NARRATIVE REVIEW

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Vasopressin Use in the Support of Organ Donors: Physiological Rationale and Review of the Literature

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OBJECTIVES: The objective of this review was to depict the physiological and clinical rationale for the use of vasopressin in hemodynamic support of organ donors. After summarizing the physiological, pharmacological concepts and preclinical findings, regarding vasopressin's pathophysiological impacts, we will present the available clinical data.

DATA SOURCES: Detailed search strategies in PubMed, OVID Medline, and EMBASE were undertaken using Medical Subject Headings and Key Words.

STUDY SELECTION: Physiological articles regarding brain death, and preclinical animal and human studies about the use of vasopressin or analogs, as an intervention in organ support for donation, were considered.

DATA EXTRACTION: Two authors independently screened titles, abstracts, and full text of articles to determine eligibility. Data encompassing models, population, methodology, outcomes, and relevant concepts were extracted.

DATA SYNTHESIS: Following brain death, profound reduction in sympathetic outflow is associated with reduced cardiac output, vascular tone, and hemodynamic instability in donors. In addition to reducing catecholamine needs and reversing diabetes insipidus, vasopressin has been shown to limit pulmonary injury and decrease systemic inflammatory response in animals. Several observational studies show the benefit of vasopressin on hemodynamic parameters and catecholamine sparing in donors. Small trials suggest that vasopressin increase organ procurement and have some survival benefit for recipients. However, the risk of bias is overall concerning, and therefore the quality of the evidence is deemed low.

CONCLUSIONS: Despite potential impact on graft outcome and a protective effect through catecholamine support sparing, the benefit of vasopressin use in organ donors is based on low evidence. Well-designed observational and randomized controlled trials are warranted.

KEY WORDS: catecholamines; hemodynamic support; organ donation; organ procurement; vasopressin

In 2020, the new Canadian guidelines for the management of neurologically deceased organ donors were published. Following a systematic review of the topic and based on low certainty of evidence, the panel of experts conditionally suggested IV vasopressin as a first-line vasoactive agent for hypotension over the use of norepinephrine (1). Although several observational studies suggest a potential benefit of vasopressin on hemodynamic parameters, prescribing habits and expert opinions have probably largely contributed to this decision. A Canadian survey of intensive care physicians published before the guidelines revealed that 41.5% of clinicians prefer vasopressin over other vasopressors to treat hypotension in donors (2). However, the preference for

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KEY POINTS

Question: There is no worldwide consensus on the use of vasopressin as first-line vasopressor in the hemodynamic support of neurologically deceased organ donors.

Finding: Preclinical data show that brain death leads to enhanced vasopressin sensitivity and that hemodynamic support of donors can be achieved even with physiological doses of vasopressin. Mainly observational studies in humans suggest that vasopressin use results in greater organ procurement, at least in part through decreased need for other catecholamines. Risk of bias is concerned with low quality of evidence.

Meanings: Vasopressin may have direct beneficial actions on graft outcome and a protective effect through catecholamine support sparing. Despite these encouraging results, well-designed prospective studies and randomized controlled trials are still needed.

vasopressin as a first-line vasopressor for this indication is not universal. A systematic review of international organ donor management guidelines highlights practice variability around the world (3). Although the administration of vasopressin for the hemodynamic management of donors seems a commonly adopted practice in Canada, the analysis of worldwide recommendations suggests that equipoise still exists and that the unclear benefit of this pharmacological agent warrants further research. The objective of this narrative review was to describe the physiological rationale for the use of vasopressin in hemodynamic support of neurologically deceased donors and to highlight the limitations of previously reported studies in the literature.

PHYSIOLOGY AND PHARMACOLOGY

Antidiuretic hormone (ADH), also known as arginine vasopressin, is a small 9-amino acid peptide released in circulation in response to an increase in plasma osmolarity or a decrease in blood volume (4).

Endogenous ADH is synthesized in the magnocellular neurons of the hypothalamus and secreted in the blood from the posterior pituitary gland. It exerts its physiological effects by binding to a family of membrane protein receptors, three of which are identified (**Table 1**): V1a, V2, and V3 (also called V1b) (5). V1a receptors are located mainly on vascular smooth muscle cells, but are also present in the liver, brain, and adrenal glands (4, 6).

