 days). The 30-day mortality was 12/25 (48%); the 1-year mortality was 17/25 (68%).
Conclusions: Our data in this study were comparable to the literature regarding the most favorable timing for the initiation and the weaning of ECMO as well as

the outcome. There are many reports on ECMO therapy from other cardiac centers, nevertheless the role and adequate use of ECMO for patients with ARDS have not been definitively established.

P133

EXTRACORPOREAL VENO-VENOUS COOLING DEVICE AND PATIENT MODELING FOR THERAPEUTIC MILD HYPOTHERMIA

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Aim: Beneficial effects of therapeutic mild hypothermia are documented after cardiac arrest and brain trauma. Extracorporeal veno-venous cooling is effective, safe and fast as demonstrated in a clinical study. Aim of this work was to develop a numerical model of veno-venous cooling including human thermoregulation during the cooling process.
Methods: A veno-venous cooling device and a 2-compartment (core-peripheral) model of the human thermoregulation were combined. The cooling device was characterized and modeled using *in vitro* set-up data and joined with a model of human thermoregulation from literature. The combined model was then compared to temperature recordings from 8 patients (84 ± 20 kg; 6 males; 58 ± 17 yrs old) who underwent veno-venous cooling.
Results: The numerical model could reproduce the temperature traces in the cooling device and the patterns of the patient core temperatures with a root mean square error of 0.40 ± 0.30°C and a maximum absolute error of 0.87°C. The median time to reach core temperatures of 34°C were 7.5 min (IQR 5.8-11.8 min) for the clinical trial vs. 7.7 min (IQR 4.6-13.0 min) for the patient model.
Conclusions: The combined cooling device and patient model provides a better understanding of the device-patient interaction and allows the prediction of temperatures for different patients. Furthermore, the model gives insight into the heat flow rates within the human core and periphery and can be used as a tool for future optimization of cooling strategies.

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THE CHANGES OF HEMORRHEOLOGY CAUSED BY CARDIOPLEGIA IN DIABETIC CONDITIONS

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Aim: Blood cardioplegia has been used for cardiac surgery because of its advantage like superior oxygen-carrying capacities than crystalloid counterpart. Hyperkalemia organ-preservation solutions are known to decrease RBC deformability. Diabetes also leads to change of hemorheology. Although changes of hemorheology affect tissue perfusion, a few studies have addressed the changes of hemorrheology when blood cardioplegia is used in diabetic patients. The purpose of this study is to evaluate the change of hemorheology when cardioplegia is used in diabetic patients.
Methods: Blood from 8 healthy volunteers was used. Each sample was divided in 4 groups, and cardioplegia or glucose solution or both were added (C1: blood only, C2: blood + cardioplegia, D1: blood + 5% glucose solution, D2: D1 + cardioplagia). After all samples were incubated at T = 28°C for 30 minutes, EI (proxy for deformability), AI (proxy for aggregation), NO level, and 2,3-DPG level were measured.
Results: The level of NO was not significantly different between C1 and C2, but it was significantly different between D1 and D2. The level of 2,3-DPG was significantly different between C1 and C2, but it was not significantly different between D1 and D2. The EIs of C1 were lower than C2 at stress from 3 Pa to 10 Pa. The EIs of D1 were higher than D2 at stress from 1 Pa to 10 Pa. The AI in C1 was higher than in C2. The AI in D2 is not significantly different in both D1 and D2.
Conclusions: In diabetes, the hemorheologic changes and oxygen-carrying capacities after adding cardioplegia were different from non-diabetic condition.

P135

VARIATIONS IN APOPTOSIS AND INFLAMMATORY GENES AND CHRONIC ALLOGRAFT DYSFUNCTION IN A POPULATION OF ITALIAN RENAL TRANSPLANT RECIPIENTS

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Aim: Chronic allograft dysfunction (CAD) is the most common cause of kidney transplant failure in the medium- and long-term. Variants in the genes encoding inflammatory and apoptosis molecules have been suggested as possible genetic markers of CAD. The investigation was undertaken to identify the possible effect of interleukin 6 (IL-6), transforming growth factor beta 1 (TGFB1), Fas, granzyme B (GzmB) and serine proteinase inihibitor-9 (PI-9) polymorphisms on allograft function in a population of Italian renal transplant recipients.
Methods: This case-control study recruited 452 cadaveric kidney recipients, 305 of them with stable graft function and 147 who experienced CAD during the follow-up period of 2.9 ± 1.6 years. IL-6/G-174C, TGFB1/L10P, TGFB1/R25P and Fas/G-670A, polymorphisms were analyzed using PCR-RFLP, while GzmB/QPY/RAH and PI-9/T+207C were genotyped by primer extension followed by DHPLC.
Results: The single IL-6, TGFB1, Fas, GzmB and PI-9 polymorphisms were not associated with CAD. However, multiple logistic regression performed to test mutual effects of polymorphisms revealed that the concomitant presence of IL-6 high producer and Fas low producer genotype resulted in a 0.82-fold decreased risk of CAD (OR = 0.82; 95% C.I. = 0.73-0.84).
Conclusions: In our population of renal transplant recipients, the carriage of IL-6 high producer/Fas low producer genotype seems to confer a protective effect against graft dysfunction.

