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P164 -Murine models of renal ischaemia reperfusion injury: An opportunity for refinement using non-invasive monitoring methods

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Introduction

Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD) can be caused by Renal Ischaemia Reperfusion Injury (R-IRI) and result in significant morbidity and mortality. In order to perform pre-clinical testing of potential therapies, reproducible small-animal models of AKI and CKD are necessary.

Classical physiological parameters of renal function have been shown to be problematic due to frequent low correlation with histopathological assessments. We have started to apply non-invasive measures for monitoring of kidney function, by use of a transcutaneous device which allows repeated measurements of renal clearance of a freely filtered substance (FITC-sinistrin) to determine the glomerular filtration rate (GFR). In addition, we have implemented the use of multi-spectral optoacoustic tomography to monitor the clearance rate in individual kidneys. By combining these two powerful approaches with the RIFLE classification we have established refined models of AKI and CKD by R-IRI.

Methods

Male BALB/c mice underwent bilateral renal pedicle clamping (AKI) or unilateral renal pedicle clamping with delayed contralateral nephrectomy (CKD) under isoflurane anaesthetic. Transcutaneous GFR monitoring and multi-spectral optoacoustic tomography (MSOT), in addition to serum biomarkers and renal histopathology, were used to identify and standardise variables within these models.

Results

Transcutaneous GFR measurements allowed us to determine in the AKI model that total and pre-clamping anaesthetic time were the most important predictors of severity after R-IRI. We found that standardising pre-clamping anaesthetic time to 30 mins resulted in a more predictable AKI model.

By combining MSOT monitoring of renal clearance with transcutaneous GFR measurements we established a survivable CKD model. The contralateral nephrectomy was performed on day 14 when the injured kidney is functioning optimally, which still led to a persistent reduction in the GFR and increasing collagen deposition until the end point at day 42.

Discussion

We demonstrate here that non-invasive monitoring of global (transcutaneous GFR) and individual (MSOT monitoring) renal function after R-IRI is feasible, reproducible and correlates well with classical markers of renal injury. This facilitates refinement of kidney injury models and enables the degree of injury seen in pre-clinical models to be translated to those seen in the clinical setting. Thus, future therapies can be tested in a clinically relevant manner.