Commercially available vasopressin is a synthetic form of ADH. Its onset of pressor effect occurs within 15 minutes, with a plasma half-life of 4–20 minutes when administered as a single IV bolus (4). Vasopressin must be administered parenterally as it is hydrolyzed by trypsin and its short half-life necessitates a continuous infusion when used as a vasopressor. When administered subcutaneously, the antidiuretic effect of vasopressin lasts 2–8 hours (4). Metabolism of exogenous vasopressin occurs in the liver and kidneys and resulting metabolites are not considered pharmacologically active. A small proportion of the drug is eliminated unchanged in urine (4). Of the three other synthetic analogs of ADH, desmopressin is the most used synthetic analog of ADH to treat central diabetes insipidus (DI), which acts more specifically on V2 receptors than V1a (7).

PATHOPHYSIOLOGY OF BRAIN DEATH

Following catastrophic brain injury, intracranial pressure increases, and cerebral herniation into the brainstem eventually ensues leading to brainstem ischemia in a rostrocaudal fashion or alternatively caudorostral fashion (5) (**Fig. 1**). Midbrain ischemia causes parasympathetic activation, then progresses to the pons with sympathetic stimulation that leads to the classical "Cushing reflex" (8). Ischemic progression to the vagal cardiomotor nucleus of the medulla oblongata causes loss of tonic vagal stimuli and baroreceptor reflexes, with unopposed sympathetic stimulation. Following the catecholamine storm, there is a reduction in sympathetic outflow associated with reduced cardiac output and profound vascular vasodilation, leading to hemodynamic instability.

During cerebral herniation, significant reductions in blood supply to the posterior pituitary gland cause cellular dysfunction and impaired ADH production (6). Undetectable levels of vasopressin have frequently been documented in animals and humans (9–12). Importantly, central DI occurs in as many as 87% of neurologically deceased donors and is often associated with hypotension (8, 13).

TABLE 1.
Vasopressin Receptor Subtypes

Receptor	Anatomical Distribution	Intracellular Signaling	Physiological Action
V1R	Vascular smooth muscle	G-protein-coupled stimulation of PLC and release of intracellular calcium	Vasoconstriction
	Platelets		Platelet aggregation
	Hepatocytes		Glycogenolysis
	CNS		ACTH release
	Adrenal cortex		
V2R	Renal distal tubule	G-protein-coupled stimulation of adenylyl cyclase and cAMP generation	Insertion of AQP2 water channels and induction of AQP2 synthesis
	Renal collecting duct		
	Vascular endothelium		Release of von Willebrand factor and factor VIII
V3R (also known as V1bR)	Anterior pituitary gland	G-protein-coupled stimulation of PLC and release of intracellular calcium	ACTH release

ACTH = adrenocorticotropin hormone, AQP2 = aquaporin-2, CNS = central nervous system, cAMP = Cyclic adenosine monophosphate, PLC = phospholipase C, V1R/V2R/V3R = Vasopressin 1/2/3 Receptor.

METHODS

Literature search was done in OVID Medline and EMBASE for preclinical animal studies, and observational and interventional clinical studies (Medline search, **Supplemental Digital Content 1**, http://links.lww.com/CCX/B176). For the clinical studies, we confronted and complemented our findings with an existing systematic review (14) and with the research done (https://www.cmaj.ca/content/cmaj/suppl/2020/04/03/192.14.E361.DC1/190631-guide-1-at.pdf) for the recently published Canadian guideline on Management of the neurologically deceased organ donor (1).

We conducted quality and risk of bias assessment of the presented clinical studies, by two independent evaluators, using the RoB 2 tool (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials) for randomized controlled trials and the Robins-1 tool for the observational trials (https://methods.cochrane.org/bias/risk-bias-non-randomized-studies-interventions). After a review of the articles, the evaluators rated the risk of bias according to the tools guidelines and discussed differences until an agreement was reached. Studies that did not have a control group were not evaluated for risk of bias.

PRECLINICAL DATA

Given the relatively high incidence of posterior pituitary failure in neurologically deceased donors, vasopressin use in early studies aimed at correcting central DI. Blaine et al (15) demonstrated that continuous IV infusion of low-dose vasopressin (2–10 μUI/kg/min) in hemodynamically stable brain-dead pigs corrected DI-related hypernatremia and polyuria. Vasopressin has since been replaced by desmopressin for the management of DI in the absence of hemodynamic instability, as the latter is highly selective for the renal collecting duct V2 receptors and has little or no pressor activity in humans.

