

Vasopressin, Norepinephrine, and Vasodilatory Shock after Cardiac Surgery

Another “VASST” Difference?

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H AJJAR *et al.*¹ designed, conducted, and now report in this issue an elegant randomized double-blind controlled trial of vasopressin (0.01 to 0.06 U/min) versus norepinephrine (10 to 60 µg/min) post cardiac surgery with vasodilatory shock (Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock After Cardiac Surgery [VANCS] trial). Open-label norepinephrine was added if there was an inadequate response to blinded study drug. Vasodilatory shock was defined by hypotension requiring vasopressors and a cardiac index greater than $2.2 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. The primary endpoint was a composite: “mortality or severe complications.” Patients with vasodilatory shock within 48 h post cardiopulmonary bypass weaning were eligible. Three hundred patients were included, and there was a highly significant decrease in the primary endpoint in the vasopressin compared to the norepinephrine group (absolute risk reduction 17%, number needed to treat 6). There was also a significantly lower rate of atrial fibrillation in the vasopressin versus norepinephrine group (perhaps expected because of lack of β_1 -adrenergic stimulation with vasopressin). The vasopressin group also had sparing of norepinephrine (shorter duration), shorter duration of study drug infusion, shorter intensive care unit stay, shorter duration of dobutamine, less acute kidney injury, less need for renal replacement therapy, and lower sepsis-related organ failure assessment scores than the norepinephrine group. The authors conclude that vasopressin is superior to norepinephrine in vasodilatory shock



“[The use of] ...vasopressin infusion for treatment of vasodilatory shock after cardiac surgery may improve some clinically important outcomes.”

after cardiac surgery. There was no difference in 28-day mortality in the composite—the vasopressin signal was driven by severe complications and not by mortality in the mortality or severe complications composite.

Strengths of VANCS include the blinded randomized treatment, careful follow-up, calculation of the composite outcome, achieving adequate and planned sample size, and evaluation of vasopressin pharmacokinetics.

Nearly 20 yr ago, Landry *et al.*^{2–6} discovered relative vasopressin deficiency and benefits of prophylactic (*i.e.*, pre cardiopulmonary bypass) and postoperative low-dose vasopressin infusion in patients with vasodilatory shock after cardiac surgery. Previous trials of vasopressin versus norepinephrine in cardiac surgery were small and underpowered for mortality assessment.^{2–6}

Vasopressin stimulates arginine vasopressin receptor 1a, arginine vasopressin receptor 1b, V2, oxytocin, and purinergic receptors causing vasoconstriction (V1a), corticosteroid axis stimulation (V1b), and antidiuresis (V2), as well as release of procoagulant von Willebrand multimers (V2). Mechanisms of vasopressin benefit in VANCS include sparing of norepinephrine⁷ or other nonhemodynamic effects (because hemodynamics such as mean arterial pressure, cardiac index, lactate, and fluid balance were similar in vasopressin and norepinephrine groups). Trials of vasopressin versus norepinephrine in septic shock show no difference between vasopressin and norepinephrine in efficacy or adverse effects,^{8–11} contrasting with the possible efficacy and the atrial fibrillation avoidance benefit of

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vasopressin in the randomized controlled trial by Hajjar *et al.*¹ Dunser *et al.*¹² found fewer tachyarrhythmias with vasopressin compared with norepinephrine in vasodilatory shock. Why was vasopressin possibly beneficial in vasodilatory syndrome after cardiac surgery in VANCS¹ but not in septic shock in the Vasopressin and Septic Shock trial (VASST; registered with <http://www.controlled-trials.com>, ISRCTN94845869; supported by grant no. MCT 44152 from the Canadian Institutes of Health Research, Ottawa, Canada) or Vasopressin versus Noradrenaline as Initial therapy in Septic shock trial (VANISH)?^{8,11} The most obvious difference is the primary outcome—mortality and severe complications in VANCS, 28-day mortality in VASST,⁸ and kidney failure-free days in VANISH.¹¹ Although vasopressin doses in VASST, VANISH,¹¹ and VANCS¹ were similar, peak vasopressin levels on vasopressin treatment were much lower in the VANCS (20 to 25 pmol/l) than in the VASST (80 to 100 pmol/l) or the VANISH pilot trial^{10,11} (300 pmol/l). Perhaps lower vasopressin levels in VANCS are the optimal vasopressin level in vasodilatory shock due to septic shock or post cardiac surgery. This aligns with the observation that the vasopressin beneficial signal in VANCS was restricted to lower rates of adverse effects of vasopressin.

Aspects of variability of patient response to vasopressin infusion and other purported mechanisms of action of vasopressin (and V1a agonism) deserve emphasis. Interindividual responses to vasopressin may be due to polymorphisms of leucyl/cystinyl aminopeptidase, the enzyme that catalyzes vasopressin¹³ or the V1a receptor. Recently, V1a agonism^{14–16} was found to decrease vascular leak in models and possibly in patients with septic shock,¹⁷ perhaps by limiting increases in angiotensin-2,^{16,18} and may be another reason for vasopressin's efficacy in the trial by Hajjar *et al.*¹

Hajjar *et al.*¹ note that vasodilatory shock after cardiac surgery is common in patients previously treated with β -blockers or angiotensin-converting enzyme inhibitors. In their trial, 65% of patients were on β -blockers and 46% of the norepinephrine group and 35% of the vasopressin group were on angiotensin-converting enzyme inhibitors. The vasopressin benefit occurred in patients with or without β -blockers, but only in the patients on angiotensin-converting enzyme inhibitors. These are hypothesis-generating *post hoc* subgroup analyses to be interpreted with caution. Perhaps Hajjar *et al.*¹ discovered a novel interaction of vasopressin with angiotensin-converting enzyme pathways, a possible scenario from a biological standpoint.

