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Post-Transplant Hypotension in Kidney Recipients—Vasopressin to the Rescue?

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Kidney transplantation confers the highest survival benefit to patients with end-stage kidney disease. Allograft injury at the time of transplantation has a major impact on both short- and long-term graft functions. The denervated kidney allograft impairs the hemodynamic response to sympathomimetics and defense against extracellular fluid volume depletion.[1,2] It is not surprising, therefore, that hypotension in the perioperative period has been associated with higher rates of delayed graft function (DGF). In a single-center analysis of 106 deceased donor recipients, the odds ratio for slow graft function was 1.51 (95% CI: 1.15–1.99) for every 5 mm Hg reduction in mean arterial pressure (MAP).[S1] In a study of 20 cases of primary nonfunction of the transplanted kidney matched to 40 controls, recipient MAP < 80 mm Hg during the 3 months before transplantation was associated with MAP (4.32, 1.41–13.2).[S2] In a recent study of 1127 recipients from brain dead donors, preexisting recipient hypotension (MAP < 80 mm Hg) was associated with DGF.[S3] Importantly, among the 18 paired kidneys with one hypotensive and one normal-hypertensive recipient treated with the same induction therapy, the incidence of DGF was higher in patients with preexisting recipient hypotension (66.7% vs. 22.2%).[S3]

Hypotension in the recipient inflicts hypoperfusion of the graft; resultant ischemia leads to switching of cells from oxidative metabolism to anaerobic glycolysis, leading to the accumulation of lactic acid and intracellular acidosis. Simultaneously, a chain of reaction happens that include inhibition of sodium ion/potassium adenosine triphosphatase (Na^+/K^+ ATPase), disruption of cytoskeletal proteins, leakage of lysosomal enzymes, intracellular accumulation of calcium, and production of reactive oxygen species in the mitochondria. The cells respond to ischemia by rapidly decreasing their metabolic activity and increasing the expression of genes that are cytoprotective or related to cellular regeneration.[3] In deceased donor kidneys, this adaptive response is lower as compared with live donor kidneys, posing a higher risk of graft injury related to hypoperfusion.[S4] During the reperfusion phase, the intracellular pH normalizes. The restoration of normal oxygen induces a burst of reactive oxygen species production that results in activation of lipid peroxidation and protein carbonylation resulting in membrane damage and DNA injury.[4] The combination of mitochondrial dysfunction, increased reactive oxygen species production, and calcium ion overload eventually results in induction of apoptosis (Figure 1). In addition, there is a generalized inflammatory response mediated by cytokines and chemokines leading to neutrophil recruitment in the graft, activation of the complement cascade, increased adhesion molecules, endothelial cell activation, and generation of vasoactive mediators contributing to tissue injury. Ischemia-reperfusion injury increases allograft immunogenicity with enhancement of NOD-like receptor signaling pathway and increased abundance of hematopoietic stem cells, M2 macrophages, monocytes, regulatory T cells (Tregs), conventional dendritic cells, and pro B-cells.[5] There is amplification of humoral response leading to raise in antibody production.[6]

The etiology of hypotension in kidney transplant recipients in the perioperative period is multifactorial. Acute hypotension may occur, especially in deceased donor transplants, mainly in the context of volume depletion due to ultrafiltration to dry weight in the dialysis session before transplant. Hypotension is associated with the use of dialysate with low sodium, low magnesium, and low calcium concentrations. In addition, acetate-based dialysate and higher