Interestingly, although relatively large amounts of vasopressin are required to increase blood pressure under normal conditions (16), vasopressin has more significant hemodynamic effects in neurologically deceased organ donors. In their seminal study published in 1974, Cowley et al (17) found that decapitated dogs maintained with a small continuous infusion of norepinephrine exhibited nearly 8,000-fold increased pressor sensitivity to physiological doses of IV vasopressin when compared with neurologically intact dogs. Increased pressor sensitivity to vasopressin was also seen, albeit to a lesser extent, in baroreceptor-denervated and unanesthetized dogs. Later studies identified that vasopressin-induced vasoconstriction is counterbalanced in vivo by a decrease in cardiac output mediated through central sympathetic efferent activity inhibition and baroreflex potentiation (18). Thus, when these complex neurological processes are lost, as is in the case of organ donors, vasopressin is

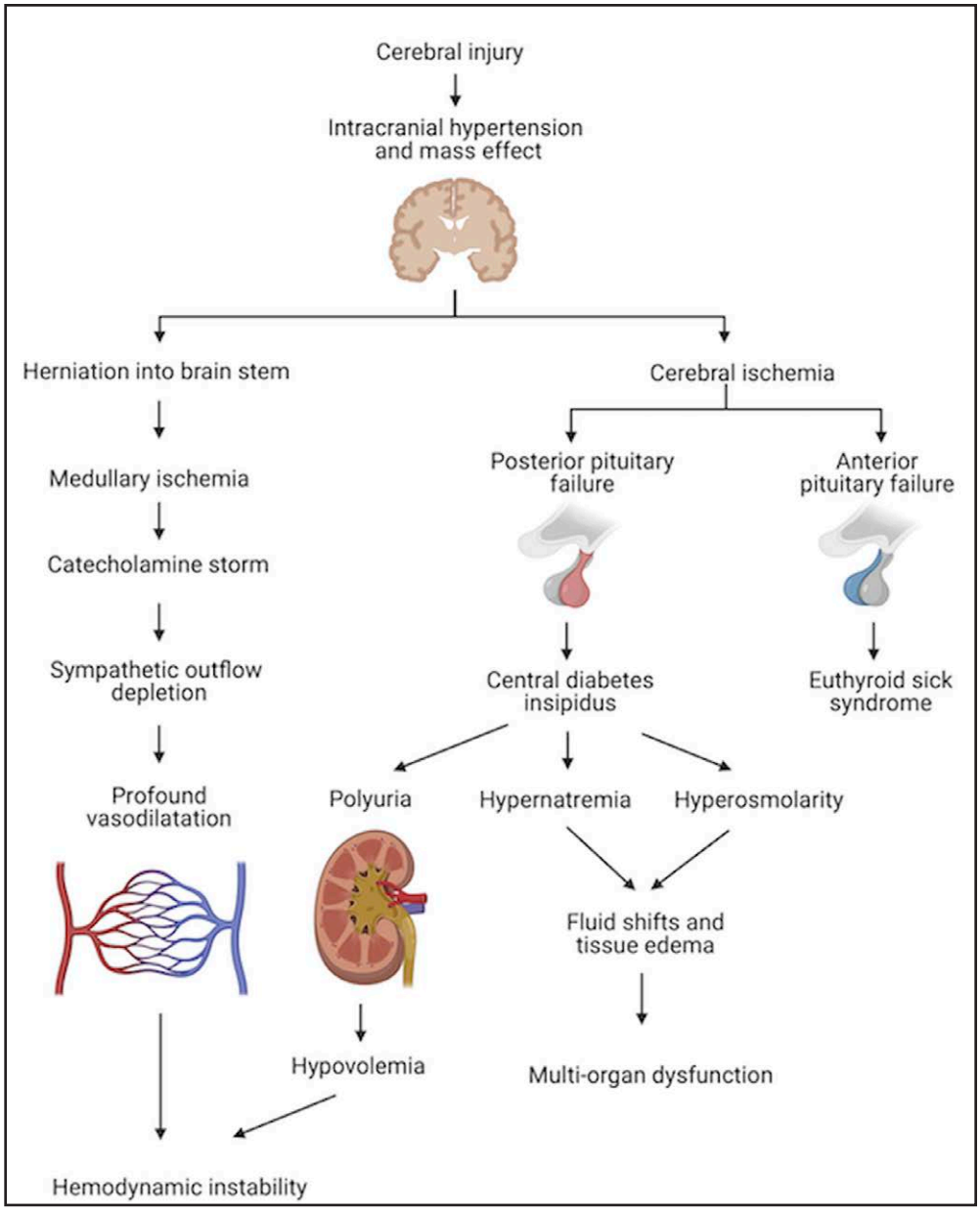

Figure 1. Pathophysiology of brain death. Catastrophic brain injury ultimately leads to intracranial hypertension and brainstem herniation. Catecholamine depletion from medullary ischemia-related events following the autonomic storm leads to profound reduction in sympathetic outflow. Hypotension can develop, which is exacerbated by fluid loss from associated central diabetes insipidus. Figure created with BioRender.com.

able to increase blood pressure even at physiological doses (0.01–0.04 IU/min) (19). In addition to its own potent vasoconstrictor effects, vasopressin potentiates norepinephrine-induced vasoconstriction (20). Using a model of hemodynamically unstable brain-dead pigs, Manaka et al (21) found that vasopressin (0.1 IU/kg/hr) but not epinephrine (2 µg/kg/hr) infusion alone modestly increased blood pressure whereas combined administration of the two resulted in synergistic and sustained increases in blood pressure.

A theoretical disadvantage of vasopressin is reduced organ preservation due to tissue ischemia. When administered in high doses (> 0.04 IU/min), vasopressin can cause vasoconstriction in virtually all vascular beds (22). Regional blood flow to skeletal muscle, skin, and fat seems to be the most sensitive to vasopressin, followed by coronary, splanchnic, and