TRANSPLANT INTERNATIONAL

LECTURES

KIDNEY I

V007 EFFECTS OF DOPAMINE DONOR PRETREATMENT ON GRAFT FUNCTION AFTER KIDNEY TRANSPLANTATION: FIVE-YEAR FOLLOW-UP OF A RANDOMIZED CONTROLLED TRIAL

*U. Benck[1], P. Schnülle[2], A. Habicht[3], L. Renders[4], M. Zeier[5], K. Heller[6], P. Pisarski[7], B. Banas[8], B.K. Krämer[1], M. Jung[1], K. Lopau[9], C.-J. Olbricht[10], H. Weihprecht[11], P. Schenker[12], H.W. De Fijter[13], B. Yard[1], W.H. Schmitt[2]
[1]V. Medizinische Klinik, Universitätsmedizin Mannheim, Mannheim, Germany; [2]Nierenzentrum Weinheim, Weinheim, Germany; [3]LMU, Klinikum der Universität München, Transplantationszentrum, München, Germany; [4]Nephrologie, Klinikum rechts der Isar, TU München, München, Germany; [5]Nierenzentrum Heidelberg, Heidelberg, Germany; [6]Medizinische Klinik 4, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [7]Klinik für Allgemein- und Viszeralchirurgie, Universitätsklinikum Freiburg, Freiburg, Germany; [8]Nephrologie, Universitätsklinikum Regensburg, Regensburg, Germany; [9]Medizinische Klinik und Poliklinik I, Universitätsklinikum Würzburg, Würzburg, Germany; [10]Nephrologie, Katharinenhospital Stuttgart, Stuttgart, Germany; [11]Transplantationszentrum, Klinikum Augsburg, Augsburg, Germany; [12]Chirurgische Universitätsklinik, Universitätsklinikum der Ruhr-Universität Bochum, Bochum, Germany; [13]Nephrologie, Universitätsklinikum Leiden, Leiden, The Netherlands

Introduction: A previous multicenter randomized controlled trial (clinicalTrials.gov Identifier: NCT00115115) reported reduced dialysis requirements after kidney transplantation with dopamine donor pretreatment. Data on long-term graft outcomes are needed.
Methods: We calculated five-year graft survival from follow-ups at 60 European centers. We analyzed intention-to-treat and on-study-medication and produced survival estimates as tertiles of dopamine exposure because infusion times varied by treatment arm (range 0–1,929 min). Recipients with functioning grafts at three months were analyzed separately to differentiate early events from long-term consequences of the trial intervention.
Results: Follow-up was complete in 99.2%. Overall graft survival was 72.6 vs. 68.7%, (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.61–1.19; $P = 0.35$), and death-censored graft survival was 83.3 vs. 80.4%, (HR 0.84, 95% CI 0.54–1.29; $P = 0.42$) in the treatment and control arms, respectively. The HR decreased to 0.46 (95% CI 0.23–0.94; $P = 0.03$) in recipients with functioning grafts at three months, whose donor had received dopamine >270 min. It remained significant after adjusting for donor age (HR 1.05, 95% CI 1.02–1.08; $P = 0.001$), delayed graft function (HR 2.05, 95% CI 1.12–3.73; $P = 0.02$), biopsy-proven rejection (HR 2.13, 95%CI 1.16–3.93; $P = 0.02$), and repeat transplants (HR 2.49, 95% CI 1.19–5.20; $P = 0.02$). There were no differences of graft survival on intention-to-treat.
Conclusion: Dopamine administered for >270 min provided a long-term graft survival advantage independent of early events after transplantation.

V008 A NEW AUTOMATED KIDNEY PERFUSION SYSTEM: MAINTAINING PHYSIOLOGICAL CONDITIONS AND MONITORING ORGAN FUNCTION

*W. Markgraf[1,2], M. Gransow[1], F. Tetschke[1], S. Koch[1], M. Janssen[3], M. Stöckle[3], H. Malberg[1], C. Thiele[1]
[1]Institut für Biomedizinische Technik, TU Dresden, Dresden, Germany; [2]UniversitätsCentrum für Orthopädie und Unfallchirurgie, Universitätsklinikum Carl Gustav Carus, Dresden, Germany; [3]Klinik für Urologie und Kinderurologie, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany

Introduction: Current cold transplantation technologies have reached their limits. One alternative is normothermic machine perfusion (NMP), providing the possible benefits of reducing the preservation injury, improving the grafts viability and allowing its assessment. However, automated long-term NMP systems, preserving kidneys ex-vivo and monitoring their functional parameters have yet to be developed.
Methods: We designed a novel device for temperature and pressure controlled, whole-blood perfusion of isolated kidneys, providing adequate oxygen and nutrients supply at physiological flow rates and body temperature. The perfusate is oxygenated, decarboxylated and heated through a membrane oxygenator. A roller pump provides the arteria renalis with a pulsatile flow from a small cardiotomy reservoir, which in turn is gravity-fed by venous backflow. The kidney is permanently stored in a hard shell, adapted to its specific shape. Various hemodynamic parameters are continuously monitored.
Results: Experiments were carried out to show the feasibility of this system. We successfully perfused 50 porcine kidneys up to 12 h. New functional correlations were confirmed, e.g. a correlation between the cold ischemia time and the settling time of the kidneys blood flow.
Conclusion: We introduced a new, automated, ex-vivo kidney perfusion system, and showed the possibility of assessing function parameters during long-term NMP.

BASIC SCIENCE I

V011 DONOR BRAIN DEATH LEADS TO DIFFERENTIAL IMMUNE ACTIVATION IN SOLID ORGANS WITHOUT ACCELERATING ISCHEMIA REPERFUSION INJURY

*P. Ritschl[1], M.I. Ashraf[1], R. Oberhuber[2], C. Fabritius[2], T. Resch[2], S. Ebner[2], M. Sauter[3], K. Klingel[3], J. Pratschke[1], K. Kotsch[2]

[1]Department of General, Visceral, and Transplantation Surgery, Charité-Universitätsmedizin, Berlin, Germany; [2]Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Innsbruck Medical University, Innsbruck, Austria; [3]Department of Molecular Pathology, University Hospital Tübingen, Tübingen, Germany

Background: Braindeath (BD) has been proposed to influence graft quality and to accelerate ischemia reperfusion injury (IRI). A comparative analysis of inflammation between different solid organs following BD is still missing and the detailed influence of BD accelerating IRI still needs to be comprehensively addressed.

Methods and Results: By applying a murine model of BD we demonstrated, that organs following 4 h of BD were characterized by distinct inflammatory expression patterns. For instance, Lipocalin 2 (LCN2), a marker of acute kidney injury, was selectively induced in BD livers but not in kidneys ($P < 0.01$). BD resulted further in significantly reduced frequencies of $CD3^+CD4^+$, $CD3^+CD8^+$ T cells and $NKp46^+$ NK cells in the liver ($P < 0.01$, $P < 0.01$ and $P < 0.05$ respectively), whereas BD kidneys and hearts were characterized by significantly lower frequencies of conventional dendritic cells ($P < 0.01$ and $P < 0.05$). Impact of donor BD was further tested in syngeneic models of kidney (KTx) and heart transplantation (HTx) illustrating that organs derived from BD or sham donors display comparable gene expression levels, intragraft lymphocyte frequencies, and graft function 20 h post transplantation. Moreover, the deposition of the complement factorC3d detected in small vessels and capillaries in cardiac syngrafts was not significantly different between BD and sham transplanted groups. Solely NK cell numbers derived from BD syngrafts demonstrated organ specific variation (increased in KTx and decreased in HTx, $P < 0.01$ respectively). No influence of donor BD on graft survival was detected in an allogeneic heart transplantation setting (C57BL/6 grafts into Balb/C recipients).

Conclusion: We showed for the first time that solid organs are characterized by a varying inflammatory profile following BD characterized by cytokine and lymphocyte expression patterns. However, BD does notaccelerate IRI in syngeneic KTx and HTx.

V012 NK CELLS OF KIDNEY TRANSPLANTED PATIENTS DISPLAY AN ACTIVATED PHENOTYPE THAT IS INFLUENCED BY IMMUNOSUPPRESSION AND PATHOLOGICAL STAGING

*C. Neudörfl[1], U. Hoffmann[1], K. Daemen[1], J. Keil[1], M. Stevanovic-Meyer[1], A. Zierau[1], A. Akhdar[1], F. Lehner[2], H. Haller[3], C. Blume[4,3], C. Falk[1]

[1]Inst. f. Transplantationsimmunologie, Medizinische Hochschule Hannover, Hannover, Germany; [2]Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Medizinische Hochschule Hannover, Hannover, Germany; [3]Klinik für Nieren- und Hochdruckerkrankungen, Medizinische Hochschule Hannover, Hannover, Germany; [4]Inst. f. Technische Chemie, Leibniz Universität Hannover, Hannover, Germany

The impact of NK cells after kidney transplantation (KTx) is discussed controversially, they may play a role in rejection and in tolerance induction. We investigated phenotype and function of peripheral NK cells of KTx patients compared to healthy donors. NK markers (CD16, CD226), activation markers (HLA-DR, CD25) and inhibitory receptors (CD94/NKG2A) were analyzed by flow cytometry. IFN-γ production following PMA/Ionomycin (P/I) stimulation in the presence or absence of immunosuppressive drugs was detected by ICS or ELISpot, supernatants were tested for other cytokines by multiplex analyses.

NK cells of KTx patients have significantly reduced CD16 and CD226 surface expression but increased levels of HLA-DR and CD25, indicating an activated phenotype. Upon P/I stimulation, IFN-γ production was associated with CD16 down modulation, abrogated by CNI. IFN-γ as well as production of other cytokines like TNF-a, IL-10 and IL-31 was decreased by CNI. IFN-γ production of stimulated cells in KTx patients was not impaired while other cytokines like IL-13 and IL-31 were produced at significantly lower levels. Cytotoxins were not affected by immunosuppression.

Thus, NK cells of KTx patients are impaired by immunosuppression, especially the NFAT-dependent cytokine production despite IFN-γ. Taken together, NK cells may serve as sensor for immunosuppression.

