URINARY MARKERS OF RENAL CELL APOPTOSIS ARE ELEVATED WITH EXOGENOUS NOREPINEPHRINE

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Background: Acute renal failure (ARF) is the leading cause of mortality and morbidity during the perioperative period and in the ICU (1). Renal cell apoptosis contributes significantly to the pathogenesis of ARF (2). Previous laboratory studies demonstrated that chronic exposure to catecholamines (e.g. norepinephrine (NE) and epinephrine) caused apoptosis in cardiac myocytes and alveolar epithelium (3). During the perioperative period and in the ICU, exogenous NE infusion is common. We hypothesized that the cells collected from urine of patients receiving NE would show increased molecular markers of apoptosis. We also hypothesized that the apoptotic markers can be detected before these patients manifest signs of renal injury, such as elevated serum creatinine (Cr) and Cr clearance.

Methods: After obtaining IRB approval, two groups of patients were enrolled in the study. One group received NE infusion for 3 days and control group did not. Controls were matched for hemodynamic parameters (MAP, HR), age, sex and postoperative days. Patients with pre-existing renal impairment were excluded from the study. Fresh urine samples were collected daily for 3 days to measure Cr clearance and plasma Cr. Urine collected on the third day of NE infusion were centrifuged and RNA from sedimented cells isolated for semi-quantitative reverse transcriptase polymerase reaction (RT-PCR) analyses of proapoptotic genes (Caspases 3, 8, 9 and bax) and a house keeping gene (GAPDH).

Results: Cells collected from patients receiving NE (N=5) displayed significantly increased expression of pro-apoptotic mRNA for caspase 3 ($380\pm100\%$ of control, $p<0.05$), caspase 8 ($370\pm100\%$ of control, $p<0.05$), caspase 9 ($250\pm30\%$ of control, $p<0.05$) and bax ($220\pm50\%$ of control, $p<0.05$) compared to cells collected from the control group. Neither NE nor control group patients had increases in plasma Cr or decreases in Cr clearance during the 3 day period.

Conclusion: Cells collected from patients treated for 3 days with NE showed increased expression of pro-apoptotic genes which occurred before changes in routine markers of renal function. Our preliminary data will lead to a future prospective study to include more patients with longer follow-up period. We aim to determine whether changes in molecular markers of renal dysfunction (e.g., pro-apoptotic genes) predict changes in routine markers of renal function.

References

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