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LONG TERM AUTO IMPLANTATION OF AUTOLOGOUS TISSUE SMALL CALIBER VASCULAR GRAFTS (BIOTUBES)

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Aim: There are practically no small-caliber synthetic vascular grafts (<6 mm) with acceptable patency rate. We have developed autologous small-caliber vascular grafts, named "biotubes", by simple, safe and economical "in-body tissue architecture technology", which is a novel concept of regenerative medicine and one of the *in vivo* tissue engineering. In this study, we evaluated the long-term (more than 1 year) results of small-caliber biotubes using a rat abdominal aorta replacement model.
Methods: Silicone rod molds (diameter: 1.5 mm, length: 20 mm) (n = 9) were placed into subcutaneous pouches of rats, and after 1 month the implants with their surrounded connective tissues were removed. Biotubes with internal diameter of 1.5 mm were obtained as tubular connective tissues from the implants after pulling out the molds. They were auto-implanted to the abdominal aorta. At over 1 year, graft status was evaluated by ultrasonography (US), magnetic resonance angiography (MRA) and histology.
Results: US and MRA showed high patency of the grafts (patency rate was 89%; 8/9) without stenosis. Histological evaluation revealed that the luminal surfaces of all patent grafts were smooth and completely covered with endothelial monolayer. Calcification occurred regionally in the neointima layers of the half numbers of the grafts. On the other hand, there were no calcifications in others.
Conclusions: Long-term implantation results of small caliber biotubes were firstly reported. The biotubes performed as excellent vascular grafts with high patency and regeneration activity including complete endothelialization.

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OVEREXPRESSION OF MTX GENE AMPLIFICATION AND SEMI-SOLID SINGLE CLONAL SELECTION IMPROVEMENT OF BMP-4 PRODUCTION IN CHO CELLS

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Background: Bone morphogenetic protein-4 (BMP4) is a TGFβ superfamily ligand that is widely expressed from early embryogenesis through adulthood. It plays an important role in mesenchyme formation, epidermal determination,

suppression of neural induction, the development of multiple organs, and tissue repair. However, recombinant human BMP4(rhBMP4) is produced at relatively low yields in a mammalian cells.
Materials and Methods: CHO cells (DG44) were transfected with the pOptiVEC™/hBMP-4 cDNA gene constructs. HT selection was cultured in CD DG44 media (w/o HT, w/o serum) to select for stable cell lines. Genomic DNA was amplified by 1 uM MTX. Single clonal selection was performed with CD optiCHO media and semi-solid media (1:1) to obtain expressing single clones of high levels rhBMP4.
Results: We induced a gene amplification and single clonal selection at once by using 50% semi-solid media. This method improved the titer of rhBMP-4 as well as saving time and cost for development process.
Conclusions: The CHO cell line expressing recombinant human BMP-4(rhBMP4) at the level of 2 ug/ml could be obtained after double transfection with HT selection. And it more increased production of rhBMP-4 at the level of 4 ug/ml through MTX gene amplification and single clonal selection used in 50% Semi-solid media.

P138
DEVELOPMENT AND IMPLEMENTATION OF EVALUATION TOOL FOR INTELLECTUAL PROPERTIES CREATED IN THE STUDY OF MEDICAL DEVICES
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Background and Aim: In order to lead to the commercialization of medical devices, intellectual property (IP) created in the study must have been evaluated quantitatively under the consideration of clinical situation. Thereby, there is the possibility to promote technology transfer (TT) from academia to industry. In current generic IP evaluation in Japan, patentability and business feasibility are positioned as key indicators. In the case of TT of medical devices, it should also be considered the medical significance beyond the above two indicators. The objective of this study is to develop and use a score tool, which evaluate IP for TT specifically for medical devices.
Methods: To develop the evaluation tool, a committee consisting of TT researchers of the National cerebral and cardiovascular center (NCVC) and experts outside NCVC (including patent attorney, business coordinator, academic researcher) was established, and these subjects were discussed in meetings for the past three years.
Results: To assist in the review and decision making process of IP deliberation, a scoring evaluation tool consisting of three major criteria (1. patentability, 2. business feasibility, and 3. social aspects), which were organized into eighteen minor criteria, was developed and proposed as the guideline of IP evaluation for medical devices. This evaluation tool was implemented to improve on the objectivity of the decision making process of service invention in NCVC.
Conclusions: The scoring tool which evaluate IP for TT specifically for the medical devices was developed and implemented.

P139
DIFFERENCE IN PREFERENCE TO THE NOISE-REDUCTION ALGORITHMS FOR HEARING AID ACCORDING TO THE DEGREE OF HEARING IMPAIRMENT
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Aim: Investigating personal preferences of hearing-impaired patients for specific algorithms can improve the subjective satisfaction of the patients by applying combinations of their preferred algorithms to his/her own hearing-support device. In this study, we investigated the subjective preference of three popular noise-reduction algorithms (MBSS, LogMMSE, and Wiener-as) in 15 normal-hearing, 15 moderate hearing loss, and 15 moderately severe hearing loss subjects.
Methods: 30 testing sounds with 0 dB input signal-to-noise ratio (three different noise-reduction algorithms were applied to 10 noisy sentences) were played in random order and each subject was asked to score based on his/her subjective preference of each sound.
Results: MBSS scored highest for normal-hearing, LogMMSE for moderate loss, and LogMMSE and Wiener-as for moderately severe loss groups. There was a significant difference between MBSS and Wiener-as in the normal-hearing group ($p<0.05$).
Conclusions: The reaction tendencies of normal-hearing and hearing-impaired subjects towards a specific noise-reduction algorithm were different under some test conditions even though the two groups showed similar reactions under other test conditions.

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P140
NEW LIFE IN KIDNEY PATIENTS ON RENAL REPLACEMENT THERAPY
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Introduction of renal replacement therapy (RRT) was a revolution in medicine. It permitted a joyful life to patients without kidney function necessary for survival. Measures of HRQoL have a significant predictive value on patient survival and hospitalizations in patients with chronic kidney disease (CKD). The most used instrument for measuring HRQoL is the Short Form health survey questionnaire (SF-36). Patients with pre-dialysis CKD had higher SF-36 scores than a large cohort of HD or PD patients, but lower scores than those reported for the adult population. Kidney transplantation offers better HRQoL than dialysis. National and international collaboration could increase the number of kidney transplants. Hemoglobin level predicted both physical and mental domain scores of the SF-36. HRQoL of HD and PD patients were compared in only a few studies, mostly because these studies are difficult to interpret. PD patients generally have lower comorbidity scores at the onset of ESRD, independent of other factors influencing modality selection. Comorbid medical conditions are common in patients with ESRD, and are an important contributing factor to clinical outcomes and quality of life. Depression occurs in about 20-30% of dialysis patients. This is important because of the negative impact depression has on quality of life, but also because depression is now established as a factor that can significantly affect morbidity and mortality in ESRD patients. Sexual life satisfaction showed marked deterioration in all aged groups. Patients aged over 65 scored significantly better than younger patients on dialysis stress scales, and were generally more satisfied with life. Longitudinal studies are needed to define periods at risk for decline in HRQoL during progression of CKD.

