**O28 POST-CONDITIONING REDUCES RENAL WARM ISCHAEMIA-REPERFUSION INJURY IN AN EXPERIMENTAL LARGE ANIMAL MODEL**

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**Introduction:** Ischaemic conditioning, using short repeated sequences of intermittent ischaemia, is a novel strategy that may ameliorate ischaemia-reperfusion injury. The study aim was to assess the effects of direct and remote ischaemic conditioning in a porcine model of renal warm ischaemia-reperfusion injury.

**Method:** Pigs (45-50kg) underwent laparotomy and 60 minutes occlusion of the left renal pedicle. Animals were randomised into three groups; untreated controls (n=7); direct post-conditioning involving 6 x 15 second cycles of clamping then releasing the left renal artery, performed immediately following the 60 minutes ischaemia (n=6); or remote peri-conditioning involving 4 x 5 minute cycles of clamping then releasing the left common iliac artery, performed 20 minutes after renal pedicle clamping (n=7). Following left renal clamp release a right nephrectomy was performed and animals were recovered for 7 days.

**Result:** The direct post-conditioning group had lower area under the serum creatinine curve (1071±136 vs.1722±873µmol/L.day respectively; P=0.025) and peak creatinine levels (312±49 vs. 519±268µmol/L respectively; P=0.008) compared to control. There was a significant increase in serum levels of TNFα on day 1 in control animals but not in the conditioning groups (P=0.013). There was no difference in serum Endothelin-1, nitric oxide or superoxide dismutase levels between the groups although levels in the direct group were numerically lower. There was no mortality and no complications related to either conditioning technique.

**Conclusion:** In this in vivo large animal model direct renal artery ischaemic post-conditioning protected kidneys against warm ischaemic injury. This straightforward technique could readily be translated into clinical practice.

**Take-home message:** Ischaemic post-conditioning reduces injury in renal warm ischaemia. The technique could readily be translated into clinical practice in deceased donor transplant.

**O29 PERI-OPERATIVE GOAL-DIRECTED HAEODYNAMIC OPTIMISATION IMPROVES SHORT-TERM OUTCOMES FOLLOWING SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANTATION: A RANDOMISED CLINICAL TRIAL (NCT01619904)**

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**Introduction:** SPKT is high-risk surgery and is associated with significant peri-operative morbidity in patients with significant pre-existing co-morbidities. Protocolised, peri-operative supra-physiological optimisation (GDT) improves outcomes in high-risk individuals following major surgery. This study investigated the benefits of GDT following SPKT.

**Method:** Recipients were randomly allocated to either GDT or ST cohorts. The GDT cohort underwent peri-operative physiological optimisation, guided by lithium indicator dilution, to attain an indexed oxygen delivery of 600ml/min/m2. The ST cohort was managed according to current unit protocols.

**Result:** Thirty patients were randomised to each group (Mean age 39.96 ± 7.35 and 44.27 ± 6.83, male 13 (44.8%) and 21 (70.0%), mean BMI 25.02kg/m2 ± 3.43 and 25.39kg/m2 ± 2.91 and DBD 22 (73.3%) and 23 (76.7%) in the GDT and ST cohorts respectively). The GDT cohort (n= 29) had significantly lower critical care unit length of stays compared to the ST cohort (n= 30; 4 days (IQR 3- 5.5) and 8 days (IQR 6.0- 9.3) respectively, p<0.001, MWU). They also had shorter time to mobilisation (2.0 days (IQR 1.0- 3.0) and 4.0 days (IQR 3.0- 6.25) respectively; p<0.001, MWU) and shorter time to tolerating oral diet (5.0 days (IQR 4.0- 8.0) and 8.0 days (IQR 6.75- 10.0) respectively; p<0.001, MWU).

**Conclusion:** For the first time in a study investigating peri-operative supra-physiological optimisation in pancreas transplantation, we have demonstrated significantly improved short-term outcomes. This approach will allow more streamlined and focused management of these patients. GDT, Goal-directed therapy; MWU, Mann-Whitney U test; ST, Standard Therapy; SPKT, Simultaneous Pancreas and Kidney Transplantation
**Take-home message:**
Graft and patient survival following SPKT have plateaued while peri-operative morbidity continues to be significant. Supra-physiological peri-operative optimisation improves short-term outcomes following SPKT, suggesting more emphasis should now be given to enhancing physiological management.

