

University of Groningen

Early effects of brain death on kidney injury and outcome after transplantation

Nijboer, Wijmtje Nikeline

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:
2010

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Nijboer, W. N. (2010). *Early effects of brain death on kidney injury and outcome after transplantation*. s.n.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

CHAPTER



RATIONALE

- RATIONALE -

The unphysiologic state of donor brain death (DBD) is a risk factor for donor kidneys used in transplantation. Even totally mismatched living-unrelated grafts have better survival outcomes than kidneys retrieved from DBD donors with a very reasonable HLA match. Brain death has been known to affect the circulatory and hormonal state of the donor. In this thesis, we have focused on the progressive pro-inflammatory response to brain death in the kidney and tried to characterize these effects prior to transplantation. The **Introduction** of this thesis describes the current knowledge and concepts regarding the nature of brain death and its effects on organ quality. Irreversible cerebral injury leading to brain death is usually the result of intracranial hemorrhage or traumatic brain injury. A mass effect in the brain leads to a herniation of the brain stem with loss of stem reflexes and respiratory arrest. Shortly after brain death, high levels of proinflammatory cytokines can be detected in the peripheral blood of the donor. In most peripheral organs (heart, lung, liver and kidney), aspects of an ongoing inflammatory response can be detected. On the other hand, an upregulation of protective proteins can be found in brain death. Microarray analysis is a powerful tool to study this response in more detail.

In **Chapter 3**, we focus on the kidney to study the effects of BD on inflammatory response and stress-related heat shock proteins at organ level. We obtained kidney biopsy specimens and serum during organ retrieval from BD and living organ donor controls. With these biopsy specimens immunohistochemistry and semiquantitative reverse transcriptase-polymerase chain reaction were performed. These data, as well as clinical and laboratory parameters from BD donors were recorded and related to outcome data of recipients of those kidneys.

Many BD donors have a higher endotoxin load and more bacterial translocation from the gut compared to living donors. This endotoxemia might trigger a decrease in vascular integrity leading to increased permeability of the intestine by influencing the Angiotensin-Tie ligand-receptor system, which could also lead to the increased inflammatory response seen in peripheral organs. A decreased Angiotensin 1/Angiotensin 2 ratio is associated with increased morbidity and mortality during sepsis, while an increased ratio can maintain vascular integrity and dampen the inflammatory response. This ratio was studied in donor serum in **Chapter 4**, as well as the amount of Lipopolysaccharide Binding Protein (LBP) as a quantification of endotoxemia. As Ang-2 primes endothelium to respond to VEGF, these levels were also studied in serum. Serum levels were related to clinical transplant outcomes.

Whether or not duration of brain death is a factor in organ quality is uncertain. Leakage of detrimental substances from the brain into the circulation of BD donors and the rise in cytokine and chemokine expression in their organs during brain death suggests that early organ retrieval in BD donors is beneficial. On the other hand, the expression of protective

heat shock proteins could be seen as a mechanism by which the body tries to repair present damage. Scarce data suggests that a longer BD period might actually be better for donor organ quality. In **Chapter 5** of this thesis, we report a large retrospective analysis using data from the OPTN database that analyzes the effects of duration of brain death (BDdur) on outcome after kidney transplantation. 20,773 kidney donor and recipient couple data were studied. In this chapter, BDdur was calculated as the period between declaration of brain death and aortic cross clamping. We calculated the effect of BDdur on delayed graft function (DGF), acute rejection and one- and three-year graft survival using binary logistic regression and Cox regression models.

The prediction of organ quality at an early time point, i.e. during donor evaluation and management, is still difficult, although donor treatment and evaluation during brain death would offer a great time frame for improvement of both allocation algorithms and the donor organ itself. Therefore, in **Chapter 6** we have tested several interesting novel urine markers to discover kidney specific injury at an early stage. We evaluated urinary levels of lactate dehydrogenase (LDH), kidney injury molecule-1 (KIM-1), heart-type fatty acid binding proteins (H-FABP), alanine aminopeptidase (AAP), malondialdehyde (MDA), N-acetyl- β -D-glucosaminidase (NAG) and interleukin-18 (IL-18). These markers were compared to urinary creatinine and urinary protein as classic parameters of kidney function. Two different populations were studied: urine samples were collected from 40 kidney donors during donation, and another set from 29 transplant recipients during the first 10 days after kidney transplantation. Biomarker levels were related to delayed graft function, acute rejection and kidney function up to one year after transplantation using regression analyses.

As KIM-1 apparently has a high sensitivity for kidney injury, and is upregulated early during kidney injury, we studied this molecule in more detail in **Chapter 7**. We evaluated Kim-1 expression using real-time PCR, in situ hybridization, immunohistochemistry and a Luminex assay in a standardised rat brain death model. In this standardized model, brain death is induced by intracranial balloon inflation. Sham operated animals were compared to animals that had been brain dead for 0.5, 1, 2 or 4h. Results were confirmed in human DBD donors and linked to transplantation outcome parameters.

Ultimately, our goal is to intervene during brain death, aiming at a better balance between injury and repair, hopefully resulting in better graft survival and transplantation. In **Chapter 8**, we study the administration of (carbamylated) erythropoietin in brain death in a rat model. In this experiment we used our standardised brain death animal model and after organ retrieval we evaluated kidney function with the Isolated Perfused Kidney (IPK) model. We tested the administration of EPO, carbamylated EPO (cEPO, which is a modified molecule without the erythropoietic properties of EPO), or a vehicle, and compared these groups with sham operated animals.