P141
PROTEINURIA AS A SIGN FOR RECURENCCE OF HYDATID DISEASE
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Background: Hydatid disease may be present with proteinuria, reversible after surgery treatment.
Aim: Can proteinuria be used as a sign for recurrence of hidatid disease?
Materials and Methods: Two patients, one female 73 years old and a male 50 years old, hospitalized because of proteinuria 4,9 g/du and 2,04 d/Du g/L, respectively. Both of them have previous history of echinococcus cists (lungs and retroperitoneal in women, and liver in men), surgically removed. No proteinuria in the past.
Results: Serological test for anti-echinococcus antibodies were negative. Renal biopsy was performed in women, with finding of chronic intestitio- tubulonephritis. Computerized tomography was performed in both. Men have echinoccocus cist in kidney and women in inguinal region. Both have hypertension and impaired renal function. Treatment with Albendazol and surgery was advised.
Conclusions: Proteinuria is noninvasive procedure, which can be used in follow up of patients with history of hidatid disease as a marker of recurrence of diseases.

Artificial Organs

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APPLICATION EVOLUTION OF MARS IN ACLF PATIENTS
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Introduction: The aim of this study is to show the evolution of MARS application and the real detoxification of single substances following the engineering model indications.
Materials and Methods: Two hundred-twenty ACLF patients treated with MARS in waiting list for transplant, were enrolled in this study. Sample collections of liver parameters and cytokines targets were performed before and at different times after the beginning of the treatment in blood circuit and in the 4 points of albumin circuit. The patients were divided in three groups following the MELD score. In the first group, patients with a MELD range 20-25, in the second one, patients with MELD range 26-30 and in the third one with MELD

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range 31-35. Than the findings were inserted in an engineering model to evaluate detoxification efficiency (η), defined as the fractional reduction of the toxin concentration respect to volume blood pump, volume albumin circuit and Delta between patient albumin and circuit albumin.
Results: The MARS application was divided in three different eras. In the first era, from 1999-2004, we used the MARS only, in the second era, from 2005 to 2008, we started the study of engineering model *in vitro* and *in vivo*. In the third era, from 2009-2013, the MARS therapy with model application. Following the model, we highlighted an improvement of detoxification efficiency (η), with an increase of Responders to treatment and survival, based on the albumin concentration and the change of adsorbents after few hours.
Conclusions: The engineering model can help us set the flow rates, membrane pressure, albumin concentration predicting the time course of bound toxin removal. The correct application of artificial MARS has to be adapted to each treatment and each patient. MARS like a "personal therapy".

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A METHOD OF COUPLED PLASMA FILTRATION ADSORPTION FOR HYPERBILIRUBINEMIA IN INTRA-ABDOMINAL INFECTIOUS PATIENTS WITH MULTIPLE ORGAN FAILURE

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Aim: This study aimed to investigate the efficacy and safety of coupled plasma filtration adsorption (CPFA) in intra-abdominal infectious (IAI) patients complicated with progressive hyperbilirubinemia and multiple organ failure (MOF).
Methods: Seven patients were studied with a total of 12 CPFA sessions. Hepatic and renal functions, blood routine test and coagulation function before and after CPFA session detected were analyzed. Hemodynamic parameters included blood pressure and the dose of norepinephrine during CPFA session. Hemorrhage was the primary adverse event.
Results: Through a CPFA cession, there was a significant decrease of total bilirubin (16.7 ± 5.9 mg/dl vs. 7.9 ± 3.4 mg/dl; P<0.001), direct bilirubin (12.5 ± 4.4 mg/dl vs. 6.3 ± 2.1 mg/dl; P<0.001), indirect bilirubin (4.2 ± 2.7 mg/dl vs. 1.6 ± 1.0 mg/dl; P<0.001), blood urea nitrogen (BUN; 15.7 ± 12.6 mg/dl vs. 12.6 ± 10.4 mg/dl; P<0.001), creatinine ((92.1 ± 82.1 μmol/L vs. 74.8 ± 56.2 μmol/L; P<0.001). Instantaneous blood clearances of total bilirubin in CPFA were 28.5 ± 12.3 ml/min (0.5 h), 22.3 ± 9.5 ml/min (2 h), 17.0 ± 4.1 ml/min (4 h), and 11.7 ± 3.7 ml/min (6 h). Coagulation function deteriorated after CPFA and recovered 2 days later. Hemodynamics was stable and the dose of vaso-active agents decreased after CPFA. No hemorrhage event occurred since CPFA within 48 h.
Conclusions: CPFA is an effective and safe method for IAI patients with progressive hyperbilirubinemia and MOF.

P144

OPTIMIZATION OF THE FLUIDIZED-BED BIOREACTOR FOR USE IN THE SUPPLIVER BIOARTIFICIAL LIVER DEVICE

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Aim: We developed a new extracorporeal circuit monitored by the Prismaflex® device (Gambro) which included fluidized bed bioreactors hosting hepatocytes. In this study, we *in vitro* investigated both biological and mechanical properties of the Bioartificial liver.
Methods: C3A spheroids were encapsulated in the presence of microparticles of glass to control the alginate beads density. We tested 3 concentrations of particles with two cell densities. Glucose consumption, albumin and ammonia release were observed. The diffusion of fluorescent albumin was followed by confocal microscopy. Different levels of filling of the bioreactor were also achieved.
Results: Particles of glass were essential to create an adequate fluidization and consequently optimal mass transfer. These microparticles were in spatial competition with cells but did not perturb their metabolism. Compression experiments were performed to compare their shear modulus.
Conclusions: Regarding these results and the constraints of the whole extracorporeal circulation (plasma flow rate, thermal exchange), a concentration of 20 mg of microparticles for 10-15 millions of cells per ml of alginate solution seemed to be the best configuration. The filling ratio of beads in the bioreactors could reach 60%. Four bioreactors of 250 ml represent about 15% of the hepatocytes in a liver which is a reasonable target for extracorporeal liver supply.

