



## Preventive GC7 reduces brain death-induce renal injuries in a preclinical porcine model

S. Giraud, T. Kerforne, Philippine Couturier, S. Inal, P. Hannaert, M. Tauc, T. Hauet

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## O16 USE OF HYPOTHERMIC MACHINE PERFUSION FOR LIVING DONORS' KIDNEYS

J. Malaise, M. Beaunoyer, M. Lallier, A. Barama, A. Duclos, P. Daloze  
Département de Chirurgie, Université de Montréal, Montréal, Canada

**Introduction:** Hypothermic machine perfusion (MP) has been widely studied in deceased donor kidneys and has been shown to improve kidney graft preservation. Paired exchange programs create a need for donors or kidneys to travel. As some adverse experience occurs, we explore the use of MP using the universal cannula for a short renal artery without an aortic patch.

**Methods:** From November 2013, 49 kidneys from living donor underwent MP using Belzer's machine perfusion solution. Nine kidneys travelled to a pediatric transplantation center. All kidneys were retrieved by laparoscopic nephrectomy. A Gel-sealed hand-assist access device permitted rapid extraction of the graft.

**Results:** The mean first ischemic time was 2 min. No delayed graft function or primary nonfunction occurred, and there was no graft loss or patient death. At the start of MP, mean renovascular resistance (RR) was  $0.93 \pm 0.59$  (SD) mmHg/mL/min, mean perfusion flow (PF) was  $39 \pm 44$  mL/min and mean temperature was  $7.4 \pm 0.8^\circ\text{C}$ . Mean pump time was 2 h 25 min  $\pm$  38 min. At the end of machine perfusion, mean RR was  $0.28 \pm 0.13$  mmHg/mL/min, mean PF was  $98 \pm 52$  mL/min and mean temperature was  $6.0 \pm 0.8^\circ\text{C}$ .

In several grafts, very high renovascular resistances were noted, which is unexpected in living donation. No pre- or intraoperative conditions could explain this phenomenon.

**Conclusions:** As renovascular resistance at the start of MP was independently associated with primary nonfunction of kidneys retrieved after cardiac death, high values were unexpected for living donor kidneys. The results probably reflect the impact of warm ischemia on the graft. Especially in pediatric kidney transplantation, high renovascular resistance may have a deleterious effect that MP may prevent.

## O17 IL-33 CONTRIBUTES TO KIDNEY ISCHEMIA-REPERFUSION-INDUCED INJURY IN MICE

M. Ferhat<sup>3,2</sup>, A. Robin<sup>3,1</sup>, S. Giraud<sup>3,1</sup>, J.M. Goujon<sup>6,2,3</sup>, T. Hauet<sup>3,5,2</sup>, J.M. Gombert<sup>4,2,3</sup>, A. Thierry<sup>7,2,3</sup>, A. Herbelin<sup>3,1</sup>

<sup>1</sup>CHU de Poitiers; <sup>2</sup>Faculté de Médecine et de Pharmacie, Université de Poitiers; <sup>3</sup>IRTO MIT INSERM U1082, Poitiers; <sup>4</sup>Laboratoire d'Immunologie, CHU de Poitiers; <sup>5</sup>Laboratoire de Biochimie, CHU de Poitiers; <sup>6</sup>Service d'anato-mo-pathologie, CHU de Poitiers; <sup>7</sup>Service de Néphrologie-Hémodialyse-Transplantation rénale, CHU de Poitiers, Poitiers, France

**Introduction:** Ischemia-reperfusion injury (IRI) is a major cause of acute kidney injury (AKI) which is characterized by leukocyte infiltration and renal tubular injury. We hypothesized that alarmin release by necrotic cells during IRI contributes to tissue damage leading to renal failure. In this study, our objective was to investigate the involvement of the alarmin/cytokine IL-33 in the pathogenesis of renal IRI.

**Methods:** Ten-to-twelve week-old wild-type (WT) and IL-33-deficient (IL-33<sup>Gt/Gt</sup>) male C57BL/6 mice were subjected to 32 min of unilateral kidney ischemia or a Sham operation. After reperfusion, blood samples were collected and kidneys were harvested to assess kidney function, IL-33 levels by ELISA, leukocyte infiltration by flow cytometry, IL-33 expression by western blot, RTqPCR and immunofluorescence staining.

**Results:** At steady state, IL-33, which was expressed in the nucleus of peritubular cells, was released from WT kidney tissue shortly after IR. Its local loss was revealed by immunofluorescence staining and confirmed by western-blot, as was a concomitant increase in IL-33 plasma levels. Moreover, transcripts of IL-33 were upregulated in the WT kidney 6 h post-IR. IL-33<sup>Gt/Gt</sup> mice were less sensitive to kidney damage following IR than their WT counterparts, as attested by both lower creatinine levels and tissue damage. From a mechanistic standpoint, our findings are consistent with the hypothesis of a key role of IL-33 in the recruitment of NKT cells and of neutrophils which are known for their deleterious effect during IR. Indeed, the decreased susceptibility of IL-33<sup>Gt/Gt</sup> mice to kidney damage was associated with the loss of recruitment of NKT cells and an attenuated neutrophil infiltrate. Remarkably, *HIF1 $\alpha$*  was upregulated after IR in WT mice but not in IL-33<sup>Gt/Gt</sup> mice, thereby suggesting an *HIF1 $\alpha$* /IL-33 regulatory circuit.

