



Dopamine induces Hemoxygenase-1 in kidneys of brain dead donors



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Introduction

Chronic rejection remains the most common reason for late transplant loss. With identical HLA-match the long term survival of kidneys from living donors is far superior to cadaveric organs. Besides time of ischemia, brain death itself is widely discussed as an non-allo-antigen-dependent factor for the development of chronic transplant failure.

In a retrospective clinical study performed with data from Euro-Transplant, we were able to demonstrate significant improvement of long term transplant survival when the brain-dead organ donor was treated with dopamine. Reasons for this observation are not understood yet; literature research leads to contradictive data regarding the influence of catecholamines on transplant prognosis.

Therefore our study aims on the investigation of mechanisms of alterations in kidney tissue after dopamine administration, which may be responsible for an improvement of transplant survival. The study was performed in a brain-death model in rats.

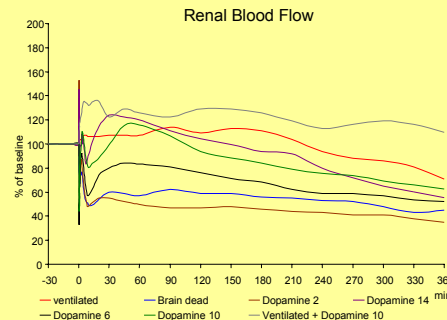
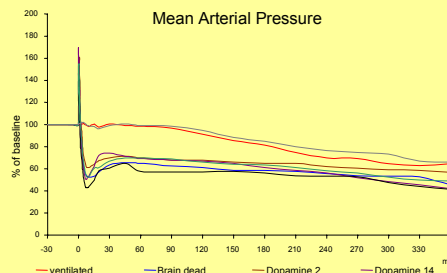
Methods

Brain death was induced in male F344-Fisher rats and verified by EEG monitoring. The animals were ventilated over 6 hours and monitored regarding their hemodynamic and respiratory status. Subjects were excluded when they showed signs of instable hematocrit or hypoventilation.

Groups of 5 animals were treated with 2, 6, 10, or 14 $\mu\text{g} / \text{kg} / \text{min}$ respectively. Identically treated non-brain dead animals served as controls. After 6 hours kidneys were harvested and cryo-conserved. Using the ABC-method an immune histological evaluation regarding the macrophage / monocyte infiltration (ED 1) was performed on 6 μm cryo slides. Hemoxygenase-1 (HO-1), an endogenous anti-oxidant, was detected using western blot. After extraction of the protein fraction from kidney tissue, 30 μg were analyzed on a 10% SDS-PAGE-Gel and transferred to a PVDF membrane with the semidry-blot-method. Hemoxygenase antibodies were visualized in a chemiluminescence procedure.

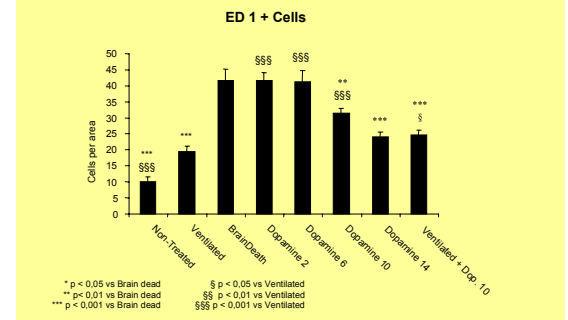
Results

Hemodynamics



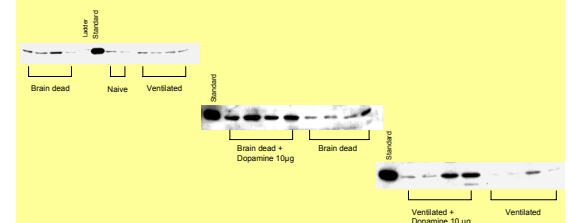
Immunohistology

Kidneys of brain dead animals were characterized by an augmented monocyte / macrophage infiltration. This infiltration could be inhibited with dopamine, more effective applying higher doses. In contrast infiltration was promoted by dopamine treatment in non-brain dead animals. (statistics: ANOVA)



Western-Blot

Hemoxygenase-1, an endogenous anti-oxidant, is induced by oxydative stress and serves cytoprotective means. Dopamine administration lead to raised Hemoxygenase-1 induction, while this effect was hardly noticeable in controls.



Summary

Dopamine administration to brain dead donors preceding transplantation leads to a reduction of monocyte / macrophage infiltration as well as an induction of hemoxygenases-1 in kidneys independently from systemic hemodynamic effects.

Effectiveness of dopamine in brain dead organ donors may be explained by a reduced transplant immunogenicity and an elevated tolerance towards oxidative stress.