renal circulations (23). At lower doses, vasopressin has even been shown to induce vasodilatation in coronary and pulmonary circulations through endothelium-dependent nitric oxide release (24, 25). Still, few animal studies have investigated tissue perfusion in the context of brain-dead models' hemodynamic support. One study found that a maximal vasopressin dose of 0.04 IU/kg/hr decreased superior mesentery artery blood flow without causing tissue ischemia in brain-dead pigs (26), whereas no effects on hepatic energy metabolism were reported in another study (21). It should be noted that the bulk of our experimental insight into the hemodynamic consequences of vasopressin emanates from animal models of septic or hemorrhagic shock, which may not necessarily extend to vasoplegic neurologically deceased donors. Nevertheless, these studies generally support the notion that low vasopressin infusion rates (≤ 0.04 IU/min) do not impair vital organ perfusion (22, 27).

In addition to providing hemodynamic support, vasopressin has been shown to limit pulmonary injury

associated with neurological death to the same extent as norepinephrine, but without cardiac ischemia. Infusion of high-dose vasopressin (mean dose of 0.27 IU/kg/hr) reduced pulmonary capillary leak, limited pulmonary edema, and systemic inflammatory response, and prevented metabolic acidosis in brain-dead Wistar rats (28).

CLINICAL DATA

Data supporting the use of vasopressin in hemodynamic management of neurologically deceased donors mostly stems from small clinical studies focused on hemodynamic effects (**Table 2**). These studies generally compared the use of adrenergic agonist support with or without vasopressin, with reports on various outcomes, including survival until cardiac arrest, sensitivity to vasopressors, recipient survival, and organ viability or function. Most studies found that the addition of vasopressin allowed for prolonged hemodynamic stability (29–31). Additionally, Yoshioka et al (29) determined that the addition of vasopressin to an epinephrine infusion in six neurologically deceased donors significantly prolonged the time to cardiac arrest in comparison with epinephrine alone (n = 10). The combination of vasopressin and epinephrine was also found to stabilize urine output and creatinine clearance for up to 14 days (31).