The mortality rates were high—16 and 15% at 28 days and 17 and 16% at 90 days (norepinephrine *vs.* vasopressin)—in VANCS¹; remarkably, mortality rates were not reported in previous smaller trials of vasopressin *versus* norepinephrine for vasodilatory shock¹² after cardiac surgery.^{2,5,6,19}

There are limitations of the current trial, including that it is a single-center trial. The major limitation is that the primary endpoint was changed after the trial had enrolled some patients, an important protocol amendment. How many

patients had been included by then? Was a change in protocol registered? How did this alter the sample size and power calculations? The sample size and power calculation of the initial endpoint (days alive and free of organ dysfunction [Brussels score]) should be stated. The authors explain well the rationale and process for changing the primary endpoint in the electronic supplement. Interestingly, the vasopressin group had significantly more days alive and free of cardiovascular and renal dysfunction compared to the norepinephrine group.

There is concern about generalizability of these results in other countries and healthcare settings. The lengths of intensive care unit stay (6 days) and hospital stay (10 to 13 days) appear prolonged because patients with vasodilatory shock have more profound derangements after cardiac surgery that extend intensive care unit and hospital stays. The literature is sparse regarding expected lengths of stay after vasodilatory shock complicating cardiac surgery, which is the reason that Hajjar *et al.*¹ changed the primary outcome. It would also be useful to understand how the lengths of stay of vasodilatory shock patients compared to those of patients in the hospital of Hajjar *et al.*¹ in Brazil who did not have vasodilatory shock post cardiac surgery.

In summary, this remarkable trial shows that in settings such as the study hospital, vasopressin infusion for treatment of vasodilatory shock after cardiac surgery may improve some clinically important outcomes. Pocock and Stone²⁰ emphasize limitations of “positive” trials, including having the primary *P* value merely less than 0.05 as being inadequate to change practice (they suggest *P* < 0.001; *P* was 0.0014 in VANCS), magnitude of the treatment benefit (absolute risk reduction was 16%—impressive—in VANCS), having an important primary outcome (mortality and severe complications are clinically important), careful inspection of composite outcomes (vasopressin decreased severe complications), having supportive secondary outcomes (atrial fibrillation was lower with vasopressin), consistency across subgroups (some consistency; *e.g.*, β -blockers yes/no subgroups), stopping early (not the case in VANCS), flaws in trial design or conduct (the change in primary endpoint in VANCS as discussed), and applicability to a reader's patients, an issue I addressed. Accordingly, this trial deserves replication in other multicenter healthcare settings to create confidence about generalizability. A selective V1a agonist may be more effective than vasopressin by limiting von Willebrand factor release and vascular leak, rationales for future randomized controlled trials of V1a agonism in vasodilatory shock after cardiac surgery.

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Competing Interests

Dr. Russell reports patents owned by the University of British Columbia (UBC), Vancouver, Canada, that are related to PCSK9 inhibitor(s) and sepsis and the use of vasopressin

in septic shock. He is an inventor on these patents. He is a founder, director, and shareholder in Cyon Therapeutics Inc., Vancouver, Canada (developing a sepsis therapy). He has share options in Leading Biosciences Inc., San Diego, California. He is a shareholder in Molecular You Corp., Vancouver, Canada. He reports receiving consulting fees from Merck, Kenilworth, New Jersey (developing antibiotics), Leading Biosciences (developing a sepsis therapeutic), Ferring Pharmaceuticals, Copenhagen, Denmark (manufactures vasopressin and is developing selepressin), Grifols, Barcelona, Spain (sells albumin), La Jolla Pharmaceuticals, La Jolla, California (developing angiotensin II; he chairs the DSMB of a trial of angiotensin II), CytoVale Inc., San Francisco, California (developing a sepsis diagnostic), Asahi Kasei Pharmaceuticals of America, Waltham, Massachusetts (AKPA; developing recombinant thrombomodulin). He reports having received an investigator-initiated grant from Grifols that is provided to and administered by UBC.

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Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock After Cardiac Surgery

The VANCS Randomized Controlled Trial

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ABSTRACT

Background: Vasoplegic syndrome is a common complication after cardiac surgery and impacts negatively on patient outcomes. The objective of this study was to evaluate whether vasopressin is superior to norepinephrine in reducing postoperative complications in patients with vasoplegic syndrome.

Methods: This prospective, randomized, double-blind trial was conducted at the Heart Institute, University of Sao Paulo, Sao Paulo, Brazil, between January 2012 and March 2014. Patients with vasoplegic shock (defined as mean arterial pressure less than 65 mmHg resistant to fluid challenge and cardiac index greater than $2.2 \text{ l} \cdot \text{min}^{-2} \cdot \text{m}^{-2}$) after cardiac surgery were randomized to receive vasopressin (0.01 to 0.06 U/min) or norepinephrine (10 to 60 $\mu\text{g}/\text{min}$) to maintain arterial pressure. The primary endpoint was a composite of mortality or severe complications (stroke, requirement for mechanical ventilation for longer than 48 h, deep sternal wound infection, reoperation, or acute renal failure) within 30 days.

Results: A total of 330 patients were randomized, and 300 were infused with one of the study drugs (vasopressin, 149; norepinephrine, 151). The primary outcome occurred in 32% of the vasopressin patients and in 49% of the norepinephrine patients (unadjusted hazard ratio, 0.55; 95% CI, 0.38 to 0.80; $P = 0.0014$). Regarding adverse events, the authors found a lower occurrence of atrial fibrillation in the vasopressin group (63.8% vs. 82.1%; $P = 0.0004$) and no difference between groups in the rates of digital ischemia, mesenteric ischemia, hyponatremia, and myocardial infarction.