**Conclusion:** This study underlines a possible new role of IL-33 as an innate-immune mediator during kidney IR injury.

## O18 PREVENTIVE GC7 REDUCES BRAIN DEATH-INDUCED RENAL INJURIES IN A PRECLINICAL PORCINE MODEL

S. Giraud<sup>6,3,7</sup>, T. Kerforné<sup>6,2,7</sup>, P. Couturier<sup>6,3,8</sup>, S. Inal<sup>3,5,6</sup>, P. Hannaert<sup>6,4,7</sup>, M. Tauc<sup>1</sup>, T. Hauet<sup>6,3,7,8,5</sup>

<sup>1</sup>Université de Nice-Sophia Antipolis, LP2M, CNRS-7370, Nice; <sup>2</sup>CHU de Poitiers, Département d'Anesthésie-Réanimation; <sup>3</sup>CHU de Poitiers, Service de Biochimie; <sup>4</sup>CNRS; <sup>5</sup>FHU SUPORT; <sup>6</sup>INSERM U1082; <sup>7</sup>Université de Poitiers, Faculté de médecine et pharmacie, Poitiers; <sup>8</sup>Plateforme Labellisée IBiSA MOPICT GenESI INRA, Surgères, France

**Introduction:** N1-guanyl-1,7-diaminoheptane (GC7), an inhibitor of eIF5A, exhibits anti-inflammatory features and promotes anoxic/ischemic tolerance. Thus, GC7 pretreatment could be useful in order to protect organs submitted to ischemia before transplantation in heart-beating donors.

**Methods:** Using a pig brain death donation preclinical model, we carried out the *in vivo* evaluation of GC7 pre-treatment (3 mg/kg iv bolus), after brain death, at the beginning of the 4 h-reanimation, after which one kidney was collected, cold-stored (18-h in UW), and allo-transplanted in a double-nephrectomized recipient. Groups were defined as follows (n = 6 per group): healthy (Control), untreated Brain death (BD) and GC7-treated BD (GC7).

**Results: R1.** At the end of 4 h-reanimation, GC7 decreased (80–100%,  $p < 0.05$ ) BD-increased markers: (i) eIF5A hypusination, (ii) tissue levels of reactive oxygen species markers (CellRox staining and Aconitase), (iii) tissue levels of nitrotyrosine, and (iv) the mitochondrial-dependent apoptosis pathway (Bax/Bcl-2 proapoptotic ratio, Caspase-9). In addition, GC7 increased (2 to 6-fold,  $p < 0.05$ ) the expression of anti-oxidant proteins (SOD2 and HO-1, as well as PGC-1 $\alpha$ , Nrf2, and total & p-Sirtuin1 & 3). **R2.** At the end of cold storage, GC7 treatment normalized BD-dependent decrease of SOD2 and HO-1 proteins expression ( $p < 0.05$ ). In addition, GC7 significantly restored the BD-dependent increase of the Bax/Bcl-2 (proapoptotic) ratio ( $p < 0.05$ ).

**Conclusion:** After the reanimation phase, preventively given GC7 proved protective for kidneys against brain death-induced injuries; during the cold storage phase, GC7 appeared to preserve antioxidant defences and to protect mitochondria. Early and long-term, post-transplantation propagation of observed protective effects are currently evaluated.

## O19 LONG TERM OUTCOME IN PEDIATRIC RENAL TRANSPLANT: A SINGLE-CENTER EXPERIENCE

S. Dorent-Marcelino, M. Tsimaratos, F. Garaix

Service de Pédiatrie Multidisciplinaire, CHU Timone Enfants, Marseille, France

**Introduction:** Kidney transplantation is the treatment of end stage renal failure in children (IRCT). The current problem of the IRCT is not patient survival but the quality of life of transplant recipients. One of the challenges of pediatric renal transplantation is also to study long-term outcome after of transplants. Few studies report more than 20 years of follow-up. In this context, we analyzed the evolution of pediatric renal transplants performed in our single center (CHU Timone-Enfants).

**Methods:** We analyzed 146 pediatric renal transplantations performed between 1974 and 2013. We compared the cohort before 1994 (group 1, 42 grafts), to the 1994–2003 one (group 2, 45 grafts) and the 2004–2013 one (group 3, 59 grafts). Patient survival and graft survival at 1, 5, 10, 15 and 20 years were studied and the characteristics of the rejection, the occurrence of lymphomas and education and social outcome.

**Results:** The patient survival is at 1, 5, 10 and 20 years of 96%, 93.8%, 91.8% and 90%. No deaths found in group 3. The patient survival is significantly different between group 1 and group 2 and 3. The graft survival is at 1, 5, 10, 15 and 20 years of 90.7%, 80.1%, 70.2%, 64.8% and 56.7%. The graft survival is at 1 year in group 1, 2 and 3 respectively of 83%, 91% and 95% and at 5 years respectively of 61.6%, 86.7% et 86%. 44% of grafts will experience at least one rejection. Six lymphomas (4%) are observed. 67% of children in groups 2 and 3 have a normal education. 61% of adults late in the monitoring of groups 2 and 3 have a employment or training.

**Conclusion:** The long-term outcome of our cohort is well compared to what is described in the literature. Nevertheless, improving graft survival remains very long term a challenge.

## O20 IMPACT OF THE TRANSITION CONSULTATION IN RENAL TRANSPLANTATION

J. Perrin<sup>2</sup>, S. Burtay<sup>1</sup>, S. Gentile<sup>1,2</sup>, F. Garaix<sup>1,2</sup>, M. Tsimaratos<sup>1,2</sup>

<sup>1</sup>CHU Conception; <sup>2</sup>CHU Timone, Marseille, France

**Introduction:** Kidney transplantation is the treatment of choice for end stage renal disease. 80% of transplanted children reach adulthood with a functioning graft. Since therapeutic adherence and therefore renal graft survival are altered during adolescence, the transfer of these patients in adult care carries an increased risk of graft dysfunction. The transfer is defined as moment of switch from paediatrician to the adult medicine specialist. The transition is a program designed to prepare patients to transfer.