**O30 A ROLE FOR HELMINTH PARASITES IN ACHIEVING IMMUNOLOGICAL TOLERANCE IN TRANSPLANTATION**
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**Introduction:** Helminth parasites currently infect more than one quarter of the global human population. It is now well established that their success as parasites is the result of active immunomodulation of the host immune response. Helminth-induced immunomodulation can be beneficial to the host, particularly by suppressing harmful allergic and autoimmune responses. Accordingly, we hypothesised that helminth secretions reduce the immune response to allograft transplantation and may offer a therapeutically tractable approach.

**Method:** To test this hypothesis, under Home Office Licence, C57BL/6 mice were implanted with subcutaneous minipumps delivering a continuous infusion of secreted products from the mouse intestinal parasite, Heligmosomoides polygyrus (equivalent to 7 µg of protein per day). Simultaneously, fully allogeneic skin grafts were performed from BALBc donors. Seven days later, lymphocytes were isolated from allograft draining lymph nodes and analysed by flow cytometry.

**Result:** Flow cytometric analysis reveals a 41.7% increase in the mean percentage of CD4+CD25+Foxp3+ regulatory T cells (of total CD4+ cells) in treated vs. untreated mice (p=0.0085). Treatment with parasite products also increased mean expression of the regulatory cell surface receptor, Programmed Cell Death 1 (PD-1), specifically in the effector CD4+T cell population, by 62.2% (p=0.03).

**Conclusion:** Our results demonstrate that helminth-derived products can powerfully induce regulatory immunological mechanisms in the presence of a fully-allogeneic transplant. This was achieved at physiological concentrations, similar to those experienced by millions of asymptomatic chronically-infected humans worldwide. Identification of specific immunomodulatory molecules secreted by helminth parasites may lead towards development of safe and effective novel therapeutic strategies.

**Take-home message:**
Helminth parasites have a direct evolutionary pressure to powerfully dampen human immune responses whilst causing minimal harm. We have identified synergistic mechanisms by which helminth products can protect against allograft rejection; this may form the basis for safe novel therapeutic options.

**O31 RECONDITIONING OF KIDNEYS AFTER INADEQUATE IN-SITU PERFUSION USING EX-VIVO NORMOTHERMIC PERFUSION**
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**Introduction:** Inadequate in-situ perfusion during organ retrieval is a significant problem in renal transplantation. Many of these kidneys are rejected for transplantation due to a high risk of additional ischaemic injury and microvasculature thrombosis. This study describes the resuscitation of discarded kidneys after inadequate in-situ perfusion using EVNP.

**Method:** Twenty-one human kidneys were retrieved but then deemed unsuitable for transplantation due to inadequate in-situ perfusion. After a period of static cold storage, kidneys were perfused for 60 minutes with an oxygenated red cell based solution at 36°C. Renal function was measured throughout perfusion and a visual assessment of each kidney made at the end of EVNP.

**Result:** Nineteen out of 21 kidneys (90%) were from DCD donors. The mean donor age was 55 ± 15.7y (range 31-77y) and warm ischaemic time 12.2 ± 2.2minutes. The mean cold ischaemic time was 24.7 ± 14.3h (range 7-71h). During EVNP, 3 kidneys had a poor renal blood flow (Mean 41.8 ± 17.6ml/min/100g) combined with a low urine output (7 ± 3ml). They appeared mottled and purple at the end of EVNP and were considered non-recoverable. The remaining 18 kidneys had a mean renal blood flow of 70.1 ± 28.0ml/min/100g and total urine output of 101 ± 72ml. These EVNP parameters were within the range of kidneys in a successful clinical series. On visual inspection they all appeared perfused and suitable for transplantation.