P145

EVALUATION OF A NEW METHOD OF REBUILDING BILE DUCTS IN SCAFFOLDS IN WHOLE LIVER TISSUE ENGINEERING

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Aim: Severe liver disease has been a major cause of death. As non-severe liver disorders can be alleviated with either non-cell based or cell based artificial extracorporeal liver support, cirrhosis, however, needs to be treated with whole organ transplantation. Different approaches of artificial liver have thus been studied and developed in order to compensate for organ shortage. The concept of whole-liver engineering has been brought up already by B. Uygun et al. The aim is to create transplantable liver grafts by reconstructing the liver tissue *in vitro*. The strategy of rebuilding bile ducts in whole liver scaffolds is challenging and is the subject of this study.
Methods: The bile ducts are reconstructed by the method of whole-liver engineering which includes decellularization and recellularization. The native rat organs are harvested, and were subjected to a series of decellularization steps. After being perfused by detergents at increasing concentrations, the grafts are sterilized with antibiotics. The bile duct epithelial cells are cultured in lab and repopulated on the decellularized liver matrix in ex vivo along with hepatocytes. It is then evaluated and analyzed by H&E staining, immunofluorescent staining, albumin ELISA assay, etc.
Results: From the acellular matrix that acquired from decellularization, the microstructure of the liver is well preserved. The recellularized liver grafts also represent significant successes.
Conclusions: The data so far have shown that the idea of whole-liver engineering including rebuilding bile ducts is suitable for transplantable liver graft reconstruction.

P147

CONSTRUCTION OF HEPATOMA TISSUE BY CO-CULTURE OF MOUSE HEPATOCELLULAR CARCINOMA AND FIBROBLASTS ON ELECTROSPUN NANOFIBROUS MEMBRANES

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Aim: Construction of hepatoma tissue can be applied to the development of new treatments of liver cancer. In this study, we investigated the co-culture of mouse hepatocellular carcinoma (Hepa 1c1c7) and mouse murine embryonic fibroblasts (MEF) on electrospun nanofibrous membranes.

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Methods: Electrospun nanofibrous membranes were applied to construct a hepatoma tissue sheet due to the fact that microstructure of nanofibrous membranes are very similar to the natural extracellular matrix (ECM). Mouse fibroblasts, which are an integral component of tissue architecture, were co-cultured with Hepa 1c1c7 to make a better microenvironment than mono-culture ones. We measured the hepatic albumin expression level to determine cellular function and examined the effect of fibroblasts on the hepatocellular morphology and spheroids. The difference between the construction of co-culture and mono-culture cell sheets were checked by histological studies and immunofluorescent analysis.
Results: Our research indicates that co-culturing mouse hepatocellular carcinoma and fibroblasts on electrospun nanofibrous membranes was able to make a hepatoma tissue for investigation of liver cancer treatments.
Conclusions: For future work, we have a plan to apply this investigated method for other cancer types. The developed tissue also will be assembled with a microchannel to create a tumor-on-a-chip.

P148
OPTIMIZED OPTICAL GLUCOSE READER FOR TRANSCUTANEOUS GLUCOSE MEASUREMENTS
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Aim: The development of a single-port closed-loop system aims for continuous glucose monitoring, insulin dose calculation and continuous insulin infusion as a "all-in-one" artificial pancreas system. The glucose sensor is based on two luminescent dyes with different excitation wavelengths grafted on standard insulin infusion sets, showing a glucose-sensitive and O_2-sensitive luminescence, respectively. Here we present an optimized optical reader for reliable transcutaneous read-out of the sensors.
Methods: The system is divided into an integrated optoelectronic reader that is located on the skin over the infusion set with the optical sensor layers and a separate signal processing unit. This design allows miniaturizing the reader for maximum convenience of the patient. Bright SMD LEDs with custom collimating optics and large area photodiodes are combined with optical interference filters for spectral discrimination between the glucose and the reference O_2 channel.
Results: The sensor measures only Ø25 mm at 7 mm height, allowing convenient continuous wearing. The reader can be integrated in standard 90° infusion sets with 0.4 mm steel cannula. The sensor is characterized in terms of signal intensity, channel cross-talk, optical background and signal to noise ratio. Interstitial glucose and O_2 in animal models are compared to blood values.
Conclusions: The optimized optical glucose reader shows promising performance valuable for the further development of the innovative single-port artificial pancreas system.

P149
INFLUENCE OF CELL REMOVAL TREATMENT ON DERMIS MECHANICAL BEHAVIOUR
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Aim: Knowledge of the mechanical behaviour of skin is required by various medical disciplines, such as dermatology, surgery and traumatology. More specifically, this work was focused on one specific skin layer: the dermis. The aim was to verify the influence of the decellularization treatment on its properties.
Methods: Skin specimens were subjected to uniaxial static tests performed with the Bose Electroforce® 3200. Experimental data were represented with engineering and real time stress-strain curves. Descriptive parameters were identified from stress vs. strain curves, and they were subsequently compared through multivariate analysis of variance to determine the influence of the specimen cut orientation and of duration of the decellularization treatment.
Results: Dermis samples which had been decellularized for 5 to 6 weeks, exhibited mechanical properties comparable with native dermis. The ultimate tensile strength and the maximum Young's modulus was shown to be considerably higher in real time curves than in engineering ones: 3-4 times and up to 7 times respectively for ultimate tensile strength and Young's modulus.
Conclusions: Real-time curves should be used when modeling dermis behaviour, while engineering curves should be confined to comparative analysis, where they are able to provide indications with a higher repeatability and a simpler experimental set up.