Conclusions: The authors' results suggest that vasopressin can be used as a first-line vasopressor agent in postcardiac surgery vasoplegic shock and improves clinical outcomes. (ANESTHESIOLOGY 2017; 126:00-00)

VASOPLEGIC syndrome, characterized by low arterial pressure with normal or elevated cardiac output and reduced systemic vascular resistance,¹ occurs in 5 to 25% of patients undergoing cardiac surgery. Patients who develop vasoplegic shock after cardiac surgery are at higher risk of organ failure and have increased mortality and longer hospital length of stay.^{2,3}

Administration of norepinephrine is currently considered the standard treatment for vasoplegic shock, but all catecholamines have adverse effects, including arrhythmias and myocardial ischemia.⁴ Furthermore, in severe vasoplegic states,

What We Already Know about This Topic

- Vasoplegia is common after cardiac surgery and due in part to insufficient endogenous vasopressin; the optimal management is unknown

What This Article Tells Us That Is New

- A single-centre double-blind controlled trial randomized 330 patients with vasoplegic syndrome to receive vasopressin or norepinephrine. In patients receiving vasopressin, the primary endpoint (mortality or severe complications) occurred in 32%, compared with 49% receiving norepinephrine, and atrial fibrillation was less frequent (63.8% vs. 82.1%)

vascular smooth muscle cells may become unresponsive to norepinephrine because of complex mechanisms that include activation of adenosine triphosphate-sensitive K^+ channels, increased nitric oxide synthesis, adrenoceptor desensitization, and vasopressin and corticosteroid deficiency.⁵ Vasopressin, an essential stress hormone released in response to hypotension, stimulates a family of receptors: arginine vasopressin receptor 1a (AVPR1a), AVPR1b, AVPR2, oxytocin receptors, and purinergic receptors. Vasopressin binds to AVPR1a to promote vasoconstriction through several pathways, including modulation of adenosine triphosphate-sensitive K^+ channel function and nitric oxide production and enhancement of the vascular response to catecholamines.⁶ Furthermore, it may have cardioprotective and nephroprotective effects in patients with vasodilatory shock.^{7,8} Vasopressin may, therefore, be an attractive, alternative agent for the treatment of vasoplegic syndromes.

Several, small randomized trials have shown that vasopressin infusion effectively increases arterial pressure and systemic vascular resistance and decreases catecholamine requirements in patients with or at risk of vasoplegic syndrome after cardiac surgery, with no increase in adverse events.^{9–11} However, none of these studies directly compared vasopressin with norepinephrine, and importantly, none was adequately powered to detect significant differences in clinically relevant outcomes. We, therefore, conducted a randomized, double-blind trial comparing these two agents in patients with vasoplegic syndrome after cardiac surgery. Our hypothesis was that administration of vasopressin to patients with vasoplegic shock after cardiac surgery would be associated with fewer postoperative complications compared to norepinephrine administration.

Materials and Methods

Study Design

The Vasopressin *versus* Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery study was designed as a prospective, randomized, superiority, double-blind, and

controlled trial. The study trial was performed at the Heart Institute, Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil. Patients were enrolled between January 2012 and March 2014. The study protocol was approved by the local ethics and research committee (Comitê de Ética para Análise de Projetos de Pesquisa, Sao Paulo, Brazil; number, 0352/08). The study protocol was registered at ClinicalTrials.gov (NCT01505231).

Patients

All adult (more than 18 yr of age) patients who were scheduled for coronary artery bypass graft surgery, valve replacement, or repair surgery with cardiopulmonary bypass (CPB) were assessed for eligibility on the eve of their procedure by the study coordinator, and written informed consent was obtained. Patients were randomized to the study drug if they required vasopressor drugs for vasodilatory shock within 48 h after CPB weaning. Vasodilatory shock was defined as refractory hypotension (mean arterial pressure [MAP], less than 65 mmHg) resistant to fluid challenge (at least 1,000 ml crystalloid) and associated with a cardiac index greater than $2.2 \text{ l} \cdot \text{min}^{-2} \cdot \text{m}^{-2}$. Exclusion criteria included aortic surgery, heart transplantation, preoperative use of vasopressor therapy, presence of a ventricular assist device other than an intraaortic balloon pump, severe hyponatremia (Na^+ , less than 130 mEq/l), acute coronary syndrome, acute mesenteric ischemia, history of Raynaud disease, pregnancy, and neoplasm.

Randomization and Masking

Eligible patients were randomly assigned, in a 1:1 ratio, to receive either vasopressin or norepinephrine according to a computer-generated random list. Opaque randomization envelopes, prepared by the chief statistician, were given to the pharmacy to ensure allocation concealment. The anesthesiologist or intensivist in charge of the patient contacted the central pharmacy to obtain the allocated vasopressor. Norepinephrine or vasopressin solutions were prepared by the pharmaceutical team (aware of the two treatments) in identical bags, identified with the name of the patient, the hospital registration number, and the study identification number. All other clinical staff, investigators, research team, patients, and families were unaware of the treatment assignments for the duration of the trial.

Study Treatment Protocol

Full details of the surgical and anesthetic technique are given in the Supplemental Digital Content (<http://links.lww.com/ALN/B337>). After the procedure, all patients were admitted to the surgical intensive care unit (ICU) for postoperative care, and hemodynamic monitoring was maintained for 48 h.

Vasopressin (30 U; BioLab Sanus Farmaceutica, Brazil) and norepinephrine (30 mg; Hypofarma, Brazil) were mixed in identical 250-ml intravenous bags of 5% dextrose in water, with final concentrations of 0.12 U/ml vasopressin

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and 120 µg/ml norepinephrine. The vasopressor infusion was titrated to maintain an MAP of at least 65 mmHg. The study-drug infusion was started at 5 ml/h and increased by 2.5 ml/h every 10 min during the first hour to achieve a maximum target rate of 30 ml/h, so that vasopressin doses ranged from 0.01 to 0.06 U/min and norepinephrine doses from 10 to 60 µg/min. If the target MAP was not reached and further vasopressor support was required, open-label norepinephrine was started in addition to the study drug.

When the targeted MAP was exceeded, any open-label norepinephrine was tapered first; only if the open-label norepinephrine could be weaned completely, tapering of the study drug was commenced. If vasopressor support was required during the same admission to the ICU after a patient had been weaned from the study drug, the study drug was preferentially restarted, unless other exclusion criteria had been met.