PSYCHOSOMATICS

V015 PHYSICIAN REPORTED ADHERENCE WITH IMMUNOSUPPRESSANTS IN RENAL TRANSPLANT PATIENTS: PREVALENCE, AGREEMENT, AND CORRELATES

*M. de Zwaan[1], S. Pabst[1,2], A. Bertram[2], M. Schiffer[2]
[1]Psychosomatik und Psychotherapie, Medizinische Hochschule Hannover, Hannover, Germany; [2]Nephrologie, Medizinische Hochschule Hannover, Hannover, Germany

Even though addressing adherence to immunosuppressants (IS) is essential it is notoriously difficult. We aimed at investigating 1) the prevalence of non-adherence with IS as estimated by the physicians; 2) the agreement between the physicians' estimate and other adherence measures, and 3) the difference between adherent and non-adherent patients according to the physicians' estimation with regard to socio-demographic variables, transplant-related variables, and psychological patient factors.

All patients attending the outpatient clinic of the Department of Nephrology for a follow-up visit from November 2014 to February 2015 were screened and 238 patients met the inclusion criteria

Adherence with IS was assessed with several measures: self-reported adherence was assessed with the 4-item Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS) and the adherence subscale of the German version of the Transplant Effect Questionnaire (TxEQ). The physicians were asked to estimate the patients' adherence to IS on a scale ranging from 1 = very good to 5 = very poor. For the analysis "very good" and "good" were combined as adherent. More objective adherence measures included rejection treatment within the previous 12 month and IS serum level variability using the coefficient of variance of the trough levels of the last 13 months.

Psychological variables were assessed with the 14-item Hospital Anxiety and Depression Scale (HADS) and the Questionnaire of Perceived Social Support (FSozU-7).

The physicians rated 9.2% ($n = 22$) of the patients as being non-adherent. There was no agreement between the physicians' estimate of adherence and the patients' self-assessments, IS serum level variability, and allograft rejection. Physician's ratings of adherence were independently related to female sex, non-German native language, higher symptoms of depression and anxiety, and less perceived social support. Physicians might rely on observable and interactional cues including sex, language, and psychopathology to make inferences about an individual patient's adherence. Also, overestimation of IS adherence may impede physicians' ability to provide high quality care for their renal transplant patients.

V016 PSYCHIATRIC OUTCOME AFTER LIVER TRANSPLANTATION

*D. Eser-Valeri[1], O. Pogarell[1], M. Guba[2]
[1]Klinik für Psychiatrie und Psychotherapie, Ludwig-Maximilians Universität, München, Germany; [2]Klinik für Allgemeine, Viszeral-, Transplantations-, Gefäß- und Thoraxchirurgie, Ludwig-Maximilians Universität, München, Germany

Background: Alcoholic cirrhosis (AC) is one of the most common indication for liver transplantation (LTX) worldwide. LTX is frequently the only treatment modality for alcohol-related (ARLD) end-stage liver disease. Survival 1- to 5-years post-LTX is comparable or even better in AC than for patients with other LTX-indications. However, a higher occurrence of neurological and psychiatric complications has been reported in AC patients and attributed to putative structural injury after prolonged alcohol-use.
Methods: Case notes of 277 patients, transplanted from 2007 to 2012 at the LMU University Hospital were reviewed for demographic data, details of liver disease, survival rates and psychiatric complications.
Results: A total of 70 adults (25%) had ARLD liver disease. Length of sobriety was 45 month (± 8 month) before LTX. ARDL patients had a comparable 5-year survival rate. Occurrence of psychiatric complications did not differ between ARLD (23%) and other indications (22%).
Conclusion: Psychiatric outcome was comparable between ARLD and patients with other LTX-indications. This favorable outcome might be attributable to the long pre-LTX lengths of sobriety in this population, underlining that structured psychiatric pre-transplant selection methods are eligible to choose good candidates with ARLD who achieve outcomes similar to patients with other diagnoses.

LIVING DONATION I

V020 BIRTH WEIGHT AS A MARKER OF NEPHRON NUMBER: PREDICTING LIVING KIDNEY DONOR OUTCOMES

*T. Schachtner[1,2], P. Reinke[1,2]
[1]Nephrologie, Charité Universitätsmedizin Berlin, Berlin, Germany; [2]Berlin-Brandenburg Center for Regenerative Therapies, Charité Universitätsmedizin Berlin, Berlin, Germany

It has been demonstrated that low birth weights give rise to a reduction in nephron number with increased risks for hypertension and renal disease. Its impact on renal function in kidney donors, however, hasn't been addressed.

To investigate the impact of birth weight, kidney weight, and volume on kidney function, we collected data from 91 living kidney donor/recipient pairs before nephrectomy, at 12, 36, and 60 months after nephrectomy.

Donors remaining kidney function showed a strong positive correlation with birth weight at 12, 36, and 60 months ($P < 0.05$). The strongest link was observed in donors >50 years ($R = 0.535$, $P < 0.001$ at +12 months). Daily proteinuria at +12 months showed a negative correlation with birth weight ($P = 0.009$). Donors with new-onset hypertension showed significantly lower birth weights and higher uric acid levels ($P < 0.05$). Donor birth weight showed a positive correlation with allograft function ($P = 0.031$) and negative correlation with the number of antihypertensive drugs in the recipient ($P < 0.05$).

Low donor birth weight predisposes donors to inferior remaining kidney function, hypertension, and proteinuria. The strong correlation in elderly donors may be attributed to a reduced renal functional reserve due to the decline of renal function with age.

V021 KIDNEY FUNCTION AFTER LIVING DONATION: DOES SURGERY AFFECT THE REMAINING KIDNEY? ARE THERE DIFFERENCES BETWEEN LAPAROSCOPIC HAND-ASSISTED AND OPEN SURGERY?

*K. Fischer, G. Gürel, G. Theil, K. Weigand, P. Fornara
Universitätsklinik und Poliklinik für Urologie, Martin-Luther-Universität Halle-Wittenberg, Halle/Saale, Germany

Background: We investigated if the glomerular filtration rate (GFR) and urinary proteins can provide information regarding the state of the remaining kidney after donor nephrectomy.
Methods: From 1998 to 2008, we performed 32 open and 41 hand-assisted laparoscopic donor nephrectomies. The following parameters were measured pre- and postoperatively up to one year after living donation: as marker of glomerular filtration rate (GFR) we followed up on creatinine and cystatin C in serum, as marker of quality of glomerular filtrate we looked at total protein and the higher molecular weight urinary proteins immunoglobulin G, albumin and transferrin, as markers of tubular function we followed up on the low-molecular urinary proteins retinol binding protein, α1 microglobulin and ß2 microglobulin and the urinary enzyme N-acetyl-ß-D-glucosaminidase.
Results: 1 year after kidney donation the values of creatinine and cystatin C are about 30% above its initial value. After the surgery, there was an increase of about 50–60%. After only 6 months, the GFR improved, regardless of surgical method. The high molecular weight urinary proteins reached their maximum concentrations at 1–3 days after the surgery. They then dropped to reference range within one month. The tubular function markers were still increased even 1 year after kidney donation. This is true for both kinds of surgery.
Conclusion: There is no difference observed between open and handassisted-laparoscopic donor nephrectomy in regards to GFR. Urinary proteins behave in the same fashion. Whether the detection of low-molecular weight urinary proteins reflect a tubular damage has yet to be discussed.

IMMUNOLOGY I

V024 NON-INVASIVE DIAGNOSTIC MARKERS FOR DIFFERENTIATION BETWEEN BKV-ASSOCIATED NEPHROPATHY AND ACUTE REJECTION IN RENAL TRANSPLANT PATIENTS

*C. Dang-Heine[1], B. Weist[1], B. Rudolph[2], M. Nienen[3], E. Novotna[4], P. Nickel[4], T. Westhoff[3], P. Reinke[1], N. Babel[1,3]

[1]Brandenburg Centrum für Regenerative Therapien (BCRT), Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]Pathologie, Charité – Universitätsmedizin Berlin, Berlin, Germany; [3]Universitätsklinik Marien Hospital Herne, Herne, Germany; [4]Charité – Universitätsmedizin Berlin, Berlin, Germany

BKV-associated nephropathy (BKVAN) causing graft impairment is often difficult to be distinguish from acute rejection (AR). A misdiagnosis may be detrimental to the patient, because the treatment strategies are diametrically opposed. Diagnostic markers especially of non-invasive nature allowing differentiation between AR and BKVAN will be of great importance.

In the present study 38 renal transplant patients including BKVAN (n = 13), AR (n = 13) and transplant patients with stable graft function (n = 12) were analysed. Expression of urinary mRNA for cytotoxic markers like *granzyme B (GB)*, *programmed cell death-1* (*PD1)*, and T cell regulatory markers like *FOXP3*, *GATA3* and *GAL1* and also mRNA for *CD3* and *HPRT* were measured by quantitative real time PCR. Additionally protein expression of PD1, CD3 and GB were analysed by immunohistochemical staining in kidney graft tissue biopsies.

The expression of urinary *GB*, *FOXP3*, *GATA3* and *GAL1* mRNA in urinary cells were significantly higher in AR patients compared to patients with BKVAN (P = 0.015, P = 0.026, P = 0.01, P = 0.038, respectively) or stable graft function (P = 0.001, P = 0.026, P = 0.004, P = 0.001, respectively). In contrast, the protein expression of PD1 and GB in biopsies was higher in AR and BKVAN compared to the patients with stable graft function.

In this study we identified non-invasive diagnostic markers including *FOXP3*, *GB*, *GATA3* and *GAL-1* in urine facilitating a distinct delimitation of BKVAN and AR.

V025 URINE-DERIVED CELLS AS NOVEL TOOLS FOR MONITORING ALLO-REACTIVITY IN KIDNEY-TRANSPLANT PATIENTS

*C. Thieme[1], B. Weist[1], T. Westhoff[2], P. Reinke[1,3], N. Babel[1,2]

[1]Berlin-Brandenburger Centrum für Regenerative Therapien, Berlin, Germany; [2]Marien Hospital Herne, Ruhr University, Bochum, Germany; [3]Medizinische Klinik mit Schwerpunkt Nephrologie und Internistische Intensivmedizin, Charité – Universitätsmedizin Berlin, Berlin, Germany

Reactivity of the immune system against donor antigens determines transplant-rejection after transplantation. Analyzing the alloimmune response has been shown to predict acute rejection in previous studies. The available methods for assessing alloreactivity are based on measurements of reactivity of recipient peripheral blood mononuclear cells (PBMCs) upon stimulation by stimulator cells derived from donor spleen cells or artificial third party stimulator cell banks. Despite its potential utility, alloreactivity testing in normal clinical practice is restricted mostly by either low quantity (a limited amount of donor spleen cells) or quality (lack of sufficient matching between HLA-bank and donor HLA) of stimulator cells. The aim of this study is to establish a renewable source of donor-derived cells for alloimmunity analysis in kidney transplantation.