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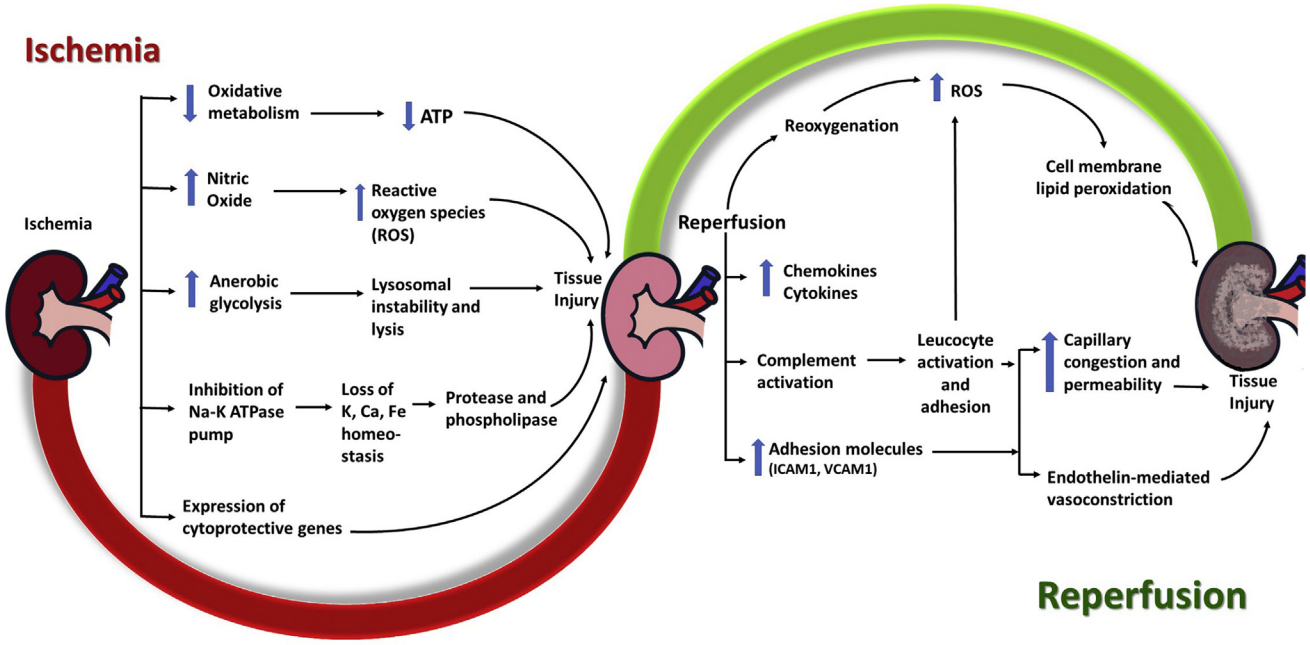

Figure 1. Ischemia-reperfusion injury in the kidney allograft. Figure depicts the pathogenesis of ischemia-reperfusion injury in the kidney allograft. ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; Ca, calcium; Fe, iron; K, potassium; Na, sodium.

dialysate temperature can lead to hypotension. Autonomic dysfunction, mainly due to impaired cardiac baroreceptor sensitivity, is common in patients with chronic kidney disease and is one of the leading mechanisms proposed for the increased risk for cardiovascular death in patients on dialysis.[S5] Furthermore, conditions that lead to decreased cardiac reserve and poor left ventricular systolic function, such as ischemic heart disease, cardiomyopathy, or valvular heart disease, are prone to develop both chronic hypotension and intradialytic hypotension. Another important cause of acute hypotension is the overzealous use of antihypertensive drugs. Rarely, the use of antithymocyte globulin intraoperatively may cause hypotension. Last, tissue ischemia induces the release of potent vasodilators, such as nitric oxide and adenosine, which further worsens hypotension.

Strategies to prevent perioperative hypotension in transplant recipients focus on avoiding dialysis-related hypotension by reducing ultrafiltration and keeping the patient above dry weight before transplant surgery, reviewing dialysate composition and temperature. Careful assessment of cardiac factors, such as heart failure, pericardial effusion, cardiomegaly, and ischemic heart disease, must be done before surgery. Antihypertensive drugs should be adjusted cautiously, and the use of long-acting drugs should be avoided. Routine use of midodrine, an alpha-1 adrenergic agonist that acts by arterial and venous vasoconstriction, to increase blood pressure in patients on maintenance dialysis is independently associated with DGF, graft failure, and death.[S6] Central venous pressure-informed volume infusion remains the conventional method for avoiding intraoperative hypotension in kidney transplantation. Maximal volume infusion until there is no further response to fluid infusion has long been considered as the best approach, but this can lead to excess fluid that can damage the vascular endothelial glycocalyx leading to fluid shift into the interstitium. Current evidence supports the concept that fluid therapy should be individualized based on dynamic indices of the intravascular volume.[S7]