**Conclusion:** Kidneys declined due to inadequate in-situ perfusion may be reconditioned by
restoring circulation and function ex-vivo. EVNP Ex-vivo normothermic perfusion DCD Donation after Circulatory Death

**Take-home message:**
It is possible to recondition kidneys after inadequate in-situ perfusion using ex-vivo normothermic perfusion. This technique could reduce the number of discarded kidneys.

**O32 EFFECTS OF DIFFERING ISCHAEMIC INSULTS ON CHARACTERISTICS DURING EX-VIVO NORMOTHERMIC PERFUSION (EVNP) OF PORCINE PANCREASES**
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**Introduction:** Pancreas transplantation has a 25-50% incidence of severe complications, many of which are manifestations of graft pancreatitis resultant from ischaemia reperfusion injury (IRI). Despite this, little is known about the mechanisms of pancreatic IRI as an appropriate experimental model has been lacking. We therefore aimed to use EVNP to evaluate the effects of differing ischaemic insults on pancreas perfusion, injury and function in a porcine model.

**Method:** In the severe injury model (n=6), pigs were killed by electrocution and exsanguination, followed by rapid laparotomy, aortic cannulation, perfusion with cold preservation solution and pancreas retrieval. In the moderate injury model (n=5) laparotomy and aortic cannulation was performed under general anaesthesia and systemic heparinisation, followed by exsanguination and 10mins of in situ warm ischaemia before cold perfusion. The mild injury model (n=5) was similar, further lacking in situ warm ischaemia. Pancreases underwent 2h of EVNP using a warmed autologous whole blood-based solution.

**Result:** Cold ischaemia times were comparable in all groups (P=0.403). The severe injury model had significantly higher pancreatic blood flow (P=0.011), with higher plasma amylase (P<0.001) and lower plasma insulin levels in response to glucose challenge (P<0.05) compared to other groups. There was no difference in the mean percentage weight gain during EVNP (58% vs. 43% vs. 50%, P=0.5825)

**Conclusion:** Pancreases with severe ischaemic injury had the worst function and developed more significant pancreatitis, as measured by amylase. This study demonstrates the feasibility of EVNP to study pancreatic IRI and potentially evaluate the quality of pancreases prior to transplantation.

**Take-home message:**
Increases in ischaemia result in differing perfusion, injury and function during EVNP in a porcine model.

**O33 DOES CARDIAC RISK QUANTIFICATION HAVE A ROLE IN ASSESSMENT FOR PANCREAS TRANSPLANTATION?**
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**Introduction:** PT is the gold-standard treatment for complicated Insulin Dependent Diabetes Mellitus. Perceptions of high cardiac risk persist, causing exhaustive cardiac investigations before listing. However, this approach is unvalidated.

**Method:** Retrospective analysis was made of patients undergoing PT, examining cardiac assessment and transplant outcomes. Patients were categorised by MPS into NP, RI and PI groups. Primary endpoints were cardiac death, patient and graft survival. Secondary endpoints were HLoS, reoperations and complications.

**Result:** 314 PTs were performed (01/01-03/14), with 152 MPS results available. (60.1% male; mean age 43.8, 82.9% SPK, 12% PAK, PTA 5.1%). 109 MPS showed NP, 24 RI and 12 PI. There was no difference in graft and patient survival between groups (p=0.31, 0.33 (log rank test)). No significant difference was seen for HLoS (NP: 32.7; RI: 53.3 PI: 35.0), mean reoperation number (NP: 0.8, RI: 0.8; PI: 1.0) or complications (NP: 2.4, RI: 1.0, PI: 1.4) (p=0.45, 0.12, 0.89 (ANOVA)). Angiography was performed in 11.1%, 100% and 83.3% of patients in NP, RI and PI groups respectively since 2011 with no revascularisations. Cardiac causes accounted for 6.5% (n=2; NP: 1, RI: 1) of 31 deaths.

**Conclusion:** MPS poorly stratifies outcome prediction for cardiovascular mortality and angiography appears unnecessary, delaying listing time. Post-operative cardiac mortality is minimal compared to waiting list, suggesting requirement of expedited workup. HLoS – hospital
Pancreas transplant recipients are at high risk of cardiovascular disease, leading to exhaustive cardiac assessment prior to listing for transplant. Our study suggests that this process may not be beneficial in predicting cardiac mortality and causes unnecessary delays in timely access to transplantation.