Urinary samples were successfully used for generating induced pluripotent stem cells in a previous study. Taking advantage of this, we established a protocol for the generation of patient-specific donor-derived stimulator cell lines using recipient's urine. Urinary samples were centrifugated, washed and the cell-pellets were seeded and cultivated with daily medium changes. The cultivated cells showed an epithelial phenotype and subsequent HLA genotyping revealed that >50% were donor-derived. Alloreactivity was proven by proliferation assay. For this, cell lines were incubated with the recipient's PBMCs in the ratios 1:1 and 1:5 (epithelial cells:PBMC) to assess the direct alloresponse. Lysed cell lines presented to recipients' PBMCs were used for indirect alloimmunity testing. A dose-dependent CD3 + Cell proliferation upon direct stimulation, and, to a lesser extent, after indirect stimulation was shown by multi-color flow cytometry.

In conclusion, we established a novel platform for monitoring alloreactivity in kidney transplant patients. Further studies are required to assess clinical utility of this assay.

ETHICS

V028 CURRENT STATUS OF ORGAN PROCUREMENT FROM PRISONERS IN CHINA

*H. Li[1], N.W. Paul[2]
[1]Institut für Pharmakologie, Universitätsmedizin Mainz, Mainz, Germany; [2]Theorie und Ethik der Medizin, Institut für Geschichte, Universitätsmedizin Mainz, Mainz, Germany

China's transplant medicine started with and relied on organ procurement from executed prisoners. On December 3, 2014, Jiefu Huang, the director of the China Organ Donation Committee and former vice-minister of health, announced that only voluntarily donated organs could be used for transplantation after January 1, 2015. Worldwide media reported that China would stop using executed prisoners as an organ source. Unfortunately, this interpretation doesn't reflect the reality. There are no changes to China's organ-donor laws or governmental regulations. The use of prisoner organs is still legal in China. Therefore, it is doubtable that the harvesting of organs from prisoners has really been stopped. In addition, the new rule has an open back door: prisoners are allowed to "voluntarily donate" organs. Even after January 1, 2015, Huang has repeatedly given such statements to Chinese media. On January 28, 2015, Huang told People's Daily that "death-row prisoners are also citizens. The law does not deprive them of the right to donate organs. If death-row prisoners are willing to atone for their crime by donating organs, they should be encouraged". Thus, death-row prisoners are still allowed or even encouraged to "voluntarily" donate organs in China. According a plan Huang announced in March 2014, these organs are integrated into the existing voluntary organ donation and allocation system and treated as voluntary donations from citizens. This is obviously against international ethical standards. If the new rule (integrating prisoner organs into the voluntary donation system) is accepted by the international medical community, China would officially bypass international ethics guidelines and the unethical practice may never end. Moreover, the new rule may facilitate forced organ harvesting from prisoners of conscience as well. Since 2006, mounting evidence suggests that prisoners of conscience are killed for their organs in China with the brutally persecuted Buddhist practice, Falun Gong, among others, being the primary target (see European Parliament resolution of December 12, 2013). By re-defining prisoners as regular citizens for "voluntary" organ donation, China's national organ donation system may be abused for the whitewashing of organs from both death-row prisoners and prisoners of conscience.

V029 ECONOMIC IMPACT OF DELAYED GRAFT FUNCTION IN EXPANDED CRITERIA DONOR KIDNEYS – A PERIOPERATIVE COST-ANALYSIS

*T. Dziodzio, R. Sucher, C. Denecke, U. Gerlach, A. Pascher, J. Pratschke, R. Öllinger
Klinik für Allgemein-, Visceral- und Transplantationschirurgie, Charité – Universitätsmedizin Berlin, Berlin, Germany

Background: The number of kidneys from extended criteria donors (ECDs) is increasing worldwide. ECD kidneys show a higher rate of delayed graft function (DGF), leading to increased postoperative morbidity, costs and poorer long term survival. In Germany, reimbursement of costs is determined by diagnosis-related groups (DRGs). Aim of this study was to perform a detailed in-hospital cost-analysis of ECD and non-ECD kidneys with respect to DGF.
Methods: Analysis of in-hospital costs and reimbursements of patients who underwent renal transplantation from January 2012 to December 2013 at our institute by analysing departmental revenues.
Results: Out of 107 post-mortem renal-transplantations 36 patients (33.6%) received an ECD and 71 patients (66.4%) a non-ECD kidney, with a post-operative DGF-rate of 61% vs 41%. Overall normal-ward and intensive-care-unit costs per patient differed in both groups (14.190€ in ECDs vs 12.046€ in non-ECDs and 13.922€ vs 3.722€ respectively). Total revenues per patient were 1.097€ vs 7.217€ ($P = 0.02$). Amongst recipients of ECD kidneys without DGF resulted in a revenue of 6.200€, whereas DGF caused a financial loss of −1.152€ per patient.
Conclusion: The DRG system shows a sufficing cover of costs in non-ECD and ECD kidney transplantation. However, DGF in ECD kidneys causes copious costs and is insufficiently reimbursed by the DRG system.

ORGAN DONATION

V032 DO ALTERED PATHOLOGICAL CONDITIONS AFTER LIVER REGENERATION IMPAIR THE DECELLULARIZATION PROCESS OF THE ORGAN SCAFFOLD?

*F. Mußbach[1], U. Settmacher[2], O. Dirsch[3], C. Xie[1], U. Dahmen[1]
[1]Experimentelle Transplantationschirurgie, Klinik für Allgemein-, Viszeral- und Gefäßchirurgie, Universitätsklinikum Jena, Jena, Germany; [2]Klinik für Allgemein-, Viszeral- und Gefäßchirurgie, Universitätsklinikum Jena, Jena, Germany; [3]Institut für Pathologie, Klinikum Chemnitz gGmbH, Chemnitz, Germany

Background: The decellularization and repopulation of liver scaffolds is an innovative strategy in the field of liver engineering. We aim at assessing the feasibility of decellularization under altered liver conditions and started using a regenerated liver longterm after partial hepatectomy.
Methods: Explanted normal ($n = 10$) and regenerated livers ($n = 6$) more than 6 months after 70% partial hepatectomy from C57Bl/6N-Mice were subjected to portal perfusion with 1% Triton X-100 followed by 1% SDS (1 ml/min). When the resulting scaffolds appeared translucent, samples were taken for histological analysis (HE, EvG, PAS, Laminin) and DNA quantification. The scaffolds were injected with Microfil® and subjected to ex vivo imaging using μCT.
Results: Decellularization using perfusion with Triton X-100 and SDS was successful in normal and regenerated livers. Upon histological examination, the scaffolds were free of cellular or nuclear components. Similarly, the amount of residual DNA was virtually undetectable. The integrity of the extracellular matrix and the vascular tree in the acellular scaffolds was also similar in both cases.
Conclusion: This study demonstrated the feasibility of the decellularization irrespectively of a comparatively mild pathological impairment. Our results build the foundation for further studies using organs with more severe pathological conditions like steatotic and fibrotic livers.

V033 THE EFFECT OF SYSTEMIC CATECHOLAMINE APPLICATION ON THE MICROCIRCULATION IN LIVER PROCUREMENT

*M. Strempel[1], D. Foltys[2], M. Kaths[2], H. Heimann[2], V. Weyer[3], H. Lang[2], O. Kempski[2], G. Otto[2]
[1]Viszeral, Gefäß und Transplantationschirurgie, Klinikum Köln Merheim, Köln, Germany; [2]Allgemein, Viszeral- und Transplantationschirurgie, Universitätsmedizin Mainz, Mainz, Germany; [3]Inst. für med. Biometrie, Epidem. und Inform., Universitätsmedizin Mainz, Klin. der Gutenberg-Universität Mainz, Mainz, Germany

Introduction: The most vulnerable part in liver transplantation remains the biliary system. There is evidence, that insufficient perfusion during multi-organ procurement plays a major role in the pathogenesis of post-transplant ischemic damages leading to morbidity and mortality as well as graft loss. Due to frequent haemodynamic instability of the donor, there is a necessity for catecholamine application in a high percentage of procurement operations. Evidentially the flow rate inside the hepatic artery is decreased in the presence of catecholamines.
Material and methods: Fifteen German landrace pigs underwent multiorgan procurement receiving in situ and ex situ perfusion consecutively while external pressure was applied to the perfusion solution and increased stepwise. Arterial flow rates and pressure in the hepatic and renal artery were measured before and during perfusion. Five animals received catecholamines over a period of 30 min prior to in situ perfusion. In order to visualise the perfusion success on the microcirculation, coloured MP were administered after perfusion and detected by microscopy.
Results: Ex situ perfusion was able to generate significantly higher values of pressure and flow at all measuring positions compared to in situ perfusion. When comparing the catecholamine group to the non-treatment group, in situ perfusion deteriorated under catecholamine treatment while ex situ perfusion achieved higher values of flow and pressure. MP count revealed the same pattern underlining these observations.
Conclusion: Our results point out the crucial importance of arterial ex situ pressure perfusion, especially in case of previous catecholamine exposure.