Recipients with continuing hypotension unresponsive to the above-mentioned measures will require administration of vasopressors, a class of drugs that induce vasoconstriction and hence elevate MAP, or inotropes, a class of drugs that increase cardiac contractility. Many drugs have both effects. The main categories of vasopressors and inotropes used in the treatment of acute hypotensive states and shock include α-1 adrenergic vasopressors (norepinephrine, epinephrine, phenylephrine, and dopamine), V1a receptor antidiuretic hormone (vasopressin), beta-1 adrenergic inotrope (dobutamine), and phosphodiesterase enzyme 3 inhibitor inotrope (milrinone). Routine use of "renal dose" dopamine is not recommended and can be harmful.[S8] There is a dearth of good quality evidence guiding the choice of inotropes for kidney transplant

recipients. In principle, this must depend on the underlying etiology of hypotension; for example, norepinephrine for cardiogenic and hypovolemic shock, epinephrine for anaphylactic shock, phenylephrine when tachyarrhythmias preclude the use of norepinephrine, and dobutamine for cardiogenic shock with low cardiac output and maintained blood pressure. Septic shock in the immediate post-transplant period is rare. Norepinephrine is the initial pressor of choice for septic shock.

Vasopressin, a hormone synthesized in the hypothalamus and released by axons in the posterior pituitary in response to extracellular fluid tonicity, has short half-life of approximately 5 to 15 minutes in the circulation. It is used as a second-line agent in the management of vasodilatory shock as an add-on to norepinephrine or in the management of anaphylaxis that is unresponsive to epinephrine. Vasopressin, also called arginine vasopressin or antidiuretic hormone, acts on the V1a receptors located on the vascular smooth muscle cells and is a pure vasoconstrictor. Its effects are dose-dependent—higher doses may decrease heart rate, stroke volume, and cardiac output, increasing the risk of precipitating ischemia in patients with coronary artery disease. Stimulation of V2 receptors causes an increase in cyclic adenosine monophosphate, which increases water permeability in the kidney tubules and urine osmolality. In healthy subjects, the impact of vasopressin on the vasomotor tone is marginal; in septic shock, after an initial and transient increase, plasma levels of vasopressin decrease until day 4.[7] Clinical trials, thus far, have not found superiority of vasopressin. Nevertheless, vasopressin is not inferior to norepinephrine, is not associated with higher rates of adverse effects, and allows a reduction of norepinephrine infusion rates and fastened weaning from norepinephrine. The short biological half-life and the lack of specificity for V1 and V2 receptors, with the resultant side effects, are some of the serious limitations of this drug.[8]

In the current issue of *KI Reports*, Jan *et al*.[9] revealed the results of a retrospective analysis of 45 adult deceased donor kidney transplant recipients from 2012 to 2017 who required vasopressin for hypotension (vasopressin group), compared with 90 propensity score-matched deceased donor kidney transplant recipients who were normotensive (no vasopressin group). Recipients with septic, hemorrhagic, and cardiogenic shock were excluded. The study group had lower systolic and diastolic blood pressures in the operating room. The median start time for vasopressin was 2 hours (interquartile range: 1–6) post-deceased donor kidney transplant. Vasopressin was started at 2 units/h (interquartile range: 2–3), and the maximum dose was 4 units/h (median). Although the rate of DGF was similar in the 2 groups (6.7% vs. 5.6%; $P = 1.0$), serum creatinine at 12 hours, 24 hours, and on discharge was significantly higher in the vasopressin group. This difference was not found at 12 months post-transplant. There was no difference in graft survival and death-censored graft survival at median follow-up of 3.9 years in the vasopressin group and 5.3 years in the no vasopressin group. In multivariable analysis, vasopressin use was not associated with kidney graft survival. There was no difference in serum sodium level and no increased rate of arrhythmias in the vasopressin group. However, the vasopressin group had a higher incidence of non-ST segment elevation myocardial infarction in the post-operative period (31% vs. 2%; $P < 0.0001$). This study is limited by its small sample size and retrospective nature which could lead to confounding by variables that were not matched by the propensity score analysis. Furthermore, as the no vasopressin group was normotensive, there is confounding by indication. The etiology of hypotension is not clear, and no information is available about the presence of ischemic heart disease at baseline. Importantly, some patients in the vasopressin group were initially started on dopamine until they were moved to an intensive care unit to start vasopressin. Moreover, approximately 50% of patients in the vasopressin group received a second and 9% a third pressor. Similarly, in the no vasopressin group, 16% of patients received dopamine for low urine output. Despite these limitations, this study merits being the first report on the use of vasopressin in deceased donor kidney transplant and informs about its safety, which could pave the path for future larger prospective randomized trials.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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