**O34 A DOUBLE BLINDED RANDOMISED CONTROLLED TRIAL OF REMOTE ISCHAEMIC CONDITIONING IN LIVE DONOR RENAL TRANSPLANTATION**

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**Introduction:** RiC may reduce the effects of ischaemia reperfusion injury and improve initial graft function in renal transplantation. The aim of this study was to assess the effects of RiC in live donor kidney transplantation.

**Method:** Recipients of a live donor kidney transplant were randomised into either a control group (n = 40) or Remote Ischaemic Conditioning (RiC) (n = 40). RiC was performed by applying 4 cycles of 5 minutes ischaemia using a lower limb tourniquet prior to reperfusion. Serum creatinine and eGFR was measured up to 1 month post-transplant.

**Result:** Two patients were excluded in the control group due to complications during surgery. Donor and recipient age and gender were similar in both groups (P >0.50). There were no complications associated with the RiC procedure. Four patients had DGF in the control group (10.5%) compared to 0 in the RiC (P=0.052). The creatinine reduction ratio (CRR2) was <30% in 8 patients in the control group compared to 13 in the RiC (P=0.212). There was no significant difference in serum creatinine or eGFR levels up to 7 days post-transplant or at 1 month between the groups (Cr Day 7; control 151±120 vs RiC 136±40 µmol/L; P=0.250, eGFR control 54±21 vs RiC 51±16ml/min; P=0.636; Cr 1 month; control 128±39 vs RiC 133±35 µmol/L; P=0.575; eGFR control 53±14 vs RiC 53±16 ml/min; P=0.925).

**Conclusion:** RiC did not improve early graft function in recipients of a live donor kidney transplant. Further studies are needed to assess the effects of different conditioning strategies in renal transplantation. RiC Remote Ischaemic Conditioning DGF Delayed graft function

**Take-home message:** Remote conditioning did not improve early graft function in recipients of a live donor kidney transplant.

**O35 DIVERSITY OF THE TAPASIN KNOCK-OUT MICE T CELL REPERTOIRE**

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Efficient priming and activation of specific CD8+ T cells relies on the interaction between their TCRs and stable peptide-MHC I (pMHC) complexes. Selection of stable peptides to be loaded on MHC I molecules occurs in the ER in a process assisted by tapasin, a chaperone bound to MHC I in the peptide loading complex. In the absence of tapasin, pMHC surface expression is reduced due to a lower overall stability and a different peptide hierarchy is presented, leading to a different CD8+ T cell response hierarchy. Lower pMHC surface expression also impairs thymic selection with CD8+ T cell numbers reduced 4 to 5 fold. The effect on the T cell repertoire diversity and on the immunodominance hierarchy is unknown. We investigated the T cell repertoire diversity of tapasin knock-out (Tpn KO) mice, and compared it to wild-type (wt) C57BL/6 mice, by assessing the diversity of TCR Vbeta distribution. The overall distribution of Vbeta families within the CD8+ T cell population was very similar between naive wt and Tpn KO mice and the CD8+ T cell response against model epitopes (vaccinia B8R 20-27 and LCMV gp276-286) was as diverse in Tpn KO mice than in wt mice. We are currently investigating by tetramer pulldown assays how the Tpn KO naive T cell precursor frequencies for specific epitopes have been affected by the impaired thymic selection and how this could influence the CD8+ T cell response hierarchy.

**Take-home message:** The CD8+ T cell response against model epitopes was as found to be as diverse in Tapasin knockout mice as in wild type mice.