In another randomized controlled trial (n = 24) study comparing the administration of vasopressin (0.3 UI/kg/min) to placebo in neurologically deceased donors hemodynamically supported by dopamine, vasopressin increased blood pressure, reduced inotrope requirements and decreased plasma osmolality (32). Although myocardial ATP levels (a potential marker of myocardial function after transplantation) were higher in vasopressin-treated donors, there was no statistical difference in early graft (heart, kidney) function (32). Interestingly, the addition of vasopressin (0.04–0.1 UI/min) in hypotensive donors increased mean arterial pressure (MAP) and reduced adrenergic agonist requirements even in the absence of clinical DI. This finding is consistent with preclinical data suggesting that neurologically deceased donors have enhanced pressor sensitivity to vasopressin, independent of pituitary failure (33). Administration of a single bolus of terlipressin (1 mg) also improved MAP and reduced norepinephrine requirements by approximately 39% in neurologically deceased donors with norepinephrine-refractory shock, although it did not affect the renal or liver graft quality in transplant recipients (34). Taken together, these studies support the role of vasopressin in hemodynamic support of neurologically deceased donors in conjunction with other vasopressors.

The catecholamine-sparing effects of low-dose vasopressin may also apply to pediatric donor populations, according to one retrospective case-control study (35). Although these studies are promising, they were limited by very small sample sizes and did not show improved graft function outcomes.

In the early 2000s, the use of vasopressin in donor support was supported by retrospective studies investigating the benefits of hormonal replacement therapy (HRT) on organ procurement. Vasopressin was often administered in the setting of a 3-drug HRT (methylprednisolone, triiodothyronine [T3], and vasopressin) although some studies also included insulin. Retrospective analyses of the United Network for Organ Sharing database identified a 22.5% increase in organ procurement with donor HRT (36). Patients who received hearts from HRT-treated donors also demonstrated a significantly greater survival rate at 1 month (96.2% vs 92%) and at 1 year (89.9% vs 83.9%) compared with non-HRT-treated donors (37). In a prospective randomized double-blind trial, where 80 potential heart donors were allocated to receive T3, methylprednisolone, both drugs or placebo, neither T3 nor methylprednisolone treatment (alone or in combination) increased the number of hearts procured (38). Interestingly, a post hoc analysis revealed that vasopressin administration and its subsequent reduction in norepinephrine was associated with a significant increase in cardiac index and a beneficial reduction in systemic vascular resistance (38). These findings corroborate the hypothesis that vasopressin improves cardiac graft viability at least partly through reduction of catecholamine toxicity.

The most convincing evidence regarding the isolated HRT potential of vasopressin on organ outcomes comes from two large retrospective studies (10,431 and 12,322 patients) from the Organ Procurement and Transplantation Network database (39, 40). In both studies, the organ procurement yield was retrospectively compared between donors exposed and nonexposed to vasopressin. Plurad et al (39) found that vasopressin exposure was associated with a 40%

TABLE 2.
Characteristics of Clinical Studies Informing Evidences

Study	Design	No. of Donors	Intervention	Outcomes Measured	Key Findings
Yoshioka et al (1986) (29)	Prospective interventional trial	16	Donors were assigned to norepinephrine infusion alone or with vasopressin infusion	Mean donor survival time	Vasopressin addition improved mean time to cardiac arrest from 1 d to 23 d
Kinoshita et al (1990) (31)	Prospective observational trial	10	Donors were supported hemodynamically with norepinephrine and vasopressin infusion	Mean donor survival time and cardiac structural changes on biopsy	Vasopressin and norepinephrine allow for sustained (> 1 wk) hemodynamic support without injuring cardiac tissue
Pennefather et al (1995) (32)	Randomized prospective trial	24	Donors randomized to receive vasopressin infusion or saline after initial resuscitation	Hemodynamic profile, inotrope requirements, and myocardial ATP levels	Vasopressin increased blood pressure, reduced inotrope requirements, and increased myocardial ATP levels
Chen et al (1999) (33)	Prospective interventional trial	12	Hemodynamically unstable donors without diabetes insipidus were treated with vasopressin infusion	Hemodynamic profile and pressor support requirements	Vasopressin increased MAP and allowed complete discontinuation of catecholamine support in some donors
Blasco et al (2008) (34)	Retrospective observational trial	20	Donors treated with norepinephrine alone or with one dose of terlipressin were compared	Hemodynamic profile and graft outcomes following terlipressin administration	Terlipressin increased MAP in norepinephrine-resistant shock without affecting renal or hepatic graft quality
Katz et al (2000) (35)	Retrospective case-control trial	63	Pediatric donors who received vasopressin (titrated to urine output) vs those who did not	Dose, type, and number of pressors and inotropes. Organ function at recovery and 48 hr posttransplant	Exposure to vasopressin was associated with higher incidence of weaning from pressor/inotrope support
Venkateswaran et al (2009) (38)	Prospective randomized double-blind trial	80	Donors were randomized to receive T3, methylprednisolone, both, or placebo. Vasopressin was initiated after hormone or placebo	Difference in cardiac index at end-assessment	No difference in cardiac index between hormone or placebo. Post hoc analysis found that norepinephrine substitution with vasopressin was associated with improved cardiac index
Plurad et al (2012) (39)	Retrospective case-control trial	10,431	Donors who received vasopressin vs those who did not	Incidence of high-yield organ procurements (recovery of > 3 organs)	Exposure to vasopressin was associated with higher high-yield (> 3) organ procurement and independently predicted high-yield procurement
Callahan et al (2014) (40)	Retrospective case-control trial	12,322	Donors who received vasopressin vs those who did not	Donor lung function, rate of successful lung procurement, and the incidence of graft failure in recipients	Exposure to vasopressin was associated with improved donor lung function, a higher number of lung grafts recovered, and a higher mean number of organs recovered overall
Bloom et al (2015) (41)	Prospective observational trial	961	Critical care and demographic data were analyzed	Donor liver graft use and survival	Use of any dose of vasopressin was associated with more liver grafts selected for transplant