Nanobiotechnology & Drug Delivery

P150
MODIFIED COATING OF LIPOSOME ENCAPSULATED HAEMOGLOBIN WITH POLYETHYLENE OXIDE
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Aim: Liposome Encapsulated Haemoglobin (LEH) has been already introduced as an artificial oxygen carrier nanoparticle with the potential substitution capability for red blood cells. However, the synthesis process of current LEH yields low haemoglobin (Hb) loading due to the instability of LEH encapsulation. Therefore, the surface coating of LEH with a stable polymer would be beneficial.
Methods: Bovine Hb is encapsulated by hydrating a dry-film lipid (comprising 0.4 mM Cholesterol and 0.6 mM Dipalmitoylphosphatidylcholine) through a phosphate buffer solution blended with glutamine antioxidant. In the next step, the size of synthetized particles is decreased to nano-range using a high-pressure homogenizer. The synthesis process is modified by the insertion of polyethylene oxide (PEO) through the solution during the cascade of homogenization.
Results: Coated LEH with 2.5, 5, 10 and 40% w/w of PEO present an increase of the total Hb loading yield of 27 ± 3, 33 ± 2, 39 ± 2 and 45 ± 2% respectively, compared to non-coated LEH with a loading yield of 20 ± 1%. On the contrary, the size of coated LEH increase gradually from 107 ± 3 nm to 228 ± 3 nm by raising the concentration of PEO from 2.5 to 40% w/w while non-coated LEH shows the size of 98 ± 3 nm.
Conclusions: Coating of LEH with PEO during its synthesis process increases its stability, and subsequently, enhances its efficiency by elevating the total Hb loading yield. However, the effect of the increase of particle size should be further investigated.

P151
ARTIFICIAL OXYGEN CARRIER LIPOSOME-ENCAPSULATED HEMOGLOBIN AS THE PLASMA OXYGENIZER
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Aim: Since liposome-encapsulated hemoglobin (LEH) has a low specific gravity similar to plasma and different O_2-affinity from that of red blood cell (RBC), it is currently impossible to measure, but calculate/assume O_2 contents in the blood of animals infused with LEH.
Methods: We examined effects of LEH administration in the blood content of oxygen containing molecules, including CO_2, O_2 and CO in non-human primates undergoing steady-state gas inhalation study. Plasma and whole blood radioactivity were sequentially monitored in the arterial blood while animals were successively breathing [^{15}O]-labeled gases ([^{15}O]CO_2, [^{15}O]O_2 and [^{15}O]CO). The monkeys received base-line measurement, underwent occlusion of the middle cerebral artery, and received LEH with different O_2-affinity and in various doses (n = 18), empty liposome (n = 4) or saline (n = 7) (T2). The [^{15}O] steady-state respiration tests were repeated immediately following reperfusion (T3) and 3-hours thereafter (T4).
Results: While radioactivity of [^{15}O]CO_2 did not change regardless of infusates, [^{15}O]CO increased in the plasma fraction in a LEH-dose-dependent manner, [^{15}O]O_2 increased in the plasma fraction in an O_2-affinity-dependent manner in the plasma fraction. These levels remained elevated for the following 6 hours, which was parallel to the calculation based on O_2 binding characteristics.
Conclusions: These results suggest that LEH serves as a plasma oxygenizer to increase O_2 content in a unit of blood and may account for benefits of LEH on ischemia/reperfusion of organs and/or tissues.

P152
LIPOSOME-ENCAPSULATED HEMOGLOBIN ENHANCES CHEMOTHERAPY TO SUPPRESS METASTASIS IN MICE
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Aim: Liposome-encapsulated haemoglobin (LEH) with high O_2-affinity ($P_{50}O_2$ = 10 mmHg, *h*-LEH) was reported to enhance tumor radiosensitivity. We hypothesize that targeted O_2 delivery to tumor hypoxia by *h*-LEH may also enhance chemotherapy.

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Methods: Doxorubicin (DXR, 0.5 or 2 mg/kg i.p.) or S-1 (4 or 8 mg/kg orally) alone or in combination with *h*-LEH (5 mL/kg i.v.) was administered for 2 weeks to C57BL/6N mice inoculated with Lewis Lung Carcinoma (LLC) in the leg. After the 2-week therapy in 6 treatment groups, mice were sacrificed for quantitative assessment of tumor growth and lung metastasis. The tumor was then evaluated for its expression of hypoxia-inducible factor-1α (HIF-1α) and matrix-metallopoteinase-2 (MMP-2) activity.
Results: Combined use of *h*-LEH and chemotherapeutic agents (DXR or S-1) showed no additional enhancement over the chemo-therapeutic agent alone. However, the combined use of *h*-LEH significantly suppressed the number and total area of metastatic colonies in the lung compared to each chemotherapeutic agent alone. While HIF-1α expression and MMP-2 activity in the original tumor was significantly suppressed in the groups of mice treated with either DXR or S-1 alone, the addition of *h*-LEH to either agent showed further enhancement of oxygen-mediated degradation of HIF-1α and suppression of MMP-2 activity.
Conclusions: While the addition of *h*-LEH to DXR or S-1 had little effect on original LLC tumor growth, it significantly enhanced suppression of lung metastasis in mice.

P153

SYNTHETIC STROMAL MODEL DRUG PERMEATION STUDIES

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Aim: Drug infiltration through the stromal layer of an organ such as pancreas or eye, is key to local bioavailability. Ocular topical application of clindamycin and lincomycin attain therapeutic levels in the cornea, aqueous humor, and iris-ciliary body, but despite structural similarity, behavioural differences occur. Clindamycin has higher overall concentration and shorter peak onset values in ocular tissues. This study describes the use of *in-vitro* permeation through a stromal model in the study of these differences.
Methods: High water content hydrogel membranes were mounted in purpose-designed permeability cells and used to determine permeation coefficients of clindamycin and lincomycin hydrochloride solutions under different conditions.
Results: The permeability coefficient for clindamycin was greater than that of lincomycin at 37°C. Lincomycin showed classic Fickian behaviour with respect to concentration and temperature. However, at low temperatures and high concentrations clindamycin deviated from this behaviour. Clindamycin had greater solubility and self-associated at higher concentrations. Both drugs influenced the water structuring of the hydrogel, but the type and extent of this was dependant on the composition and freezing to non-freezing water ratio.
Conclusions: The change in transport behaviour of clindamycin suggests the presence of complex and competitive interactions, influenced by both temperature and concentration. In-eye the increased permeation and bioavailability of clindamycin is a combination of the influence of temperature, concentration and higher partition coefficient.