**O36 EX-VIVO NORMOTHERMIC PERFUSION OF THE PORCINE SMALL BOWEL: A PROMISING EXPERIMENTAL MODEL**
**Introduction:** Ex-vivo normothermic perfusion (EVNP) provides an opportunity to study isolated organs under controlled conditions. We aimed to establish the first model of porcine small bowel EVNP and assess its suitability for the study of gut physiology, ischaemia-reperfusion injury (IRI) and therapeutic interventions in the context of transplantation. Study design Anaesthetised young adult (50-60kg) white pigs were used. The distal aorta was cannulated after laparotomy and systemic heparinisation, and blood was collected upon exsanguination. Following asystole and in situ perfusion with cold preservation solution, segments of proximal to mid-ileum (1.5-2.8m) were removed with intact vascular arcades. The small bowel was placed on an EVNP circuit after a median cold ischaemia of 5h30mins and perfused for 2h with warm re-oxygenated autologous blood. A 20% glucose solution was infused intra-luminally after 1h and plasma samples collected to investigate absorptive and secretory function. Pilot data All bowel segments (n=5) appeared well perfused and demonstrated peristalsis. The mucosa appeared healthy and non-haemorrhagic. Venous glucose levels increased from 1.5±0.79 to 18.6±11.88 mmol/L following luminal glucose administration. Blood flow was 69±40ml/min (range 48.4-128.8ml/min) at a perfusion pressure of 80mmHg and Glucagon-like peptide-1 was detected in the circulation. Forward plans This is the first report of EVNP of a small bowel segment in a large animal model, demonstrating that the viability, absorptive and secretory function can be maintained ex vivo. The model allows future study of small bowel physiology (e.g. hormone production) and investigation of mechanisms and therapeutic interventions against IRI (e.g. leucocyte depletion and drug treatment).

**Take-home message:**
Small bowel EVNP is a promising experimental model for the study of physiology and ischaemia reperfusion injury.

**O37 EX VIVO NORMOTHERMIC PERFUSION OF DISCARDED HUMAN DONOR PANCREASES**

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**Introduction:** Around 50% of pancreases retrieved for transplantation are deemed unsuitable and are discarded due to concerns about graft quality and the associated risk of complications. This decision is subjective and some declined grafts may be suitable for transplantation. Ex vivo normothermic perfusion (EVNP) prior to transplantation may allow a more objective assessment of graft quality and reduce discard rates. Study design Human pancreases retrieved but declined for transplantation underwent EVNP with ABO-compatible warm oxygenated packed red blood cells for 1-3 hours. Pilot data Four declined human pancreases were assessed using EVNP after a median cold ischaemia time of 13h19mins. Pancreas 1, declined due to retrieval injury, was from a 27-yr old donation after brain death (DBD) donor (BMI 20) and had the highest blood flow and basal and stimulated insulin secretion during EVNP. Pancreas 2 (fatty infiltration; BMI 24), was from a 51-yr old donation after circulatory death (DCD) donor and had the lowest insulin secretion. Pancreas 4 (fatty infiltration; BMI 19) was from a 46-yr old DBD donor and had markedly higher amylase levels than others. Pancreas 3 from a 14-yr old DCD donor after brain death (DBD) donor (BMI 20) and had the highest blood flow and basal and stimulated insulin secretion during EVNP. Pancreas 2 (fatty infiltration; BMI 24), was from a 51-yr old donation after circulatory death (DCD) donor and had the lowest insulin secretion. Pancreas 4 (fatty infiltration; BMI 19) was from a 46-yr old DBD donor and had markedly higher amylase levels than others. Pancreas 3 from a 14-yr old DCD donor with duodenal trauma had intermediate insulin and amylase levels. Forward plans This is the first study to assess the perfusion, injury, as measured by amylase, and exocrine function of human pancreases using EVNP and demonstrates the feasibility of the approach. Further experiments are planned to investigate influence of donor type, age, BMI and cold ischaemic times on pancreatic function and injury.

**Take-home message:**
EVNP can feasibly be used to assess perfusion, injury and function of discarded human pancreases and may allow quality assessment of grafts prior to transplantation.

**O38 THE TEMPORAL EVOLUTION OF INFLAMMATORY AND DIABETES BIOMARKERS FOLLOWING SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANTATION (NCT01619904)**

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Background: The evolution of biomarkers in sepsis and following major surgery has been delineated. Patients undergoing SPKT suffer with a significant systemic inflammatory response. However, the biomarker profile is not defined, despite the detrimental effects of pro-inflammatory cytokines on islet cell function. This study determined the expression of biomarkers in the peri-operative period following SPKT and establish a correlation to clinical outcome.