The study-drug infusion was discontinued or interrupted if any of the following predetermined serious adverse events (SAEs) occurred: acute ST-segment elevation confirmed by a 12-lead electrocardiogram, serious or life-threatening cardiac arrhythmias, acute mesenteric ischemia, digital ischemia, or hyponatremia (serum sodium level, less than 130 mmol/l). If an SAE was considered to be potentially related to the study-drug infusion, the infusion was discontinued for at least 8 h. In these cases, norepinephrine could be initiated at the discretion of the physician to maintain MAP. The study drug could be restarted if the SAE had been treated, the condition had been reversed, and the event was not thought to be a result of the study drug or study protocol.

Data Collection and Definition of Complications

After randomization, we recorded demographic, hemodynamic, and clinical data (full details are given in the Supplemental Digital Content, <http://links.lww.com/ALN/B337>), as well as the information needed to calculate the predicted risk of surgery using the additive European System for Cardiac Operative Risk Evaluation.¹² In the first 89 randomized patients, we measured serum vasopressin levels immediately after randomization and 6, 12, and 24 h after drug infusion.¹³ After discharge from the ICU, clinical outcomes were evaluated on the regular ward, still in a blinded fashion.

Outcome Measures

The initial primary outcomes were days alive and free of organ dysfunction at 28 days based on the Brussels criteria used in the Vasopressin *versus* Norepinephrine Infusion in Patients with Septic Shock (VASST) study.¹³ However, after the trial had already started, because of the lack of outcome data in cardiac surgery, the study management committee decided that a more appropriate endpoint for cardiac surgery patients would be a composite endpoint of mortality or severe postoperative complications within 30 days after randomization. Details are described in the Supplemental Digital Content (<http://links.lww.com/ALN/B337>). We, therefore, used a modified Society of Thoracic Surgeons

model¹⁴ for severe complications after cardiac surgery, including stroke, requirement of mechanical ventilation for longer than 48 h, deep sternal wound infection, reoperation, or acute renal failure.

Stroke was characterized as a central neurologic deficit persisting longer than 72 h with compatible brain tomographic imaging. Deep sternal wound infection was defined by infection of the sternal wound with positive findings on cultures or suggestive findings on thorax computed tomographic scan. Acute renal failure was defined as new requirement for dialysis or an increase in serum creatinine to more than 2.0 mg/dl and double the most recent preoperative creatinine level.¹⁴

Secondary outcomes included the 30-day incidence of infection, septic shock, arrhythmias (atrial fibrillation and ventricular arrhythmias), duration of mechanical ventilation, hemodynamic effects (time to reach hemodynamic stability, changes in hemodynamic variables, and the use of dobutamine or other vasoactive agents), incidence of digital ischemia, acute mesenteric ischemia, and acute myocardial infarction, and ICU and hospital lengths of stay. We also explored the following *post hoc* endpoints: 30-day incidence of pulmonary embolism, low cardiac output syndrome, acute respiratory distress syndrome, delirium, stages of acute kidney injury (AKI) according to Acute Kidney Injury Network criteria (eTable 1 in the Supplemental Digital Content, <http://links.lww.com/ALN/B337>),¹⁵ need for renal replacement therapy (RRT), ICU readmission rate and Sequential Organ Failure Assessment score, and subgroup analysis according to the previous use of β-blocker or angiotensin-converting enzyme (ACE) inhibitors (ACEI)/angiotensin-receptor blocker (ARB).¹⁶ We also evaluated the number of patients who required additional norepinephrine, vasopressin plasma concentrations, and 90-day mortality.

Sample Size and Data Analysis

We calculated that 300 patients would be required for enrollment, randomization, and receipt of the study drug in order to detect an absolute 30% difference in the composite endpoint (30-day death or severe postoperative complications), assuming an incidence of 55% in the norepinephrine group¹⁷ and adding 5% of anticipated follow-up losses, with a two-sided α error of 0.05 and a power of 80%. A protocol-planned blinded interim analysis was conducted after 150 patients had been randomized and was intended to evaluate SAEs during the study. The O'Brien–Fleming approach was used for the stopping rule for efficacy by considering a *P* value for difference in the primary outcome rate of 0.005. A stopping rule for the difference in the mortality rate and rates of adverse events was based on a *P* value of 0.01. We considered for this interim analysis the following events: 30-day mortality and the rate of digital ischemia, mesenteric ischemia, hyponatremia, and postoperative acute myocardial infarction. The study's data safety and monitoring committee recommended that the trial should continue.

We compared follow-up measures and clinical outcomes on a modified intention-to-treat basis according to the randomized study group assignment. Patients who had undergone randomization but never received the masked drug were not included in the analysis because an exclusion criterion was identified after randomization, they were equally distributed between groups, and this did not bias outcome ascertainment. Continuous variables were compared using a Student's *t* test or Mann–Whitney *U* test, and categorical variables were compared using Pearson chi-square test, Fisher exact test, or a likelihood ratio test.

Results are expressed as means with SDs or medians with interquartile ranges. We calculated unadjusted Kaplan–Meier survival curves showing 30-day probability of the primary outcome for each group and compared the curves using the log-rank test. For the primary endpoint, we performed additional analyses using a multivariable Cox proportional hazards model, adjusting for the main factors known to predict outcomes in these patients (factors were selected for inclusion if the *P* value in the univariate analysis was less than 0.10). Unadjusted and adjusted analyses for the secondary endpoints were performed using generalized linear and logistic regression models and are presented as between-group differences or odds ratios (OR) with 95% CIs.

A two-sided *P* < 0.05 was considered statistically significant. The statistical analysis was performed using SPSS version 18.0 (SPSS Inc., USA).

Results

Study Population

From a total of 2,365 patients who were screened for eligibility preoperatively, 330 were randomized (fig. 1). Of these 330 patients, five withdrew consent and 25 did not receive the trial drug because we identified an exclusion criterion before the first dose of study drug was given (13 patients in the vasopressin group and 12 patients in the norepinephrine group had already been receiving open-label vasopressors before randomization). We did not include these 30 patients in the analysis because they had not been eligible for randomization according to the study's inclusion/exclusion criteria, they never received the masked trial drug, and they were equally distributed between groups and thus did not bias outcome ascertainment.¹⁸ We, therefore, analyzed 300 patients (149 patients in the vasopressin group and 151 patients in the norepinephrine group; fig. 1). Baseline characteristics of the two groups are shown in table 1. The study patients were characterized as intermediate risk according to the European System for Cardiac Operative Risk Evaluation; most had normal left ventricular function and underwent coronary artery bypass graft surgery (eTable 2 in the Supplemental Digital Content, <http://links.lww.com/ALN/B337>).