KIDNEY II

V037 C-SURFER: GRAZOPREVIR PLUS ELBASVIR IN TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS WITH HEPATITIS C VIRUS (HCV) GENOTYPE 1 INFECTION AND CHRONIC KIDNEY DISEASE (CKD)

*A. Bruchfeld[1], D. Roth[2], D. Nelson[3], A. Liapakis[4], M. Silva[5], H. Monsour Jr[6], P. Martin[7], S. Pol[8], M.-C. Londoño[9], T. Hassanein[10], P. Zamor[11], E. Zuckerman[12], Y. Zhao[13], M. Robertson[13], J. Wahl[13], E. Barr[13], W. Greaves[13]

[1]Nephrology, Karolinska Institutet, Huddinge, Schweden; [2]Nephrology and Hypertension, Miller School of Medicine, Miami, USA; [3]Clinical and Translation Institute, University of Florida, Gainesville, USA; [4]Yale New Haven Hospital Transplant Center, Yale University Digestive Disease, New Haven, USA; [5]Hospital Universitario Austral, Pilar, Argentina; [6]Hepatology & Transplant, Miller School of Medicine, Houston, USA; [7]Division of Hepatology, Miller School of Medicine, Miami, USA; [8]Unité Hépatologie, Hopital Cochin Université Paris Decartes, Paris, France; [9]IDIBAPS, CIBERehd, Hospital Clinic Barcelona, Barcelona, Spain; [10]Southern California Research Center, Coronado, USA; [11]Liver Unit, Carolinas Medical Center, Charlotte, USA; [12]Carmel Medical Center, Haifa, Israel; [13]Merck & Co, Inc, Whitehouse Station, USA

Introduction: We conducted a Phase 3 trial of grazoprevir (GZR, an NS3/4a protease inhibitor) and elbasvir (EBR, an NS5A inhibitor) in HCV G1-infected patients with CKD4/5.
Methods: Patients were randomized to GZR 100 mg/EBR 50 mg once-daily for 12 weeks ($n = 111$) or deferred treatment (placebo then GZR/EBR, $n = 113$). 11 patients received GZR/EBR and intensive PK sampling. The primary endpoint was sustained virologic response at follow-up week 12 (SVR12). The modified full analysis set (mFAS, patients in the immediate and PK arms who received ≥1 dose of drug, excluding deaths and discontinuations unrelated to treatment) was the primary efficacy analysis population. Safety was evaluated in the randomized GZR/EBR and placebo arms.
Results: 19% patients were CKD4, 81% CKD5, and 76% were on hemodialysis. 6/122 patients receiving GZR/EBR and 6/113 receiving placebo were excluded from the mFAS. 115/116 (99%) patients receiving GZR/EBR achieved SVR12: one patient relapsed. In the GZR/EBR versus placebo arms, rates of serious AEs were 13% vs 16%; and discontinuations due to an AE were 0% vs 4%. Most common AEs with GZR/EBR were headache, nausea, and fatigue.
Conclusion: GZR/EBR for 12 weeks was highly effective and well tolerated in patients with HCV G1 infection and advanced CKD.

V038 INFLUENCE OF INCREASED RECIPIENT BODY MASS INDEX ON OUTCOME AFTER KIDNEY TRANSPLANTATION

*J. Liese[1], N. Bottner[1], A. Schnitzbauer[1], G. Woeste[1], I. Hauser[2], W.O. Bechstein[1], F. Ulrich[1]

[1]Allgemein- und Viszeralchirurgie, Goethe Universität Frankfurt, Frankfurt, Germany; [2]Medizinische Klinik III: Kardiologie, Angiologie, Nephrologie, Goethe Universität Frankfurt, Frankfurt, Germany

The relationship between kidney transplant recipients body mass index (BMI) and outcomes after kidney transplantion (KT) is not fully understood and is discussed controversial. We studied the influence of BMI and clinically relevant outcomes among kidney transplant recipients.

Methods: In a retrospective single center study we included all patients who underwent kidney transplantation in our institution between 01/2007 and 12/2012. Beside demographic data and BMI, we analyzed the clinical course, rejection rates, delayed graft function, other adverse events as well as the new onset of diabetes mellitus and hypertonus after transplantation.
Results: During the study period we performed 386 KT (130 women, 256 men). Twenty-two patients were transplantated in the context of the ET Senior Kidney Transplant Program. We performed 23% living kidney donations. The median BMI was 25.9 kg/m^2. 17.4% of the recipients had a BMI > 30 kg/m^2 and 3.9% a BMI > 35 kg/m^2. BMI > 30 kg/m^2 was significantly associated with primary non-function of the kidney ($P = 0.037$) and delayed graft function ($P = 0.018$). The creatinine clearance 12 month after KT was significantly lower in recipients with a BMI > 30 kg/m^2. Multivariate analysis revealed recipient BMI, donor age, cold ischemic time and HLA mismatches as independent risk factors for a reduced creatinine clearance and delayed graft function.
Conclusions: Increased BMI at kidney transplantation is a predictor of adverse outcomes, including delayed graft function. These findings demonstrate the importance of careful selection of patients and pre-transplant weight reduction, although the role of weight reduction for improving graft function is not clear.

IMMUNOLOGY II

V043 C1Q-BINDING ABILITY OF DONOR-SPECIFIC ANTI-HLA ANTIBODIES FACILITATES THE IDENTIFICATION OF HARMFUL ANTIBODIES ONLY PRE-TRANSPLANT

*T. Kauke[1], C. Oberhauser[2], V. Lin[1], M. Guba[1], M. Angele[1], J. Werner[1], M. Coenen[2], M. Fischereder[3], B. Meiser[4], M. Stangl[1], A. Habicht[4]
[1]Klinik für Allgemein-, Viszeral-, Transplantation-, Gefäß- und Thoraxchirurgie, Klinikum der Universität München, München, Germany; [2]IBE, Ludwig-Maximilians-Universität München, München, Germany; [3]Nephrologie, Medizinische Klinik V, Klinikum der Universität München, München, Germany; [4]Transplantationszentrum, Klinikum der Universität München, München, Germany

Background: The impact of donor-specific (DSA) and non donor-specific (nDSA) anti-HLA antibodies detected only by solid phase assay on graft outcome after renal transplantation is still a matter of debate. Differentiating HLA-antibodies by their ability to bind the complement product C1q might enable a better risk assessment. Therefore we investigated the clinical relevance of pre- and posttransplant C1q binding HLA-antibodies on graft outcome in our center.
Methods: We analyzed the sera of 611 renal allograft recipients who were transplanted between January 2005 and December 2011. The presence of HLA-antibodies and their C1q binding capacity was studied by Luminex Assay prior and after transplantation. Acute rejection (AR) episodes, graft dysfunction (20% increase in creatinine in yearly intervals) and graft survival were assessed within a median follow-up of 4.9 years.
Results: Of 109/611 (17.9%) patients were immunized at time of transplantation with only 2.6% showing pre-existing DSA und 15.2% nDSA. After transplantation 39/611 (6.4%) recipients developed deNovo DSA and 68/611 (11.1%) deNovo nDSA. While neither pre-existing nor deNovo nDSA significantly influenced the rate of AR, graft function and/or survival, DSA significantly impaired renal function. However, pre-existing DSA influenced AR rates (C1q− vs. C1q+: 33 vs. 40%) and graft survival (C1q− vs. C1q+: 30 vs. 50%) only if they were C1q binding while the development of deNovo DSA was associated with a significant increase in AR (C1q− vs. C1q+: 50 vs. 63%), and overall graft loss (C1q− vs. C1q+: 42 vs. 55%) independently of the of their ability to bind C1q.
Conclusion: Distinguishing HLA-antibodies by their C1q-binding ability facilitates the identification of renal transplant recipients at immunologic risk only in DSA, which are pre-existing but not in those which develop deNovo post transplant.

V044 NON-HLA ANTIBODIES TARGETING ANGIOTENSIN II TYPE 1 RECEPTOR AND ENDOTHELIN-1 TYPE A RECEPTOR INDUCE MTOR SIGNALING AND ENDOTHELIAL INJURY IN HUMAN MICROVASCULAR ENDOTHELIUM

*A. Kusch, R. Catar, O. Wischnewski, D. Dragun
Charité Universitätsmedizin Berlin, Berlin, Germany

Functional non-HLA antibodies targeting G protein-coupled receptors (GPCR) Angiotensin II Type 1 receptor (AT1R) and Endothelin-1 Type A receptor (ETAR) are implicated in the pathogenesis of renal and cardiac transplant vasculopathy. Both antibodies activate canonic G-protein related ERK 1/2. While ERK signaling may represent general cellular response to agonist stimulation, the molecular link between receptor stimulation and development of vascular obliterative lesion has not been fully established yet. We hypothesized the involvement of PI3K/Akt downstream signaling target mammalian target of rapamycin (mTOR) and assessed functional consequences of AT1R- and ETAR-activation by non-HLA antibodies. Human microvascular endothelial cells (HMEC) with reliable expression of target antigens were stimulated with AT1R-Ab and ETAR-Ab containing IgG from patients with obliterative vasculopathy. Phospho-specific antibodies against ERK and mTOR downstream targets were used to assess activation of mTORC1 (pp70S6K at Thr^{389}) and mTORC2 (pAkt at Ser^{473}). Scratch assay was employed to study effect of non-HLA-antibodies on wound healing. Involvement of AT1R/ETAR activation in non-HLA antibody downstream signaling was addressed by use of specific inhibitors for AT1R (Valsartan) and ETAR (Sitaxentan). Signaling activity of both, mTORC1 and mTORC2, was increased after short and long term treatment with patient IgG compared to cells treated with IgG from healthy controls. This effect could be inhibited by preincubating the cells with specific inhibitors of AT1R and ETAR. Both, activation of mTORC1 and mTORC2 were PI3K-dependent and independent from ERK-activation. mTOR inhibitor rapamycin completely abolished non-HLA antibodies induced activation of mTORC1 and in addition mTORC2 after long term treatment. Impaired wound healing by non-HLA antibodies could be restored by either use of specific AT1R or ETAR inhibitors. We provide evidence that functional targeting AT1R and ETAR auto-antibodies induce mTORC1 and mTORC2 signalling which is independent of canonic ERK 1/2 activation in human microvascular endothelium. Our data on impaired AT1R and ETAR-dependent wound healing induced by non-HLA antibodies may provide a translational rationale for therapeutic AT1R and mTOR inhibitors in patients with non-HLA antibodies.

