A Double-Blind Randomized Trial: Prophylactic Vasopressin Reduces Hypotension After Cardiopulmonary Bypass

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Background. **Inhibition of angiotensin-converting enzyme (ACE) predisposes patients to vasodilatory hypotension after cardiopulmonary bypass (CPB). This hypotension has been correlated with arginine vasopressin deficiency and can be corrected by its replacement. In patients receiving ACE inhibition, we investigated whether initiation of vasopressin before CPB would diminish post-CPB hypotension and catecholamine use by avoiding vasopressin deficiency.**

Methods. **Cardiac surgical patients on ACE inhibitor therapy were randomized to receive vasopressin (0.03 U/min) (n = 13) or an equal volume of normal saline (n = 14) starting 20 minutes before CPB.**

Results. **Vasopressin did not change pre-CPB mean arterial pressure or pulmonary artery pressure. After CPB, the vasopressin group had a lower peak norepinephrine dose than the placebo group (4.6 ± 2.5 versus 7.3 ± 3.5 μg/min, $p = 0.03$), a shorter period on catecholamines (5 ± 6 versus 11 ± 7 hours, $p = 0.03$), fewer hypotensive episodes (1 ± 1 versus 4 ± 2, $p < 0.01$), and a shorter intensive care unit length of stay (1.2 ± 0.4 versus 2.1 ± 1.4 days, $p = 0.03$).**

Conclusions. **In this cohort, prophylactic administration of vasopressin, at a dose without a vasopressor effect pre-CPB, reduced post-CPB hypotension and vasoconstrictor requirements, and was associated with a shorter intensive care unit stay.**

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Vasodilatory shock, induced by cardiopulmonary bypass (CPB), is usually mild, requiring low doses of catecholamine vasopressor support to maintain perfusion pressure for the first few hours past CPB. However, in about 8% of cases, a more severe state of distributive shock develops (systolic arterial pressure less than 80 mm Hg despite a cardiac output of more than 5 L/min) necessitating high-dose catecholamine vasopressor therapy (norepinephrine administration more than 8 μg/min) [1]. The administration of high-dose catecholamine vasopressors is associated with complications related to end-organ hypoperfusion and prevents early intensive care unit (ICU) discharge.

The factors responsible for impaired vasomotor tone after CPB are only partially elucidated. We have previously noted an increased incidence of this shock state in patients with a preoperative history of congestive heart failure, suggesting a possible role for heart failure-induced vasodilatory factors such as tumor necrosis factor and nitric oxide [1, 2]. The preoperative use of angiotensin-converting enzyme (ACE) inhibitors is also independently associated with an increased incidence of vasodilatory shock after CPB [1]. This fact suggests that in addition to pathogenic activation of vasodilator mechanisms, a failure of vasoconstrictor mechanisms may also contribute to this form of shock [3, 4]. We have recently discovered that vasopressin is important in the maintenance of vascular tone after CPB and that a deficiency in vasopressin contributes to vasodilatory shock [5, 6]. The correction of this deficiency with low-dose vasopressin "replacement" therapy dramatically improves hemodynamics in post-CPB vasodilatory shock. In prior studies, vasopressin infusion increased arterial pressure and allowed reduction or elimination of catecholamine vasopressor requirements in post-CPB vasodilatory shock [5, 6]. Because vasopressin, at low doses, has little effect on blood pressure in normotensive subjects but becomes a potent pressor in vasodilatory shock, the drug could be an ideal prophylactic agent for patients at risk [7, 8]. Thus, we conducted a double-blinded randomized trial of low-dose vasopressin infusion initiated before CPB in patients receiving ACE inhibitors and therefore at risk for post-CPB vasodilatory hypotension. End points included incidence of hypotensive episodes, catecholamine requirements, and ICU length of stay.

Material and Methods

Informed consent was obtained from 33 patients using a protocol approved by the Columbia Presbyterian Medical Center Institutional Review Board. Patients undergo-