Primary Outcome

The primary outcome, a composite endpoint of death or severe postoperative complications within 30 days after

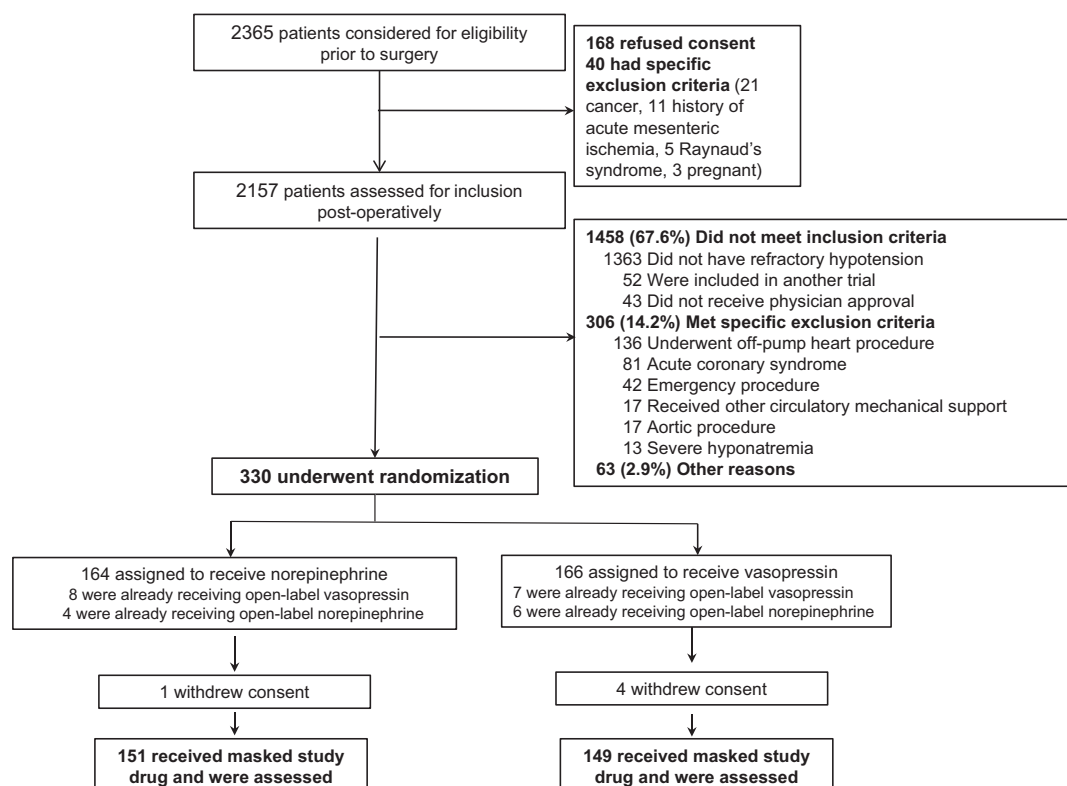


Fig. 1. Study flowchart.

Table 1. Baseline Characteristics of Study Patients

Variable	Norepinephrine (n = 151)	Vasopressin (n = 149)
Age (yr), mean and SD	55 ± 13	54 ± 14
Weight (kg), mean and SD	70 ± 13	73 ± 14
Height (m), mean and SD	1.63 ± 0.08	1.65 ± 0.09
Sex, n (%)		
Female	71 (47.0)	67 (45.0)
Male	80 (53.0)	82 (55.0)
Diabetes mellitus, n (%)	67 (44.0)	71 (47.6)
Hypertension, n (%)	77 (51.0)	74 (49.7)
History of acute myocardial infarction, n (%)	66 (43.7)	56 (37.6)
Congestive heart failure, n (%)	50 (33.1)	65 (43.6)
COPD, n (%)	65 (43.0)	54 (36.2)
Chronic renal failure, n (%)	44 (29.1)	37 (24.8)
Liver disease, n (%)	24 (15.9)	26 (17.4)
Excessive alcohol use, n (%)	31 (20.5)	31 (20.8)
Cancer, n (%)	12 (7.9)	6 (4.0)
β-blocker use, n (%)	97 (64.2)	97 (65.1)
Statin use, n (%)	27 (17.9)	26 (17.4)
ACEI/ARB use, n (%)	70 (46.4)	53 (35.6)
LVEF, n (%)		
> 60	79 (52.3)	79 (53.0)
40–60	50 (33.1)	40 (26.8)
< 40	22 (14.6)	30 (20.1)
IABP use	11 (7.3)	15 (10.1)
EuroSCORE, median (IQR)	5 (4–6)	5 (4–7)

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; IABP = intraaortic balloon pump counterpulsation; IQR = interquartile range; LVEF = left ventricular ejection fraction.

surgery, occurred in 74 patients in the norepinephrine group (49.0%; 95% CI, 41.0 to 57.0) and in 48 patients in the vasopressin group (32.2%; 95% CI, 24.7 to 39.7; hazard ratio [HR], 0.55; 95% CI, 0.38 to 0.80; $P = 0.0014$; absolute risk reduction, 16.8%; 95% CI, 5.7 to 27.3; table 2). Adjusted analyses yielded similar results (HR, 0.52; 95% CI, 0.36 to 0.75; $P = 0.0005$). This represents a number needed to treat of 6 (95% CI, 4 to 18) to avoid the composite outcome. The probability of the primary outcome occurring until day 30 was lower in the vasopressin group than in the norepinephrine group ($P < 0.0001$; fig. 2). Vasopressin reduced significantly the occurrence of acute renal failure as compared to norepinephrine (10.3% *vs.* 35.8%; $P < 0.0001$; HR, 0.26; 95% CI, 0.15 to 0.46).