P154

COAXIAL ELECTROSPINNING OF FIBERS AS A PROCESS TO ENCAPSULATE ANTISEPTIC DRUGS

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Aim: The first step in wound healing is to clear the area using antiseptic and/or antimicrobial agents. Benzoin can be used as a model antiseptic agent encapsulated into a drug delivery carrier. Electrospinning (E-Spin) has been acknowledged as a versatile technique for the production of fibers to encapsulate therapeutics.
Methods: Both single jet and coaxial jet E-Spin were used as a method to produce fibers. Polycaprolactone (PCL) and Benzoin (BZ) were dissolved in 99,8 Vol.% 2,2,2-Trifluoroethanol (TFE) at concentrations of 170 mg/mL and 17 mg/mL respectively for the single jet E-Spin. For the coaxial jet E-Spin the same solution was used for the core while a 50 mg/mL solution of Poly-lactic acid (PLA) in the same solvent was used for the sheath. Morphology of the fibrous scaffolds as well as fiber diameter and pore size were examined by Scanning Electron Microscopy (SEM). Samples of defined dimensions were incubated in an acetate buffer resembling skin pH at 37°C inside a water bath and the absorbance was measured by using a UV-Vis spectrophotometer to evaluate the cumulative release of BZ and investigate the release mechanism.
Results: The coaxial approach resulted in fibers with an average diameter of 1.83 μm and an average pore size of 16.11 μm^2. Furthermore, the release time prolonged for 7 days; the amount of drug released in the first 8 hours was reduced from 65.1% to 11.65% and the encapsulation efficiency increased from 87.5% to 97.1% in contrast to single jet electrospun fibers, following a Fickian diffusion.
Conclusions: Core-shell fibers with the antiseptic agent inside the core can be considered as drug delivery carriers for sustained release in wound healing applications in clinical practice.

P155

NOVEL DRUG DELIVERY SYSTEM BASED ON BIODEGRADABLE NANOPARTICLES LOADED WITH EVEROLIMUS.

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Background: Most of drug eluting stents used in the treatment of coronary artery disease are covered with durable polymers which impair arterial wall healing. The aim of the present study is to test a novel method of intra-arterial application of biodegradable nanospheres containing antiproliferation drug – everolimus.
Methods: The first phase of study was creation of optimal polymer for drug releasing nanoparticles. Then everolimus pharmacokinetics was evaluated in pre-clinical tests on the porcine model. Twenty eight coronary segments were injured with angioplasty balloon pre-dilatation. Subsequently, nanospheres with everolimus suspended in normal saline (100 μg/2 ml) were delivered by microporous delivery catheter – Clerway. Treated segments were isolated at following time points: 1 hour, 1, 7, 28 and 90 days. Concentration of everolimus at each time point was assayed with standard liquid chromatography (HPLC) method.
Results: The study showed high everolimus concentrations in arterial tissue early on after nanoparticles delivery (9,19 ng/mg ± 3,94 at 1 hour and 8,84 ± 2,00 ng/mg at 24 hours) followed by its gradual decrease from 7,54 ± 1,92 ng/mg at 7 days follow-up through 6,45 ± 1,47 at 28 days to 1,15 ± 0,40 ng/mg at the last day of the study.
Conclusions: Our study showed that this method may be useful in clinical settings where stents or permanent polymers are not required. It gives opportunity for multiple drug delivery during a single procedure.

P156

STUDY ON THE PROPERTIES OF STERILIZED RODS WITH RISPERIDONE

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Aim: The sterilization process of implantable formulations is one of the key stages in obtaining medicinal products. The aim of this study was to determine the influence of this process on the properties of implantable terpolymer rods containing risperidone (RSP).
Methods: The rods were obtained by extrusion from poly(L-lactide-glycolide-trimethylene carbonate) (57:18:25). RSP was introduced into the polymer matrix at the ratio of 0.11:1. Sterilization was performed by using an electron beam accelerator (10 MeV, 360 mA) at the dose of 25 kGy. The composition and chain structure were examined by nuclear magnetic resonance spectroscopy. Thermal properties were characterized by differential scanning calorimetry. The morphological study was performed with scanning electron microscopy.
Results: No significant influence of the sterilization process on terpolymer composition or the average lengths of appropriate blocks was observed. However, a decrease of the glass transition temperature was noted and noticeable differences in morphology were observed.
Conclusions: Electron beam radiation exhibits evident advantages in the sterilization process of terpolymer material and is worthy of consideration in the processing of implantable rods with RSP.
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P157

GENERATION OF NITRIC OXIDE-CONTAINING GAS MIXTURES VIA CONTROLLED UVA-PHOTOLYSIS OF NITRITE SOLUTIONS

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Aim: Nitric Oxide's (NO) importance in the body can be seen in its different roles; from its use in treatments of pulmonary pathologies to its benefits in wound healing. One setback of NO therapies is the high costs associated with its

storage, acquisition and delivery methods. The National Institute of Health, estimates that inhaled NO therapies can be up to 12,000 USD/patient. To reduce some of these costs, a device for bed-side sustained production of NO has been developed.
Materials and Methods: The method consists of an aqueous solution of sodium nitrite that is irradiated by UVA in the presence of ascorbic acid and exhausted by a carrier gas (air); this process induces a NO formation due to the photodecomposition of nitrite ions in the solution. For the experimental procedure, an aqueous solution (PBS) of sodium nitrite in the presence of ascorbic acid was irradiated by UVA. Different UVA irradiance as well as carrier gas flows in the system were tested.
Results: By controlling the UV irradiation and the carrier gas flow of the reaction mixture, different NO levels can be achieved (10-1000 ppm). Gas concentrations of 200, 400 and 800 ppm were produced continuously and steadily for up to 5 hours.
Conclusions: We present a new, simple, and safe device for the on-demand generation of NO-containing gas mixtures with therapy-relevant concentrations and time durations.