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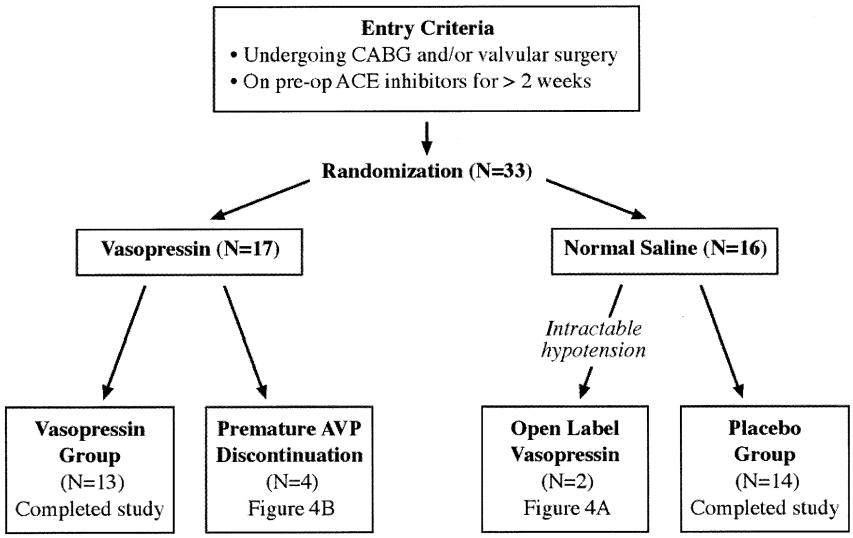

Fig 1. Disposition of patients in prophylactic vasopressin trial. (ACE = *angiotensin-converting enzyme;* AVP = *arginine vasopressin;* CABG = *coronary artery bypass grafting;* pre-op = *preoperative.*)

ing coronary artery bypass grafting or valvular surgery were eligible for the study if they had been on ACE inhibitor therapy for at least 2 weeks preoperatively and up to the day of surgery. Using the method of simple random sampling, we assigned patients to receive either vasopressin (0.03 U/min) or an equal volume of normal saline (2 mL/h) for the duration of the study. The study drug was started 20 minutes before the initiation of CPB and was maintained for a maximum of 72 hours or until the patient was stable off all catecholamine vasopressors and being discharged from the ICU. Investigators, clinical staff, and patients were blinded to the identity of the study drug. The same group of attending cardiac anesthesiologists, intensivists, and cardiac surgeons cared for all patients and followed their standard practices with regard to patient care. They were allowed to administer any medication deemed clinically indicated, including open-label vasopressin if intractable vasodilatory shock supervened. If an attending physician administered open-label vasopressin to a study subject for post-CPB vasodilatory shock, which is the standard of practice at our institution, that subject's data were segregated and reported separately. In patients with low flow states, the use of vasopressin, albeit at concentrations higher than 0.3 U/min, correlates with a higher incidence of peripheral ischemia [9, 10]. Thus patients who manifested hypovolemic or cardiogenic shock (cardiac index less than 1.8 $L \cdot min^{-1} \cdot m^{-2}$ 15 minutes after CPB) were to be removed from the study; no patient met this removal criterion. The study algorithm and disposition of patients are shown in Figure 1.

Hemodynamic data were recorded continuously during administration of the infusions; cardiac output was measured per routine with a definite measurement at 15 minutes after CPB ended to determine continued participation in the protocol. The hemodynamic data of the first 5 patients of the study were not recorded before the study drug (no base line) was initially infused. The literature clearly demonstrates that vasopressin at the doses used in this study does not affect the hemodynamics of normotensive patients (as these study subjects were before CPB) [7, 8]. However, we thought that documenting this phenomenon in the pre-CPB state for this study would be prudent. Thus, for all 28 subsequent patients, hemodynamic recordings were started 30 minutes before administering the study drug. Blood samples for vasopressin were drawn 15 minutes before administration of the study drug, 60 minutes on bypass, 90 minutes off bypass, and at 90 minutes after completion of the infusion. Episodes of hypotension (systolic blood pressure less than 90 mm Hg for longer than 5 minutes), and peak norepinephrine dose were noted. Norepinephrine peak dose was recorded because it is our institution's primary vasoconstrictor after CPB and was the first-line and most aggressively used vasopressor in all study subjects who received vasoconstrictors. The duration of catecholamine (ie, norepinephrine, phenylephrine, or epinephrine) vasopressor use and complications were also recorded. Intensive care unit lengths of stay and intubation times were recorded in days, with extubation on the night of surgery through the first postoperative day recorded as day 1.

All interval data were parametrically analyzed by the two-sample Student's t test with a p value less than 0.05 considered statistically significant. Nominal data such as gender distribution was analyzed using the Fisher exact test. Count (frequency) data such as the number of hypotensive episodes was compared using Poisson regression techniques. All data are expressed as the mean $\pm$ standard deviation.

Results

Sixteen patients were randomized to the placebo group and 17 to the vasopressin group. Two patients in the placebo group could not be weaned from CPB because of intractable vasodilatory shock and received vasopressin, which is the standard of care at our institution. Addition-

Table 1. Characteristics of Study Groups

Group	Age, y	Male Sex, %	Pre-op EF	CPB Time (minutes)
Vasopressin	60 ± 12	64	0.40 ± 0.14	116 ± 32
Placebo	62 ± 11	71	0.48 ± 0.11	110 ± 32

None of the characteristics were significantly different between groups.