Method: The temporal patterns of pro- and anti-inflammatory cytokines (interleukin (IL)-6, 10 and TNF-α), inflammatory markers (WCC and CRP) and diabetes markers (insulin, C-peptide, glucagon and resistin) were serially measured at 8 time-points in the first 72 hours post-SPKT.

Result: 46 patients were recruited to the study (November 2011- March 2014). Patterns of expression of biomarkers were delineated. Levels of C-peptide, insulin and glucagon raised significantly 30 minutes post-pancreas perfusion. Levels were significantly related to prolonged CIT (p < 0.05, linear regression model). Levels of IL-6 and IL-10 significantly peaked at 30 minutes and six hours respectively (p < 0.05, ANOVA). CRP levels rose rapidly in the post-operative period and correlated significantly with POMS (p < 0.05, Spearman Correlation).

Conclusion: This paper introduces evidence for the potential use of targeted anti-inflammatory therapies to minimise islet cell damage and improve peri-operative graft function. The delineation of diabetes marker patterns and their correlation to CIT may also have ultimate utility in defining the concept of delayed graft function in pancreas transplantation. ANOVA, Analysis of Variance; CIT, cold ischaemic time; CRP, C-reactive protein; IL, Interleukin; POMS, Post-Operative Morbidity Survey; SPKT, Simultaneous pancreas and kidney transplantation; WCC, White Cell Count

Take-home message: This study delineates the temporal evolution of inflammatory and diabetes markers following SPKT. We identify that expression of diabetes markers in the peri-operative period is related to CIT, that levels of pro-inflammatory cytokines are significantly raised at the time of pancreas allograft re-perfusion and that CRP is a predictor of early post-operative morbidity following SPKT.

O39 HYDROGEN SULPHIDE AS A NOVEL THERAPY TO REDUCE THE NEPHROTOXIC EFFECTS OF CALCINEURIN INHIBITORS
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Background: Calcineurin inhibitors have significant nephrotoxic side effects which can exacerbate ischaemia reperfusion injury in renal transplantation. Novel therapeutic agents such as H2S may reduce these harmful effects. This study investigated the effects of H2S on cyclosporine induced nephrotoxicity.

Method: Porcine kidneys were subjected to 15 minutes of warm ischaemia and 2 hours of static cold storage. They were reperfused for 3 hours with oxygenated normothermic autologous whole blood on an isolated organ reperfusion apparatus. Kidneys were treated with cyclosporine during reperfusion (N=6) or cyclosporine and 0.25 millimoles/litre of hydrogen sulphide (CsA+H2S) infused 10 minutes before and 20 minutes after reperfusion (N=6). These were compared with untreated controls (N=7).

Result: Cyclosporine caused a significant reduction in RBF during reperfusion which was reversed by H2S [AUC RBF CsA 257±93 vs. Control 477±206 vs. CsA+H2S 478±271ml/min/100g.h;P=0.024]. Urine output was higher after 2 hours of reperfusion in the CsA+H2S group (CsA+H2S 305±218 vs. CsA 78±180 vs. control 210±45ml;P=0.034). Cyclosporine treatment was associated with an increase in tubular injury which was not reversed by H2S [AUC Fractional excretion of sodium, control 77±53 vs. CsA 100±61 vs. CsA+H2S 111±57%;h;P=0.003]. Histological evaluation showed significant vacuolation and glomerular shrinkage the in CsA group. These were significantly reduced by H2S (P=0.005, 0.002).

Conclusion: H2S reversed the vasoconstriction and ischaemic changes associated with cyclosporine treatment during reperfusion. H2S has promise as a therapy to mitigate some of the nephrotoxic effects associated with calcineurin inhibitors in renal transplantation. H2S hydrogen sulphide. CsA cyclosporine. AUC area under the curve. RBF renal blood flow.

Take-home message: Hydrogen sulphide has shown promise in this study as a therapy to mitigate some of the nephrotoxic effects associated with calcineurin inhibitors in renal transplantation.