V045 BIOPSY-PROVEN REJECTION IN CHILDREN AFTER LIVER TRANSPLANTATION IS ASSOCIATED BY AN IL-12P40-MEDIATED INNATE IMMUNE RESPONSE FOLLOWED BY TH1 T CELL ACTIVATION

*C. Falk[1], I. Goldschmidt[2], F. Mutschler[2,3], E. Pfister[2], F. Lehner[4], C. Neudörfl[1], J. Keil[1], K. Daemen[1], A. Karch[5], R. Mikolajczyk[5], U. Baumann[2]
[1]Institut für Transplantationsimmunologie, Medizinische Hochschule Hannover, Hannover, Germany; [2]Pädiatrische Nieren- und Stoffwechselerkrankungen, Medizinische Hochschule Hannover, Hannover, Germany; [3]Medizinische Hochschule Hannover, Hannover, Germany; [4]Abteilung Viszeral-, Transplantationschirurgies, Medizinische Hochschule Hannover, Hannover, Germany; [5]Epidemiologie, Helmholtz-Zentrum für Infektionsforschung, Braunschweig, Germany

Background: The concept of a coordinated immune response initiated by innate and sustained by adaptive immune cells and their soluble mediators is well established for infection but it has not been demonstrated for solid organ transplantation in humans. Therefore, we wanted to identify a sequence of innate and adaptive immune reactions in children after liver transplantation that correlated with rejection as clinical outcome.
Subjects and methods: In the frame of the CHILSFree study, 32 children, aged 3 months to 16 years, were liver transplanted at MHH for end stage liver disease. Lymphocyte subsets as well as cytokines and chemokines in peripheral blood were quantified by flow cytometry and multiplex technique before, weekly up to 4 weeks after LTx.
Results: Three major patterns could be identified among T, B and NK cell subsets correlating with their respective cytokines and chemokines. A first innate response wave by IL-12p40, sCD25, TRAIL and NK cells was identified in 50% of patients. However, only if this 1^{st} wave was followed by a 2^{nd} wave of adaptive response, i.e. T cell expansion and elevated levels of IFN-g, IL-1RA, IL-13, IL-17, CCL5 and CXCL10, clinically relevant rejection was associated in form of biopsy-proven acute rejection (PBAR). In contrast, if all cellular and soluble parameters remained silent, this non-reactive status was associated with a stable transplant which was presumably achieved by sufficient immunosuppressive treatment.
Conclusion: The quantification of a panel of cellular and soluble immune markers during the first weeks after pediatric liver Tx may provide relevant information for an early detection of the risk of rejection and enable us to identify markers that allow an optimization of immunosuppressive treatment.

LIVER I

V052 A POSSIBLE ROLE OF MIRNAS AS PREDICTIVE MARKERS FOR THE RECURRENCE OF HEPATOCELLULAR CARCINOMA AFTER LIVER TRANSPLANTATION

*J. Liese[1], J. Peveling-Oberhag[2], C. Doering[3], A. Schnitzbauer[4], S. Zangos[5], M.-L. Hansmann[3], C. Mönch[6], M.W. Welker[2], S. Zeuzem[2], W.O. Bechstein[4], F. Ulrich[4]

[1]Medizinische Klinik III: Kardiologie, Angiologie, Nephrologie, Goethe Universität Frankfurt, Frankfurt, Germany; [2]Medizinische Klinik I, Goethe Universiät Frankfurt, Frankfurt, Germany; [3]Dr. Senckenberg Institut für Pathologie, Goethe Universität Frankfurt, Frankfurt, Germany; [4]Allgemein- und Viszeralchirurgie, Goethe Universität Frankfurt, Frankfurt, Germany; [5]Institut für Diagnostische und Interventionelle Radiologie, Goethe Universität Frankfurt, Frankfurt, Germany; [6]Klinik für Allgemein-, Viszeral- und Transplatationschirurgie, Westpfalz Klinikum, Kaiserslautern, Germany

With high rates of long-term survival, Liver transplantation (LT) is the treatment of choice for hepatocellular carcinoma (HCC). Nonetheless, tumor recurrence after LT remains a challenge. The aim of this retrospective study of 92 patients undergoing LT for HCC was to develop a predictive score for tumor recurrence after LT. As the key feature, microarray analysis of patients with and without HCC recurrence after LT was performed.

Of the patients, 23.9% developed a recurrence of HCC after LT, with a median disease-free survival of 10 months (3–55 months). Transplantation outside of the Milan criteria, alphafetoprotein levels and a histopathologic grade of G3 were associated with tumor recurrence. MicroRNA analysis identified significant up- regulation of 8 microRNAs and down-regulation of 5 other microRNAs in patients with tumor recurrence. Subsequently, the array data were successfully validated using real-time polymerase chain reaction. Multivariate Cox regression analysis showed that a score consisting of miR-214, miR-3187 and compliance with the Milan criteria is an independent predictor of tumor-recurrence-free survival.

Our analysis indicates that the use of a specific microRNA expression pattern in combination with limited tumor burden as defined by pre-LT radiological findings might lead to more a accurate prediction of tumor recurrence.

THORACIC ORGANS I

V058 DURATION OF CONTINUOUS-FLOW VENTRICULAR ASSIST DEVICE SUPPORT DOES NOT NEGATIVELY EFFECT ON POST-TRANSPLANT OUTCOME – RESULTS USING THE UNITED NETWORK FOR ORGAN SHARING DATABASE

*A. Bernhardt[1], A.P. Levin[2], H. Reichenspurner[1], U. Jorde[3], V. Topkara[2]
[1]Herz- und Gefäßchirurgie, Universitäres Herzzentrum Hamburg, Hamburg, Germany; [2]Columbia University Medical Center, New York City, USA; [3]Montefiore Medical Center, New York City, USA

Background: An increasing number of patients is bridged to transplant by continuous-flow left ventricular assist devices (CF-LVAD). The purpose of this study is to analyze post-transplant outcomes of heart transplant recipients bridged to transplantation with CF-LVAD after different support durations.
Methods: The United Network for Organ Sharing Database (UNOS) was reviewed to identify first-time heart transplant recipients who were bridged to transplantation with CF-LVAD from January 2011 through September 2013. A total number of 8006 patients were analyzed. Of those 2660 patients (33.23%) were bridged to transplant by a CF-LVAD. 1320 patients with a Thoratec HeartMate II and 146 patients with a HeartWare HVAD were transplanted. Patients were divided into quartiles.
Results: Mean age in heart transplant recipients was 53.8 $\pm$ 12.4 years and 77.2% were male. Mean time on device till transplant were 315.1 $\pm$ 267.8 days. Pre-transplant characteristics were not significantly different between the groups. Post-transplant survival rates were similar between the duration groups at 24 months (90.6%, 82.8%, 81.4% and 83.1, respectively; P = n.s.). PRA peak levels were lowest in the second quartile, although the acute rejection episodes were highest in this group.
Conclusions: Post-transplant survival is not affected by the duration of pre-transplant VAD support. However, PRA levels were lowest in the second groups with a higher rate of acute rejection.

V059 STABLE RENAL FUNCTION IN PATIENTS AFTER HEART TRANSPLANTATION ON MTOR INHIBITOR THERAPY IN COMBINATION WITH CALCINEURIN INHIBITORS

*M. Helmschrott[1], R. Rivinius[1], P. Ehlermann[1], L. Frankenstein[1], A. Ruhparwar[2], B. Schmack[2], T. Bruckner[3], H.A. Katus[1], A.O. Dösch[1]
[1]Kardiologie, Angiologie und Pneumologie, Med. III, Medizinische Klinik, Universitätsklinikum Heidelberg, Heidelberg, Germany; [2]Klinik für Herzchirurgie, Universitätsklinikum Heidelberg, Heidelberg, Germany; [3]Institut für Medizinische Biometrie und Informatik, Universitätsklinikum Heidelberg, Heidelberg, Germany

Background: Deterioration of renal function is an important risk factor after heart transplantation (HTX).
Aim of study: The current retrospective study analysed renal function in patients after HTX receiving a dual immunosuppressive regimen based on mammalian target of rapamycin (mTOR) inhibitors in combination with calcineurin inhibitors (CNIs), i.e. cyclosporine A (CSA) or tacrolimus (TAC), in patients after HTX. Observation period was one year after conversion.
Patients and methods: In this study, data of 82 patients with an mTOR-based immunosuppressive treatment in combination with a CNI, were retrospectively analysed. 30 patients received CSA as concomitant immunosuppressive drug, 52 patients received mTOR inhibitors in combination with TAC. Baseline renal function (serum creatinine, estimated glomerular filtration rate (GFR)) after switch to a mTOR/CNI based regimen was compared to renal function four, eight, and twelve months after conversion.
Results: Mean time after HTX was 52.7 $\pm$ 69.7 months in mTOR/CSA group and 17.2 $\pm$ 30.3 months in mTOR/TAC patients (P = 0.02851). During study period no statistically significant differences in renal function in both study groups were observed (P = ns). At baseline, serum creatinine in mTOR/CSA patients was 2.0 $\pm$ 2.3 mg/dl, in mTOR/TAC patients serum creatinine was 1.6 $\pm$ 1.0 mg/dl (P = ns). One year after conversion, serum creatinine was 2.2 $\pm$ 2.0 mg/dl in the CSA group and 1.8 $\pm$ 0.8 mg/dl in the TAC group (P = ns). Analysis of renal function by estimated glomerular filtration rate (eGFR) detected no statistically significant differences at baseline and after study period (all P = ns).
Conclusion: Our study demonstrated that the choice of CNI in combination with mTOR has no effect on renal function during one year after conversion.

KIDNEY III

V063 PLASMAPHERESIS AND ABATACEPT FOR EARLY RECURRENCE OF IDIOPATHIC FSGS AFTER KIDNEY TRANSPLANTATION

*M. Guthoff[1], H. Bunz[1], D. Baumann[1], K. Amann[1], S. Nadalin[1], N. Heyne[1]
[1]Endokrinologie und Diabetologie, Angiologie, Nephrologie und Klinische Chemie, Universitätsklinikum Tübingen, Tübingen, Germany

Background: Idiopathic focal segmental glomerulosclerosis (FSGS) is associated with a relevant risk of recurrence following transplantation. Existence of a circulating permeability factor, i.e. soluble urokinase-type plasminogen activator receptor (suPAR) has been postulated. Plasmapheresis is a therapeutic option; whereas novel concepts directly target podocyte function via SMPDL-3b (rituximab) or B7-1 (abatacept).

Clinical setting: A 20 years old patient suffered recurrence of primary FSGS early after living-donor kidney transplantation. By day 4, he developed unselective proteinuria up to 11.589 mg/g creatinine and nephrotic syndrome. Plasma concentrations of suPAR were significantly elevated with 4793 pg/ml. Renal biopsy was normal and renal vein thrombosis excluded.
Outcome: Plasmapheresis was initiated, resulting in decreasing suPAR concentrations and a reduction in proteinuria to 6724 mg/g creatinine. For stabilization of podocyte function, abatacept (5 mg/kg bwt) was subsequently administered, resulting in a rapid decrease in proteinuria to 595 mg/g creatinine. Renal allograft function was normal throughout follow-up.
Conclusion: Early recurrence of idiopathic FSGS after kidney transplantation may effectively be treated by plasmapheresis and abatacept. Our data support the concept of a dual approach with extracorporeal elimination of suPAR and direct stabilization of podocyte function, resulting in effective and sustained reduction in proteinuria.