Secondary Outcomes

There were no significant differences between groups in the 30-day occurrence of infection, septic shock, or ventricular arrhythmias (table 2). Time on mechanical ventilation during the study was similar in the two groups. By day 30, the incidence of atrial fibrillation was lower in the vasopressin than in the norepinephrine group (95 [63.8%] *vs.* 124 [82.1%]; adjusted OR, 0.37; 95% CI, 0.22 to 0.64; $P = 0.0004$).

The length of ICU stay was shorter in the vasopressin group than in the norepinephrine group (5 [4 to 7] *vs.* 6 [4 to 9] days; between-group difference, -2.28 [-3.94 to -0.62]; $P = 0.0071$; table 2). The length of hospital stay was also shorter in the vasopressin group (10 [8 to 12] *vs.* 13 [10 to 20] days; between-group difference, -3.66 [-6.01 to -1.32]; $P = 0.0022$; table 2).

In *post hoc* analyses, there were no significant differences between groups in the 30-day occurrence of pulmonary thromboembolism, low cardiac output, delirium, or acute respiratory distress syndrome (eTable 2 in the Supplemental Digital Content, <http://links.lww.com/ALN/B337>). Mortality at day 90 and ICU readmission rate were also similar between groups. The incidence of AKI according to Acute Kidney Injury Network stages 1, 2, and 3 was significantly lower in the vasopressin group than in the norepinephrine group (eTable 2 in the Supplemental Digital Content, <http://links.lww.com/ALN/B337>). More patients in the norepinephrine group required RRT than those in the vasopressin group (4 [2.7%] *vs.* 21 [13.9%]; OR, 0.17 [95% CI, 0.06 to 0.51]; $P = 0.0016$). Sequential Organ Failure Assessment scores at days 1, 2, and 3 were lower in the vasopressin group than in the norepinephrine group (eTable 3 in the Supplemental Digital Content, <http://links.lww.com/ALN/B337>).

We performed a subgroup analysis of patients regarding the use of β-blocker and ACEI/ARB. We observed that the benefit of vasopressin in reducing the primary outcome is maintained regardless of the use of β-blocker. Nevertheless, vasopressin did not reduce the primary outcome in the subgroup of patients not using ACEI/ARB (eTable 4 in the Supplemental Digital Content, <http://links.lww.com/ALN/B337>).

Vasopressor Therapy

In most cases, the study drug was started in the postanesthesia care unit before transfer to the ICU (34%) or in the first 3 h after ICU admission (51.3%). In the minority of patients (14.7%), it was started after the third hour of ICU admission until the second postoperative day.

There was no difference in MAP between the two groups immediately before the study-drug infusion (55 [50 to 60] mmHg in the vasopressin group *vs.* 58 mmHg [49 to 60] in the norepinephrine group; $P = 0.90$). Patients who received norepinephrine had a transiently lower MAP 15 min after drug infusion onset compared with patients who received vasopressin (63 [60 to 67] *vs.* 65 [62 to 70] mmHg; $P = 0.0280$); this difference was no longer present after 30 min. There were no differences between groups in the heart rate or cardiac index before or during the drug infusion (eTable 5 in the Supplemental Digital Content, <http://links.lww.com/ALN/B337>).

The duration of study-drug infusion was shorter in the vasopressin than in the norepinephrine group (34 [13 to 75] *vs.* 57 [22 to 114] h; $P = 0.0003$). The duration of inotropic support (dobutamine) was also lower in the vasopressin

Table 2. Primary and Secondary Outcomes in the Two Groups

Variable	Norepinephrine (n = 151)	Vasopressin (n = 149)	Unadjusted Odds Ratio or Hazard Ratio or Between- group Difference (95% CI)	P Value	Adjusted* Odds Ratio or Hazard Ratio or Between- group Difference (95%CI)	P Value
Primary outcome, n (%)	74 (49.0)	48 (32.2)	0.55 (0.38 to 0.80)	0.0014	0.52 (0.36 to 0.75)	0.0005
30-d mortality	24 (15.9)	23 (15.4)	0.99 (0.56 to 1.76)	0.98	1.11 (0.62 to 1.96)	0.73
MV > 48 h	13 (8.6)	8 (5.4)	0.62 (0.26 to 1.49)	0.28	0.62 (0.26 to 1.51)	0.30
Sternal wound infection	15 (9.9)	7 (4.7)	0.46 (0.19 to 1.13)	0.09	0.48 (0.19 to 1.18)	0.11
Reoperation	10 (6.6)	10 (6.7)	0.8 (0.52 to 1.23)	0.31	0.79 (0.51 to 1.22)	0.28
Stroke	4 (2.6)	4 (2.7)	1.03 (0.26 to 4.11)	0.97	1.08 (0.27 to 4.39)	0.91
Acute renal failure	54 (35.8)	15 (10.3)	0.26 (0.15 to 0.46)	< 0.0001	0.26 (0.15 to 0.46)	< 0.0001
Secondary outcomes, n (%)						
Infection	23 (15.2)	16 (10.7)	0.67 (0.34 to 1.33)	0.25	0.71 (0.35 to 1.42)	0.33
Septic shock	13 (8.6)	9 (6.0)	0.68 (0.28 to 1.65)	0.40	0.73 (0.3 to 1.81)	0.50
Atrial fibrillation	124 (82.1)	95 (63.8)	0.38 (0.22 to 0.65)	0.0004	0.37 (0.22 to 0.64)	0.0004
Ventricular arrhythmias	32 (21.2)	27 (18.1)	0.82 (0.46 to 1.46)	0.50	0.8 (0.45 to 1.43)	0.45
Length of ICU stay (d), median (IQR)	6 (4 to 9)	5 (4 to 7)	-2.42 (-4.11 to -0.73)	0.0050	-2.28 (-3.94 to -0.62)	0.0071
Length of hospital stay (d), median (IQR)	13 (10 to 20)	10 (8 to 12)	-3.76 (-6.1 to -1.42)	0.0016	-3.66 (-6.01 to -1.32)	0.0022

*Adjustment was performed for predictive variables of the combined endpoint: chronic renal failure, initial hematocrit level, and intraoperative use of epinephrine. Hazard ratio was used for primary outcomes. Odds ratio or between-group difference was used for secondary outcomes.