P158
SYNTHESIS AND ANTIBACTERIAL EVALUATION OF CALCINATED AG-DOPED NANO-HYDROXYAPATITE WITH HIGH-DISPERSIBILITY
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Aim: To improve the tolerance of germ infection through a catheter, silver (Ag) doped nano-hydroxyapatite(HAp) with high crystalline and dispersibility was synthesized using the anti-sintering agent and also evaluated the antibacterial activity.
Methods: The $Ca_{10-x}Ag_x(PO_4)_6(OH)_2$ with x = 0 and 0.2 was synthesized by co-precipitation method at 100ºC mixing with $AgNO_3$, $Ca(NO_3)_2 \bullet 4H_2O$, and $(NH_4)_2HPO_4$ in deionized water. The Ag contained calcium phosphate powder mixed with an anti-sintering agent were calcinated at 700ºC for 2 h and purified with $NH_4(NO_3)$ solution and deionized water. Finally, the Ag-doped nano-HAp was obtained. The structure, morphology, vibrational, and optical properties of the obtained samples were systematically characterized by XRD, SEM, and FT-IR. For reveal the presence of the Ag in the nano-HAp (x = 0 and 0.2), ICP-AES results were presented. The antibacterial evaluation with *E. Coli* of the nano-powder was also conducted.
Results: In the XRD profiles, the major phase, as expected, is HAp, which is confirmed by comparing data obtained with the ICCD-PDF card: 00-009-0432. At calcinated at 700ºC for 2 h by using the anti-sintering agent, the metallic Ag peak was very slightly observed. This is because that partially exchange of Ag ion in HAp structures for Ca ion in the anti-sintering agent surrounding HAp might be happened. The antibacterial activity of Ag-HAp against *E. Coli* was recognized.
Conclusions: The high-crystalline and dispersible nano Ag-HAp could be obtained by using of the anti-sintering agent. We are now trying to coat on silicone that is a long-term use of catheter substrate.

Regenerative Medicine

P159
APPLICATION OF ADSORPTIVE CARBON DRESSING ACCELERATES SKIN REGENERATION AFTER THE NON-FULL DEPTH BURN
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Aim: To evaluate the effect of early application of adsorptive carbon dressing (ACD) on the skin structure restoration after the non-full depth thermal burn in rats.
Materials and Methods: ACD is produced on a base of activated carbon fibrous materials of medical use and has adsorptive specific surface area of no less than 1800 m^2/g. Non-full depth burn of 6.3 ± 0.3 cm^2 was inflicted on the depilated dorsum of Albino rats by 97 ± 1,5°C water steam. In the first minutes after trauma the burned area was covered with ACD, moistened in cooled solution of chlorhexidine, and thin polyethylene layer to maintain humidity of ACD. Dressings were changed every day during two days only. The wound area and healing rate were monitored. The burned skin tissue samples were collected for morphological examination at the 1st, 3rd and 7th post scalding day.
Results: In the case of early use of ACD the re-epithelialization of wound defect was completed in 12 ± 1.3 days versus 21.6 ± 2.1 days for gause-covered wounds. Layers of basal cells with mitotic activity were observed in burned skin under ACD already first day after trauma. Differentiation of epidermis onto all inherent layers began at the 3rd post burn day. Burned surface had a morphological structure of normal skin in the most part of animals on the 7th day.
Conclusions: The promising approach to promote the regeneration processes and re-epithelialization of wound after non-full depth burn has been developed. It is especially important for treatment of domestic burns in children as a first premedical aid.

P160
CRYOPRESERVATION OF CELLS ENCAPSULATED WITHIN NANO-THIN POLYELECROLYTE COATINGS.
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Aim: Cryopreservation is a method which enables to store the cells for long time period and allows to obtain the appropriate amount of cells necessary for transplantation. Unfortunately, the cells isolated from organs, like e.g. hepatocytes, are susceptible to freezing damage. Encapsulation may be a method allowing to protect cells during adverse freezing conditions. Encapsulation strategies have been developed to minimize the encapsulated transplant volume. In our study the usability of nano-thin semipermeable membrane as a coating shell was evaluated for protection of the cells during cryopreservation.
Materials and Methods: Hepatocytes, isolated from living donors (according to bioethical community protocol) or hepatoma cell line HepG2 were encapsulated inside nano-thin poly-L-lysine/polyethylenimine with incorporated fullerene (PLL/PEI+f) membrane. As a comparable group, the cells were encapsulated within alginate beads. Cell viability was determined by 5-diphenyltertrazolium bromide tetrazolium (MTT) test during 8-day culture. After 4 months of cryopreservation cell viability was analyzed by using flow cytometry.
Results: After thawing, the mean yield of cells nano-encapsulated or encapsulated in microcapsules was, respectively, 70% and 100%. In MTT test the mitochondrial activity expressed as absorbance value was comparable in both types of encapsulation. The percentage of viable cells in all tested groups was on average 90%.
Conclusions: The cryopreservation within semipermeable membrane seems to be a promising way to protect cells during long-term storage in liquid nitrogen. Both encapsulation methods preserved morphology and viability of cryopreserved cells.