LIVER II

V069 REGENERATIVE RESPONSE TO BILE DUCT DAMAGE AND IMMUNE RESPONSE TO BACTERIAL INFILTRATION DETERMINE BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION

*H.H.G. Junger, S.M. Brunner, H.J. Schlitt, S. Fichtner-Feigl
University Medical Center Regensburg, Regensburg, Germany

Background: Biliary complications are a major cause of morbidity and graft failure after liver transplantation (LTx). This study aimed to clarify the molecular mechanisms behind the epithelial reaction to bile duct damage and the immune response to bacterial infiltration with respect to effects on biliary complications after LTx.
Methods: BD epithelial injury after cold storage was quantified by the BD damage score (BDDS) and correlated with patient outcome. Bacterial infiltration was determined by Fluorescence in *situ* Hybridisation (FISH) for bacterial antigens. Further, BD samples were analysed by immunohistochemistry for Aggrecan, Cytokeratin, CDH-18, CD8 CD14, whole genome microarray and gene set enrichment analysis.
Results: Patients with BD damage after cold storage with biliary complications had the highest frequency of graft failure (*P* damaged BD without biliary complications developed significantly more transplant rejection ($P = 0.009$). In damaged BDs with biliary complications reduced mRNA levels of cell-adhesion, adherens-junction and focal-adhesion-molecules (*FDR q-value* 0.049; 0.003; 0.049) were detected compared to damaged BDs without biliary complications, reflecting the regenerative capacity of the biliary epithelium. In accordance immunohistochemistry (IH) showed reduced expression of Aggrecan, Cytokeratin, CDH-18. Equal distribution of bacterial infiltration of BDs was observed in FISH analysis, however, mRNA analysis detected enrichment of gene programs characterizing immune response to bacterial infection and FC-gamma mediated phagocytosis (*FDR q-value* $8.4*10^{-4}$; 0.046). Corresponding and consecutively IH showed increased numbers of $CD8^+$, $CD14^+$ cells in BDs with enhanced regenerative capacity of the biliary epithelium.
Conclusions: These studies show that BD damage detected after cold storage is a prognosticator for biliary complications and graft loss after LTx. Functional regenerative capacities of the biliary epithelium and enhanced immune response to bacterial infiltration are able to rescue damaged BDs and prevent biliary complications after LTx.

THORACIC ORGANS II

V073 GENDER DIFFERENCES IN PATIENTS UNDERGOING MECHANICAL CIRCULATORY SUPPORT – RESULTS USING THE EUROMACS REGISTRY

*A. Bernhardt[1], B. Sill[1], T. DeBy[2], J. Gummert[3], P. Mohacsi[4], F. Wagner[1], H. Reichenspurner[1], T. Deuse[1]

[1]Herz- und Gefäßchirurgie, Universitäres Herzzentrum Hamburg, Hamburg, Germany; [2]EUROMACS registry, Berlin, Germany; [3]Herz- und Diabeteszentrum, Bad Oeyhnhausen, Germany; [4]Inselspital, Bern, Switzerland

Background: Mechanical circulatory support (MCS) is an established treatment option for patients with end-stage heart failure. Although there are numerous reports identifying sex-specific differences with respect to progression and prognosis of heart failure, little is known about gender differences in indication and outcome for patients with ventricular assist devices (VAD). Therefore, data from the EUROMACS registry were analyzed.
Methods: Between January 2011 and June 2014, a total of 1006 consecutive VAD patients were submitted to the EUROMACS registry. Demographic data, underlying cardiac diseases, and outcomes were analyzed for gender differences.
Results: In this European cohort, 168 (16.7%) patients were female and 838 (83.3%) patients were male ($P < 0.001$). ICM was less frequent in female patients (41, 24.4%) than in male patients (372, 44.4%; $P < 0.001$). At the time of VAD implantation, female patients were younger than male patients (48 $\pm$ 17 years vs. 52 $\pm$ 12 years, $P < 0.001$). Women presented in a more critical INTERMACS level compared to men (87 (51.7%) in level 1 or 2 vs. 348 (41.5%); $P < 0.001$). ECMO bridging was more often used in women (21, 12.5%) than in men (78, 9.3%; $P < 0.001$). Temporary or permanent RV support was necessary in 43 (25.6%) women and thus significantly more frequently required than in men (120, 14.3%; $P < 0.001$). Overall, female patients showed significantly inferior 1-year survival (63.7% vs. 75.3%) as well as 2-year (59.7% vs. 66.4%) and 3-year survival (51.1% vs. 60%).
Conclusion: Women, who already have an inferior life expectancy when diagnosed with end-stage heart failure, are likely to be transferred in a later and more critical clinical state for VAD implantation. They show a higher incidence of perioperative RV failure and worse long-term survival. We urge that referral strategies and implant timing be revised for female patients to improve their MCS outcome.

V074 CLINICAL RESULTS IN HEART TRANSPLANT RECIPIENTS, RECEIVING DONOR ORGANS WITH CORONARY HEART DISEASE COMPARED TO DONOR ORGANS WITHOUT CORONARY IMPAIRMENT

*U. Fuchs[1], C. Özpeker[1], B. Fujita[1], A. Zittermann[1], S. Ensminger[1], S. Wlost[1], U. Schulz[1], J. Gummert[1]

[1]Thorax- und Kardiovaskularchirurgie, HDZ NRW Bad Oeynhausen, Bad Oeynhausen, Germany

Introduction: Proof of coronary artery heart disease in donor hearts has been considered as contraindication in the majority of the heart transplant centers. Therefore, the aim of the study was to analyze outcome in heart transplant recipients, who received donor organs with positive proof of coronary heart disease (CHD) compared to recipients without coronary heart disease (NCHD) of the donor organs as controlled by coronary angiography.
Method: Between 2006 and 2008 a total number of 91 of the implanted donor hearts received a coronary angiography before heart transplantation. A total number of 16 patients received donor organs (coronary 1 vessel disease; grade of stenosis <50%) with coronary heart disease (CHD-group). In 75 patients coronary heart disease could be excluded by coronary angiography (NCHD-group). The coronary heart disease was diagnosed accidently as donors mostly had no medical or conventional treatment of the CHD. The overall survival and the incidence of initial graft failure were evaluated in both groups.
Results: The baseline characteristics such as age, diagnosis leading to heart transplantation, blood group, MHC I – status, MHC II – status, and the incidence of diabetes mellitus were comparable between the groups and showed no significant difference ($P > 0.05$). The gender differed significantly between the groups (female gender: 25.7% in the NCHD-group vs. 0% in the CHD-group; $P = 0.03$). Furthermore height ($P = 0.009$) and weight ($P = 0.019$) were significantly higher in the CHD group. Multivariate analysis revealed statistically no difference between the two groups. Overall survival and the incidence of graft failure did not differ significantly between the groups ($P > 0.05$).
Conclusion: Reflecting our results the presence of mild CHD in the donor heart seems not to reduce the prognosis such as survival and graft failure, compared to donor hearts without positive proof of CHD diagnosed via coronary angiography in heart transplant recipients.

THE HIGHLY IMMUNISED PATIENT

V087 OPTIMIZED AFTERCARE IN THE FIRST YEAR AFTER LIVING KIDNEY TRANSPLANTATION WITH THE SUPPORT OF TELEMONITORING – A SINGLE CENTER EXPERIENCE

*S. Hils[1], A. Schmid[1], L. Bogatyreva[1], D. Hauschke[2], P. Pisarski[1]
[1]Department Chirurgie, Klinik für Allgemein- und Viszeralchirurgie, Transplantationszentrum, Universitätsklinikum Freiburg, Freiburg, Germany;
[2]Department für Medizinische Biometrie und Medizinische Statistik, Universitätsklinikum Freiburg, Freiburg, Germany

Background: The constant high number of patients on the German kidney waiting list and the permanent shortage of donor organs, forces new solutions. The Transplantation Center Freiburg has always been innovative and telemedicine has been an upcoming part of the German health care system. The benefit of telemedical support, e.g. for chronic diseases has been reported in many studies.
Method: A prospectiv, randomized, controlled and open Project-Study with 50* living kidney transplanted patients (*4 drop outs) was initiated. 23 patients with standard aftercare, 23 patients with standard aftercare and additional webbased telemonitor with videocamera at home. Observation period: Oct. 2011–Apr. 2014. Repeated measure analysis at time points 0,3,6,12 months post-tx via medical reports and standardized Interviews/Questionnaires (BAASIS, ESRD-SCL, BSI-18, ALL) about: course of medical condition, adherence concerning the intake of immunosuppressive medication, psychosocial factors and economic factors.
Results: 12 months after living kidney transplantation (LKTx) significant results were reported. In the telemedicine group, at the onset of diseases, serious complications can be avoided because of an early diagnosis of infections and of acute renal failure. Significantly reduced duration (67%/$P = 0.005$) and frequency (60%/$P = 0.002$) of unplanned hospital-readmissions. Significant higher adherence to immunosuppressant medication ($P = 0.003$). Higher quality of life because of less cortisone side effects ($P = 0.004$) and less cardiac & renal dysfunction ($P = 0.050$). This results in cost reductions per telemedical patient between 3.340,24 € – 5.699,43 € in the first year after kidney transplantation because earlier adequate treatment avoids serious complications.
Conclusion: The results of this innovative aftercare procedure confirm, that patients supported with telemonitoring experience longer periods of being healthy during the first year after LKTx. It guarantees the patients an optimized follow-up and brings medical and economic benefit. It creates a win-win-situation for all participants and may help to prevent graft loss. A follow-up study and a study including kidney transplanted recipients after postmortal donation and after pancreas-/kidney donation started in 2014.