ICU = intensive care unit; IQR = interquartile range; MV = mechanical ventilation.

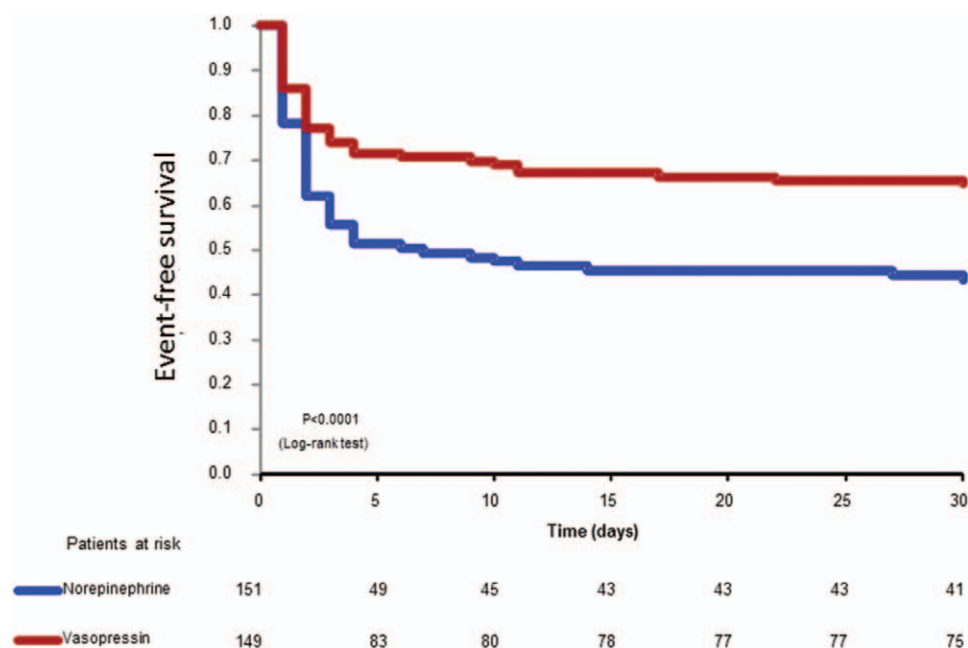


Fig. 2. Kaplan-Meier curves showing the 30-day event-free—primary outcome—survival in patients randomized to norepinephrine or vasopressin infusion. Primary outcome refers to the composite endpoint of mortality or severe complications within 30 days after randomization, including stroke, requirement of mechanical ventilation for longer than 48 h, deep sternal wound infection, reoperation, or acute renal failure.

group than in the norepinephrine group (40 [26 to 68] *vs.* 54 [33 to 89] h; $P = 0.0068$). There was no significant difference between groups in the number of patients who needed additional norepinephrine (17 [11.4%] in the vasopressin group *vs.* 29 [19.2%] in the norepinephrine group; $P = 0.06$). The amount of fluid infused and the fluid balance

were similar in the two groups (eTable 5 in the Supplemental Digital Content, <http://links.lww.com/ALN/B337>).

Regarding other outcomes and SAEs not included in the primary outcome, we found a lower occurrence of atrial fibrillation in the vasopressin group when compared to the norepinephrine group (82.1% *vs.* 63.8%; $P = 0.0004$) and

Table 3. Protocol-defined Serious Adverse Events Triggering Dose Adjustment

Variable	Norepinephrine (n = 151)	Vasopressin (n = 149)	P Value
No. of adverse events, n (%)			
0	126 (83.4)	125 (83.9)	0.52*
1	20 (13.2)	21 (14.1)	
2	4 (2.6)	1 (0.7)	
3	1 (0.7)	2 (1.3)	
Digital ischemia	2 (1.3)	3 (2.0)	0.68†
Mesenteric ischemia	2 (1.3)	3 (2.0)	0.68†
Hyponatremia	10 (6.6)	12 (8.1)	0.63‡
Postoperative AMI	17 (11.3)	11 (7.4)	0.25‡

*Likelihood ratio test. †Fisher exact test. ‡Chi-square test.

AMI = acute myocardial infarction.

no difference between groups in the rates of digital ischemia, mesenteric ischemia, hyponatremia, and postoperative acute myocardial infarction (tables 2 and 3). Patients who received norepinephrine had higher creatinine levels on days 1, 2, and 3 than those who received vasopressin. There were no differences between groups in arterial lactate, creatine kinase MB, troponin, C-reactive protein, hematocrit, or platelet count during the study (eTable 6 in the Supplemental Digital Content, <http://links.lww.com/ALN/B337>).

Vasopressin Levels

Serum vasopressin concentrations were measured in the first 89 patients (44 in the vasopressin group and 45 in the norepinephrine group) at four different time points: immediately before the study drug infusion (T0) and after 6 (T6), 12 (T12), and 24 (T24) h. In both arms, vasopressin levels increased sharply in the first 6 h; they then remained stable in the vasopressin group but decreased steadily in the norepinephrine group (eFigure 1 in the Supplemental Digital Content, <http://links.lww.com/ALN/B337>).

Discussion

This is the first prospective, randomized, double-blind study to evaluate vasopressin as the initial drug in the management of vasoplegic shock after cardiac surgery. Vasopressin reduced the composite endpoint of death or severe complications over 30 days compared to norepinephrine. Compared to norepinephrine, vasopressin reduced the rates of acute renal failure, RRT, and atrial fibrillation, without effects in mortality. Vasopressin use was associated with a shorter duration of inotropic and vasopressor therapy and shorter lengths of ICU and hospital stay. We also observed a tendency toward a reduction in sternal wound infection in vasopressin-treated patients. These benefits were observed without apparent complications.