P161
DYNAMIC CULTURE OF MESENCHYMAL STEM CELLS AND EFFECT OF MECHANICAL ENVIRONMENT ON PROLIFERATION AND DIFFERENTIATION
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Background: Mesenchymal Stem Cells (MSCs) offer considerable promise as an autologous source of cells for tissue engineering. The aim of this research was to investigate the effect of the mechanical environment on cultured MSCs. The bioreactor used in this research is designed to minimise fluid shear, so that the effect of mechanical strain alone can be studied.
Materials and Methods: MSCs of adult human origin were cultured on flexible PU substrates within a pressure actuated bioreactor. Uniaxial cyclic tensile strain was applied for up to 10 days at rates of 1500 and 3000 cycles per day. Cells were imaged using fluorescence microscopy and Scanning electron microscopy. Protein expression was evaluated using PCR.
Results: Mechanical stimulation was found to influence the proliferation, morphology, and phenotype expression of the MSCs. MSCs stimulated in osteoblastic media were observed to exhibit a stress avoidance response, aligning perpendicular to the principal strain. Proliferation was significantly affected by mechanical stimulation.
Conclusions: The mechanical environment, including the substrate and dynamic stimulation, has a very strong influence on the destination of the differentiation route in stem cells. Bioreactors providing biomimetic conditions offer a valuable means for engineering functional, differentiated bioprostheses.

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VERIFY THE EFFECT ON NERVE REGENERATION FROM INCREASED BLOOD FLOW IN THE NERVE CONTROL AREA DUE TO STELLATE GANGLION BLOCKS

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Objectives: Peripheral nerve regeneration in each part of the organism, using an artificial neural tube that we developed, is producing a good clinical outcome. However when the site of nerve injury is replaced with an artificial neural tube, there is often "regeneration pain," which is a strong pain associated invariably with progression of nerve regeneration at the stage where it is making progress. On the other hand, stellate ganglion blocks performed at pain clinics paralyze the area of the dominant nerve, and, while providing pain relief, it has been reported that they also increase the rate of tissue blood flow to the control area. If this phenomenon can be applied to "regeneration pain", it will be possible to carry out nerve regeneration together with pain relief at an earlier stage than usual.
Materials and Methods: In mature beagle dogs, a 20 mm excision was made in the inferior alveolar nerve on both sides. And on both sides an artificial neural tube (Swine-derived atelocollagen is injected into a hollow tube of polyglycolic acid mesh.) was sutured with the residual nerve. As an experiment, a stellate ganglion block was performed on the right side. After the surgery, blood flow measuring devices and thermography were used to measure changes in blood flow. After 12 weeks electrophysiological assessments and a histo-pathological analysis were carried out.
Results: Inferior alveolar nerve regeneration was observed on both sides. Electrophysiological evaluation showed no difference between the two sides. A prominent increase in blood flow was observed on the experimental side from one week after surgery. Even with thermography of the beagle's face. Also, when comparing the number of axons regenerated on the experimental side had increased by a greater number.
Discussions: The stellate ganglion block causes a marked increase in tissue blood flow to the area controlled by the nerve, and the fact that a significant increase in axon regeneration was found on the experimental side suggests that this might be an effective method of reducing "regeneration pain."

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BONE REGERATION IN THE CANINE FRONTAL SINUS IMPLANTED OCTACALCIUM PHOSPHATE AND COLLAGEN COMPOSITE

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Objectives: The human maxillary sinus is a pneumatic cavity, so dental implants are difficult to place during treatment at maxillary molar.
We have reported that implantation of OCP/Weakly-denatured collagen scaffolds can promote bone regeneration in rabbit skull defects. In this study, we implanted OCP/Weakly-denatured collagen scaffolds into canine frontal sinus, and then evaluated the degree of bone regeneration.
Materials and Methods: Atelocollagen was extracted from porcine skin with pepsin treatment.
Weakly- denatured collagen scaffold was prepared by freeze-drying the collagen solution suspending of atelocollagen at pH7.4, and by thermal-crosslinking. OCP was prepared by drop-wise addition of calcium acetate solution into sodium acid phosphate solution. OCP granules the diameters of which ranged from 199 to 298 μm was mixed with the Weakly-denatured collagen scaffold.
The bilateral bony door was made on the bone surface of frontal sinus and exfoliated carefully from the thin membrane covering inside the sinus without perforation. The scaffolds were implanted in the frontal sinus. 8 weeks after implantation, bone regeneration was evaluated by histo-pathological analysis and computer tomography (CT) scan.
Results: Histo-pathological analysis showed the bony door remaining both case and infiltration of osteoblasts and regeneration of osteons at bony door inside frontal sinuses treated with the OCP/weakly denatured collagen scaffold. Although frontal sinus treated with the Weakly-denatured collagen scaffolds were mostly filled with connective tissue.
Conclusions: OCP/Weakly-denatured collagen scaffold could promote bone regeneration effectively and the scaffold could keep the space which was suitable for infiltration of cells from surrounding tissue.

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HIGH VOLTAGE ALGINATE ENCAPSULATION OF STEM CELLS IN ALGINATE FOR TRANSPLANTATION AND CRYOPRESERVATION

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Aim: Encapsulation of stem cells in alginate 3D constructs has been shown to protect the encapsulated cells from the host immune response as well as from the ice recrystallization after cryopreservation. The commonly used encapsulation methods fail to generate alginate beads with narrow size distribution. We aimed at evaluation of high voltage to encapsulate stem cells in alginate.
Methods: We encapsulated mesenchymal stem cells in 1.6% sterilized alginate at applied voltage (15, 20, 25kV). MSCs were seeded for MTT either immediately post-encapsulation or after 24 h of pre-incubation in culture. Cryopreservation was conducted with 1°K/min cooling rate down to -80°C with 10% Me2SO (v/v) as a cryoprotectant. After being stored at -150°C for 5 days, samples were thawed at 37°C. Then derived MSCs were analyzed for metabolic activity and membrane integrity.
Results: We found no significant effect of flow rate and cell concentration on resulted bead diameter. The applied high-voltage (15-25kV) did not affect the membrane integrity and proliferation of cells post-encapsulation and cryopreservation. However, MSCs frozen after pre-incubation possessed significantly lower proliferation rate as compared to non-incubated.
Conclusions: High voltage encapsulation is a promising method to encapsulate stem cell; it can also be scaled up with an application of high cell numbers. The proliferation of MSCs may be further improved by decreasing the size of beads.