V088 ECULIZUMAB – SUCCESSFUL RESCUE THERAPY OF AN IGG ANTI-HLA DQ7 MEDIATED ACUTE ANTIBODY-MEDIATED REJECTION AND NEED FOR LIFE-LONG THERAPY

*R. Weimer[1], N. Bulut[1], P. Boide[1], L. Rainer[1], C. Wehling[2], M. Kirschfink[2], W. Padberg[3], F. Renner[1]
[1]Nephrologie/Nierentransplantation, Universität Gießen, Gießen, Germany;
[2]Institut für Immunologie, Universität Heidelberg, Heidelberg, Germany;
[3]Zentrum für Chirurgie, Universität Gießen, Gießen, Germany

Background: The anti-C5 monoclonal antibody eculizumab has the potential to effectively prevent and treat acute antibody-mediated rejection (AMR). Treatment failure has recently been attributed to C4d- or C1q-negative AMR.
Case report: We present the case of a 52 years old man with suspected chronic glomerulonephritis who received a living-donor renal transplant from his mother in 1987. After graft failure 14 years later, he was retransplanted in October 2012 (deceased donor graft from a 34 years old woman; PRA max. 2%; T/B-cell crossmatch negative). Despite rATG induction, Tacr/MMF/steroid maintenance and prophylactic immunoadsorption (IA), the pretransplant detected IgG donor-specific antibody (DSA) against HLA DQ7 (repeat mismatch; single antigen assay (SAA): MFI 4169) rose steadily (MFI 12977, day 14; C1q SAA positive). The resulting low-grade transplant glomerulitis (day 18; C4d-) was successfully treated with steroid pulses, intensified IA, IVIG and rituximab. As no DSA decline was achieved (MFI > 15 000, 1:3 dilution), one cycle of bortezomib and rituximab were administered. However, acute rATG-resistant AMR occurred on day 44 (C4d negative; S-Cr 3.9 mg/dl) and eculizumab was initiated with prompt response. A recurrent acute AMR (day 80) was caused by insufficient inhibition of the alternative complement pathway and could be resolved by dose adjustment of eculizumab resulting in long-term stable graft function (S-Cr 1.7 mg/dl). After a second cycle of bortezomib, the DSA nearly disappeared but completely recurred one year later. Genetic complement disorders were largely ruled out.
Conclusion: Eculizumab may successfully be used for rescue therapy even in C4d-negative AMR. Failure may just be a consequence of underdosing resulting in incomplete complement inhibition. DSA recurrence after bortezomib therapy did not allow termination of eculizumab treatment.

PANCREAS

V097 PRECLINICAL STUDIES ON PORCINE ISLET MACROENCAPSULATION IN NON-HUMAN PRIMATES

*S. Ludwig[1], A. Steffen[2,3], B. Zimerman[4], J. Schmid[2], U. Schubert[2], S. Heinke[2], Y. Knauf[5], F.-J. Kaup[5], T. Goldman[4], U. Barkai[4], A. Rotem[4], S. Bornstein[2,3,6], J. Weitz[1], B. Ludwig[2,3]

[1]Klinik für Viszeral,- Thorax-, und Gefäßchirurgie, Universitätsklinikum Carl Gustav Carus, Dresden, Germany; [2]Medizinische Klinik III, Universitätsklinikum Carl Gustav Carus, Dresden, Germany; [3]DZD- German Centre for Diabetes Research, Paul Langerhans Institute Dresden of Helmholtz Centre Munich, Dresden, Germany; [4]Beta-O2 Technologies, Rosh-Ha'ain, Israel; [5]Leibniz Institute for Primate Research, German Primate Center, Göttingen, Germany; [6]Division of Diabetes & Nutritional Sciences, Kings College London, London, UK

Introduction: Pancreatic islet transplantation is currently restricted to a small subset of patients due to the need for immunosuppression and shortage of donor organs. We have developed a strategy for islet macroencapsulation using the Beta O2 device that provides sufficient immune-isolation whereas islet function is maintained. Here we present the first results using the Beta O2 device on safety and efficacy for macro-encapsulated porcine islet transplantation in diabetic non-human primates (NHP).
Material and methods: Isolated porcine islets from Gottingen minipigs were integrated into the Beta O2 device. For safety assessment a total of ten healthy cynomolgus monkeys were implanted with either porcine islets containing or empty devices and followed for 6 and 12 months. For assessment of microbiological transmission, a list of 52 pathogens was tested. For efficacy assessments rhesus macaques underwent surgical sub-total pancreatectomy followed by streptozotocin (STZ) injection. Animals were transplanted at a dose of ~20.000 islets/kg BW encapsulated within the Beta O2 device and followed for 6 months. The study was carried out without immunosuppression. For metabolic assessment, blood glucose (BG) was monitored and intravenous glucose tolerance (ivGTT) tests were conducted.
Results: Regarding safety issues, we saw no presence or transmission of any pathogens. The combination of surgical sub-total pancreatectomy plus STZ resulted in complete insulin deficiency. Upon transplantation the animals showed a steadily improving glycemic control while insulin demand could be decreased. During ivGTT we observed BG kinetics comparable to healthy control animals and adequate c-peptide secretion upon glucose challenge.
Conclusion: This encapsulation strategy was for the first time applied to a preclinical model of porcine islet xenografts in diabetic NHP. We demonstrated a comprehensive safety profile and persistent graft function with regulated insulin secretion without any immunosuppressive therapy. These results may pave the way for a first clinical trial on macroencapsulated porcine islets in man.

V099 CONTRAST-ENHANCED ULTRASONOGRAPHY OF THE PANKREAS GRAFT

*M. Bialobrzecka, P. Kühn, L. Berger, A. Wunsch, R. Viebahn
Chirurgie, Knappschaftskrankenhaus Bochum, Bochum, Germany

Background: Pancreas transplantation is being performed mostly in patients with impaired kidney function. The often complications after this major surgery require an imaging method that is safe for the kidney function.
Methods: A total of 38 B-mode, duplex and CEUS exams performed using 1 ml SonoVue(Bracco) on a Siemens Acuson S2000 ultrasound machine were evaluated in 19 pancreas transplant recipients with normal pancreas transplants, grafts with non-function, grafts undergoing or after successful treatment of the rejection and during a severe pancreatitis, and has been compared with other methods (MR, CT, Biopsie).
Results: In 34 out of 38 examinations the grafts could have been visualized (in most of the cases with the Y graft). In one case of primary non function, a significant lower amount of contrast has been detected by CEUS (in comparison to CT which showed a normal perfusion).
Discussion: CEUS displays the capillary perfusion of the tissue. Edema of the pancreas graft during rejection or pancreatitis can impair capillary perfusion, which could be reflected in the amount of contrast detected and the dynamics of the influx of the contrast agent.
Conclusion: It is possible to visualize the graft using CEUS. The examination can be easily performed at the patients bed and can be used several times independently of the kidney function. Further studies and measurements (like TIC) will be needed to differentiate rejection from other post- transplantation complications using CEUS.

IMMUNOSUPPRESSION

V110 PRETRANSPLANT PROPHYLACTIC RITUXIMAB PREVENTS EBV VIREMIA IN EBV-SERONEGATIVE KIDNEY TRANSPLANT RECIPIENTS FROM EBV-SEROPOSITIVE DONORS

*T. Schachtner[1,2], P. Reinke[1,2]
[1]Nephrologie, Charité Universitätsmedizin Berlin, Berlin, Germany; [2]Berlin-Brandenburg Center for Regenerative Therapies, Charité Universitätsmedizin Berlin, Berlin, Germany

Background: Due to a striking increase in the risk of posttransplant lymphoproliferative disorder in EBV-seronegative kidney transplant recipients (KTRs) receiving an allograft from an EBV-seropositive donor, special strategies need to be defined to prevent EBV transmission and EBV replication.
Methods: Here, we studied all kidney transplant recipients (KTRs) at our single transplant center transplanted between 2008 and 2012. 17 of 402 KTRs (4.2%) were identified as EBV-seronegative recipients from an EBV-seropositive donor, among which 5 KTRs received kidneys from living donors and 12 KTRs received kidneys from deceased donors. KTRs undergoing living kidney donation were treated with a single dose of rituximab 4 weeks prior to renal transplantation. Assessment of EBV-seroconversion and EBV viremia were performed in all KTRs in follow-up.
Results: Among the 12 EBV-seronegative KTRs from deceased donors, all 12 KTRs (100%) showed EBV-seroconversion, 7 KTRs (58%) showed active EBV-viremia, and 1 KTR (8%) showed development of posttransplant lymphoproliferative disorder. In comparison 3 of 5 KTRs from living donors, who received pretransplant rituximab, remained EBV-seronegative after renal transplantation, and no KTR developed EBV viremia or posttransplant lymphoproliferative disorder in follow-up ($P < 0.05$). All KTRs, who received pretransplant rituximab, show excellent allograft function, no increase in infectious complications or malignancies.
Conclusions: Our data suggest that rituximab-mediated elimination of B-cells prevents transmission of EBV to the recipient, since EBV persistence requires the establishment of a latent infection in recipient B-cells. Pretransplant rituximab may proof useful to prevent primary EBV-infection in EBV-seronegative KTRs undergoing living kidney donation.

V111 DETECTION OF PATIENTS ON INCREASED RISK OF BKV REPLICATION BY NFAT-REGULATED GENE EXPRESSION

*C. Sommerer[1], J. Baghdadi[1], T. Theissing[1], M. Zeier[1], T. Giese[2]
[1]Nephrologie, Medizinische Klinik Heidelberg, Heidelberg, Germany; [2]Immunologie, Universitätsklinik, Heidelberg, Germany

Background: BK viremia and BK-associated nephritis are well-known complications in renal transplantation. Especially on combined tacrolimus (Tac) and mycophenolate (MPA) treatment, an increased prevalence of BK viremia has been detected. The best prophylaxis and treatment option is an individually adapted optimal immunosuppression. The first pharmacodynamics assay to measure the individual degree of immunosuppression of calcineurin inhibitors has been established by quantitative assessment of NFAT-regulated gene expression (NFAT-RGE).
Methods: Renal allograft recipients at the Transplant Center Heidelberg were included in this observational study. Immunosuppression consisted of MPA, Tac and low-dose steroids. The expression of three NFAT-regulated genes (interleukin 2, granulocyte-macrophage colony stimulating-factor, interferon-γ) was determined by qRT-PCR at Tac C0 and C1.5 at regular follow-up visits.
Results: Until now, 23 renal allograft recipients were enrolled in this ongoing cohort study (13 male, 10 female). Mean age was 48 $\pm$ 10 years. Seven allograft recipients developed significant BKV replication after renal transplantation (30.4%). Mean NFAT-RGE was significantly lower in patients who showed BK viremia compared to patients without BK viremia (30 $\pm$ 7% vs. 46 $\pm$ 23%, $P = 0.017$), whereas Tac doses and C0 levels were comparable. MPA doses did not differ significantly between both study groups. Of all three examined gene expressions, residual IFNγ gene expression proved to be the best marker to distinguish between patients on risk and patients without risk of BK replication.
Conclusions: A high immunosuppressive load is an important risk factor to develop BK viremia after renal transplantation. Tac treated renal allograft recipients with low NFAT-RGE are on increased risk to develop BK viremia. Monitoring of NFAT regulated gene expression in CNI treated transplant recipients is supposed to be a supporting tool to detect patients on risk of viral replication and provides an individual profile of response to CNIs.