ATP = adenosine triphosphate, DI = diabetes insipidus, MAP = mean arterial pressure, T3 = triiodothyronine.

increase in high-yield organ procurement (defined as recovery of four or more organs) and independently predicted high-yield procurement after adjustment for age, gender, cause of death, and other significant covariables. The association was present for an increase in procurement rates for all organs, but the contrast for heart procurement was most pronounced (38.5% vs 27.2%).

In their follow-up study, Callahan et al (40) investigated donor lung function and graft failure in transplant recipients at least one month after transplant, in addition to the rate of successful lung procurement. In association with vasopressin administration, they found a 30% increase in the number of high-yield donors, a 12% increase in the mean number of organs procured, and 30% increase in lung recovery. In difficult-to-recover donors (obese donors, donors with bacteremia, and expanded-criteria donors), vasopressin was also associated with an increase in number of organs. Consistent with preclinical data suggesting that vasopressin may limit pulmonary inflammation and edema, donors who received vasopressin had a significantly higher mean Po_2 on 100% oxygen and were significantly more likely to have a Pao_2/Fio_2 greater than 200. Despite these encouraging findings, there was no significant difference in graft failure at 12 months between grafts from vasopressin-exposed and nonexposed donors. Despite their large size and robust dataset, these studies do not provide specific donor parameters including hemodynamic improvement with vasopressin and whether vasopressin was initiated for hypotension or DI. In addition, the vasopressin-exposed group was younger and had a more traumatic brain injury, which could contribute to differences in the organs' procurement.

Other smaller observational studies have reported similar benefits of vasopressin administration on organ procurement. In a prospective observational study looking at independent predictors of liver transplantation and graft survival rate, vasopressin administration was significantly associated with graft use (41). In another prospective quality improvement study, vasopressin use was associated with a reduced rate of cardiac arrest in potential neurologically deceased donors receiving hemodynamic support (42).

Despite some promising results in the above-presented studies (Table 2), the risk of bias analysis of existing studies revealed an overall low quality and high risk of bias. The various domains of assessment, using appropriate assessment tools of randomized or nonrandomized studies, are displayed in **Supplemental Digital Content 2** (http://links.lww.com/CCX/B176).

CONCLUSIONS

Although ADH analogs are well accepted in the clinical management of DI, significant variability exists around the world regarding the use of vasopressin for donor hemodynamic support. This disparity likely stems from the lack of large randomized clinical trials demonstrating the benefit of vasopressin use on organ procurement or graft outcome. Even if it is conceivable that vasopressin may have direct beneficial actions on graft outcome through modulation of inflammatory pathways or organ viability, observations to date have at least suggested a protective effect through catecholamine support sparing. Well-designed prospective studies and randomized controlled trials are needed, to determine if its use can ultimately improve the yield of organ procurement and lead to better outcomes in transplant recipients.

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