The rationale for the use of vasopressin in the initial phase of vasoplegic shock after cardiac surgery is based on physiologic and pathophysiologic studies demonstrating the fundamental role of the vasopressin system in the maintenance of vascular tone and on the reduced plasma levels of vasopressin

in the postoperative period.^{19,20} Moreover, the occurrence of vasoplegic shock refractory to catecholamines is frequent after cardiac surgery, especially in patients previously treated with β -blockers or ACEI.²¹ The multiple effects of vasopressin on arterial tone make it a potentially useful agent in the management of vasoplegic shock after cardiac surgery.

Vasoplegic shock after cardiac surgery may have some analogies with septic shock. The VASST trial¹³ evaluated the effect of low-dose vasopressin (0.03 U/min) associated with low-dose norepinephrine compared to norepinephrine alone in patients with septic shock. The study showed no global differences between groups in 28-day mortality, but the mortality rate was lower in the vasopressin group than in the norepinephrine group in the stratum of patients with less severe septic shock. This study demonstrated the safety and efficacy of vasopressin and highlighted its role in reducing norepinephrine requirements in septic shock. In addition to the different patient population, our study did not evaluate the catecholamine-sparing effect of norepinephrine; rather, we investigated the efficacy of vasopressin administered very early as the sole initial drug in the management of vasodilatory shock.

This is the first study evaluating vasopressin plasma levels in patients receiving vasopressin alone in the treatment of vasodilatory shock after cardiac surgery. We measured plasma levels of vasopressin in a sample of 89 patients. Our values measured immediately after randomization confirm previous findings of decreased levels of vasopressin after CPB.²² Six hours after drug infusion, vasopressin levels increased in both groups, probably due to the typical physiologic response to hypotension. However, in the norepinephrine-treated patients, vasopressin levels then decreased progressively, an effect not observed in the vasopressin group, who had, at 12 and 24 h after surgery, higher levels of plasma vasopressin. This effect could explain why MAP was restored earlier and more consistently in the vasopressin-treated patients. In our study, the vasopressin plasma levels were lower than those in reports in patients with septic shock.¹⁸ We postulate that septic shock might have less depletion of brain storages of vasopressin in shock. Conversely, vasodilatory shock after cardiac surgery may be associated with a

significant reduction in cerebral production and release of vasopressin into the circulation.²²

Another interesting property of vasopressin in patients undergoing cardiac surgery is its neutral effects on myocardial oxygen consumption. In our study, vasopressin did not increase the heart rate and was not associated with a higher incidence of myocardial ischemia. Similar observations were reported in the VASST study.²³

Atrial fibrillation, a common supraventricular arrhythmia after cardiac surgery, was significantly less common in patients who received vasopressin compared to patients receiving norepinephrine. Although the pathophysiology of postoperative atrial fibrillation is complex and multifactorial, the inflammatory response in addition to increased sympathetic stimulation on the B1 receptors in the atrial myocardium is directly involved in its occurrence after cardiac surgery.²⁴ It is likely that norepinephrine, but not vasopressin, can increase adrenergic stimuli through the B1 receptors, resulting in increased atrial ectopic activity and, consequently, in a higher incidence of atrial fibrillation.

Acute renal failure is one of the most serious complications of vasoplegic shock, occurring in 23% of our patients. In our study, vasopressin administration was associated with a lower incidence of acute renal failure and a reduced need for RRT compared to norepinephrine. These findings are similar to previous studies that demonstrated that vasopressin has complex effects on renal function as result of its global hemodynamic action and vasopressin receptor stimulation. In the VASST trial, in patients in the Risk, Injury, Failure, Loss, and End-Stage Renal Failure risk category, vasopressin reduced the rate of progression to renal failure and the need for RRT compared to norepinephrine.⁸ In that study also, patients with AKI who were treated with vasopressin had a higher rate of renal recovery and lower mortality.^{8,13} Holmes *et al.*,²⁵ in a series of 50 septic patients, showed that vasopressin infusion increased MAP and diuresis. The binding of vasopressin to AVPR1a receptors on glomerular efferent arterioles results in glomerular efferent arteriolar vasoconstriction and thus increases glomerular filtration.²⁶ By contrast, norepinephrine binds preferentially to the α -1 receptors of renal afferent arterioles, decreasing glomerular perfusion pressure and filtration.²⁶ Because patients in the vasopressin and norepinephrine groups in our study had similar arterial pressures, the different rates of acute renal failure and need for RRT between the groups may be the result of beneficial effects of vasopressin on the renal vasculature. These data suggest that vasopressin administration should be started early before significant organ failure is established.

The preoperative use of ACE or β -blockers predisposes to vasoplegic shock after cardiac surgery.²¹ The subgroup analysis of our study showed that vasopressin reduced the primary outcome regardless of the use of β -blocker. On the other hand, vasopressin did not reduce the primary outcome in the subgroup of patients not using ACEI/ARB, suggesting an interaction of vasopressin with the ACE/ARB pathways. As

these data are *post hoc* analyses, they must be interpreted with caution, and future studies are needed to address this issue.

Our study is limited by its monocenter nature, but this may also increase the intrinsic value of the study by reducing noise. In addition, it was performed in a single referral center for cardiac surgery, which could compromise the generalizability of our findings. The change in the primary outcome could be initially interpreted as a limitation; however, at the beginning of the trial, few outcome data on vasoplegic patients were available in the literature; therefore, the modified Society of Thoracic Surgeons score was demonstrated to better measure outcomes in the field of cardiac surgery.

Vasopressin reduced the incidence of severe complications and lengths of ICU and hospital stays in patients with vasoplegic shock after cardiac surgery, likely because of the action of vasopressin on renal function. Moreover, vasopressin reduced the incidence of atrial fibrillation, possibly as a result of reduced exposure of patients to catecholamines. With the high incidence and severity of vasoplegic shock and its associated complications after cardiac surgery, our data suggest that vasopressin may be preferable to norepinephrine in the management of these patients.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Hajjar: ludhmila@usp.br. Raw data available from Dr. Hajjar: ludhmila@usp.br.

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