V112 MALIGNANCIES UNDER MTOR-INHIBITOR BASED IMMUNOSUPPRESSION AFTER SOLID ORGAN TRANSPLANTATION – A METAANALYSIS

*S. Wolf[1], V. Hoffmann[2], M. Angele[1], M. Rentsch[1], M. Stangl[1], J. Werner[1], M. Guba[1], *J. Andrassy[1]
[1]Chirurgische Klinik, Klinikum Großhadern, München, Germany; [2]IBE LMU München, Klinikum Großhadern, München, Germany

Introduction: Malignancies are one of the major reasons for death with functioning graft in transplantation. In the recent years, mTOR-inhibitors were shown to positively influence the occurrence and course of certain tumors. Although many reports have been published, the influence of mTOR-Is on the overall incidence of tumors irrespective of their origin is not entirely clear up to this date. This we aimed to investigate using metaanalyses on the most relevant recent transplant trials.
Methods: The current literature was searched for prospective randomized controlled trials in solid organ transplantation using the following terms ((mTOR OR sirolimus OR everolimus) AND transplant AND malignancy). These trials were required to have had at least two treatment arms, one with an mTOR-I based immunosuppression and one containing CNI. The quality of the trials was assessed using the Jadad-score (minimum score of 3). There were 1008 trials screened of which 37 could be included (pts. = 15287). The 1-year and longterm incidence of malignancies was assessed in metaanalyses.
Results: Metaanalysis on 1-year incidence of malignancy showed a reduction under mTOR-Is (RR 0.75, CI 0.55–1.02). This effect was seen when mTOR-Is were given either without CNIs or in combination with CNIs (mTOR-I w/o CNIs vs. CNIs: RR 0.84, CI 0.50–1.40; mTOR-I with CNIs vs. CNIs: RR 0.66, CI 0.42–1.05). Statistical calculations for longterm incidences is work in progress.
Conclusion: Posttransplant patients with mTOR-I treatment with or without CNIs seem to benefit in respect of cancer incidence.

BASIC SCIENCE II

V116 SECRETOME RELATED REGENERATIVE PROPERTIES OF MESENCHYMAL STROMAL CELLS ATTENUATE VASCULAR CALCIFICATION AND CAN BE ENHANCED BY MTOR INHIBITION

*B. Hegner[1], C. Kurth[1], T. Schaub[1], C. Lange[2], D. Dragun[1]
[1]Nephrologie und Intensivmedizin, Charité Universitätsmedizin, Berlin, Germany; [2]Klinik für Stammzelltransplantation, Universitätsklinikum Eppendorf, Hamburg, Germany

Recipients of kidney transplants are a high-risk population for cardiovascular events due to arterial media calcification comparable to patients with chronic kidney disease, in particular when post-transplant diabetes mellitus (PTDM) develops. Exhaustion of regenerative capacity of vascular smooth muscle cells (VSMC) and their progenitors results in osteoblast like VSMC transformation and calcification. We hypothesized that beneficial paracrine properties of mesenchymal stromal cells (MSC) can be targeted to boost their regenerative potential and mitigate the calcification process. We addressed a pleiotropic therapeutic potential of rapamycin on regenerative capacity of MSC since it modulates the mTOR-network, a glucose sensitive master regulator of cell differentiation and cell fate programs.

Osteoblastic transformation was induced in human coronary artery VSMC with high calcium and phosphate and calcitriol. Conditioned media from MSC or VSMC control was transferred to calcifying VSMC. Feeder (MSC or VSMC) and receiver cells (VSMC) were cultured under normal or high glucose conditions. Anti-diabetics with influence on mTOR signaling (metformin, insulin) or rapamycin were added.

MSC conditioned medium markedly reduced osteoblastic transformation of VSMC. High glucose had no influence on VSMC calcification. Treatment of feeder-MSC with rapamycin boosted the anti-calcifying properties of the MSC secretome with normal and high glucose. Addition of metformin was also beneficial but only in combination with high glucose. Insulin was not protective. Signal transduction analyses revealed substance specific signaling patterns of the mTOR network in calcifying VSMC. Rapamycin and metformin reduced cellular senescence and enhanced autophagy as demonstrated by western blots for $p16^{INK4a}$ and LC3B. Lack of protection observed with insulin was reflected by increased senescence, reduced autophagy and elevated apoptosis (cleaved caspase 3).

MSC secrete factors capable of protecting VSMC from osteoblastic transformation. Modulation of mTOR signaling with rapamycin or metformin enhances regenerative properties of the MSC secretome by induction of protective cell fate programs. Our findings may imply novel preventive strategies against vascular complications in transplant recipients with PTDM.

V117 THE INTRA-ADRENAL ISLET TRANSPLANTATION MODEL. CONVERGENCE OF PANCREATIC ISLETS WITH ENDOCRINE "HELPER CELLS"

*U. Schubert[1], H. Morawietz[1], S.R. Bornstein[1], B. Ludwig[1]
[1]University Hospital Carl Gustav Carus, Dresden, Germany

For restoration of β-cell function in diabetic patients, intraportal islet transplantation has evolved into a viable treatment option. However, several factors hamper a long-term success.

The idea of the adrenal tissue as an alternative niche for pancreatic islets is derived from (1) the fact that both are endocrine tissues with similar microenvironment, (2) the unique feature of extensive vascularization of the adrenal, (3) anti-apoptotic and pro-proliferative effects of various signalling molecules, and (4) the local anti-inflammatory and immunosuppressive microenvironment.

For *in vitro* analysis of islet viability and function a co-culture system of adrenal cells and pancreatic islets was established. The co-culture setting did not significantly impact on islet viability, insulin content and secretion and there is evidence that oxidative stress is markedly reduced in the presence of adrenal cells.

For *in vivo* studies, Streptozotocin induced diabetic NOD-SCID mice were used as islet recipients. For islet transplantation 300 islets were injected through the upper pole of the gland. Animals showed a fast decrease in blood glucose levels within the first days after transplantation in both groups, at around 10 days the curves between adrenal and kidney site drifted apart in favor of the adrenal site. Regardless of the transplantation site, islets showed a well preserved morphology and intense insulin staining. The intra-adrenally engrafted islets show higher vascularization compared to the kidney capsule control.

To prove our concept in a more clinically relevant system we established a large animal model. Therefore diabetic minipigs were transplanted with porcine islets into the adrenal gland and in comparison into the right liver lobe. Six weeks after transplantation c-peptide was detectible in both groups. The intra-adrenally engrafted islets show better integration into adrenal tissue and higher vascularization compared to liver control where islets stuck in the vessels. Adrenal function was not affected analyzed by ACTH-test.

These studies provide new insights into microenvironmental parameters that may benefit islet engraftment and survival. The use of "helper" cells could provide a potent supplementary factor. With adrenal cells providing both immunomodulatory and neovascularization signals, the co-transplantation with islets, e.g. within encapsulating devices may prove to be highly beneficial.

LIVING DONATION II

V126 FOSTERING LIVING ORGAN DONATION: NEEDS AND SUGGESTIONS REPORTED BY LIVING KIDNEY DONORS

*K. Schieber[1], S. Gaag[1], K. Heller[2], K.-U. Eckardt[2], Y. Erim[1]
[1]Psychosomatische und Psychotherapeutische Abteilung, Universitätsklinikum Erlangen, Erlangen, Germany; [2]Nephrologie und Hypertensiologie, Universitätsklinikum Erlangen, Erlangen, Germany

Background: Living organ donation is becoming increasingly important due to a worldwide organ shortage and a rising number of patients listed for transplantation. However, in Germany the number of living kidney donors (LKD) decreases since 2011. In this study we examined LKDs' needs and suggestions in order to enhance the process of organ donation.
Methods: A number of 136 LKD (Females: 67%; age: M = 58.9, SD = 8.7) participated in our study and completed a self-report questionnaire assessing attitudes towards the donation (Eurotold). Organ donation was provided at the University Hospital of Erlangen in the period of 2003–2014.
Results: A total of 35.3% (n = 48) of LKD reported physical stress due to the donation, whereas in 22.8% (n = 31) organ donation caused emotional distress. Self-reported needs and suggestions included: recommendations for future donors (e.g. positive experiences, dealing with health assurance), requests for detailed medical information (e.g. about surgery, rejection, health risks), for professional aftercare (e.g. rehabilitation therapy) and an easy access to psychological support (before/after donation). Furthermore, donors suggested organizing meetings with previous donors.
Conclusion: Organ donation was mostly completed without any complications. However, the LKDs' suggestions indicate the need of an extended psychosocial support including psychological help, self-aid groups and rehabilitation therapy.

V127 A PROSPECTIVE STUDY ON QUALITY OF LIFE AND FATIGUE IN LIVING KIDNEY DONORS

*S. Kröncke[1], K.-H. Schulz[1], B. Nashan[2], M. Koch[2]
[1]Medizinische Psychologie & Universitäres Transplantations-Centrum, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [2]Hepatobiliäre Chirurgie und Transplantationschirurgie & Universitäres Transplantations-Centrum, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

Background: The question whether fatigue compromises quality of life (QOL) after living kidney donation (LKD) has not yet been addressed in a prospective study in Germany.
Methods: We prospectively evaluated QOL with the Short-Form 36-Item Health Survey (SF-36) and fatigue with the Multidimensional Fatigue Inventory (MFI-20) in 30 donors 1 year after LKD.
Results: The sample consisted of 73% female donors. Mean age at donation was 54.0 years (SD = 8.7). The majority of recipients were adults (87%); 53% were the donor's child and 40% spouse/partner. There was a significant QOL decrease in the SF-36 domain "vitality" (P = 0.04). While the preoperative score was superior to the general population, the postoperative score was similar to the general population. Regarding the MFI-20, there was a significant increase in "general fatigue" (P = 0.05) and a trend towards an increase in "physical fatigue" (P = 0.06), while "reduced activity" (P = 0.31), "reduced motivation" (P = 0.27), and "mental fatigue" (P = 0.45) were not different from preoperative scores. Preoperative fatigue in the affected scales was lower compared to the general population; postoperative fatigue was similar to the general population.
Conclusion: QOL 1 year after LKD was reduced primarily in the domain affected by general fatigue. The postoperative scores were within the range of the general population.