CBP = cardiopulmonary bypass; Pre-op EF = preoperative ejection fraction

ally, 4 patients from the vasopressin group were disqualified when the study drug was inadvertently discontinued during the first 6 hours, out of protocol. The responses of the remaining 27 patients were analyzed (Fig 1).

The vasopressin group (n = 13) did not differ significantly from the placebo group (n = 14) with respect to age, sex, CPB time, or preoperative left ventricular ejection fraction (Table 1). The number of patients in the vasopressin and placebo group taking each specific ACE inhibitor, respectively, were enalapril (5 versus 2), quinapril (3 versus 1), lisinopril (4 versus 5), and captopril (2 versus 2). In the placebo group patients had also been taking fosinopril (1), benazepril (1), and other ACE inhibitor (1). No significant difference was noted in the type of cardiac procedures that patients underwent (vasopressin versus placebo group): coronary artery bypass grafting (54% versus 43%), valve procedure only (31% versus 36%), and combined revascularization and valve procedure (15% versus 21%). Of note, 3 aortic valve replacement procedures were performed in each group. The administration of vasopressin pre-CPB did not significantly change mean arterial pressure (80 ± 12 to 78 ± 11 mm Hg, p = NS), mean pulmonary artery pressure (22 ± 8 to 23 ± 8 mm Hg, p = NS), systolic pulmonary artery pressure (34 ± 6 to 33 ± 8 mm Hg, p = NS), or diastolic pulmonary artery pressure (16 ± 7 to 18 ± 8 mm Hg, p = NS). Plasma vasopressin levels before administration of

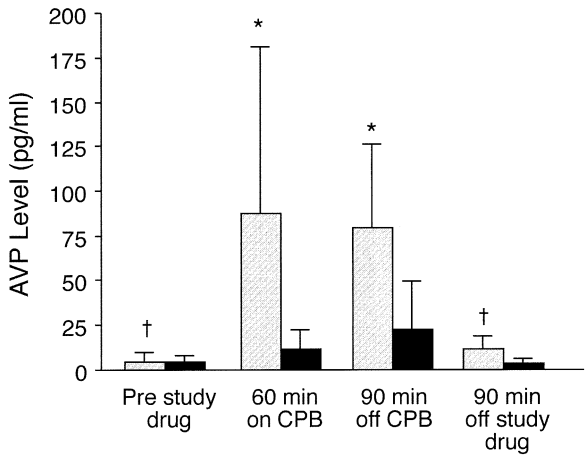

*Fig 2. Plasma vasopressin concentrations in the vasopressin and placebo groups. □ = AVP; ■ = placebo. *p < 0.05; †not significant. (AVP = arginine vasopressin; CPB = cardiopulmonary bypass.)*

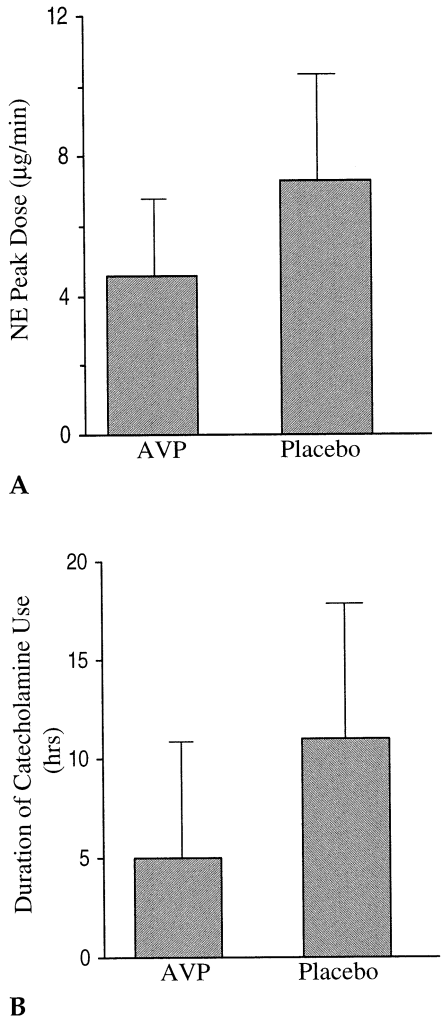

Fig 3. Catecholamine requirements in the vasopressin and placebo groups: (A) NE peak dose (p = 0.03) and (B) duration of use (p = 0.03). (AVP = arginine vasopressin; NE = norepinephrine.)

the study drug were similar in both groups. After initiation of the study infusion, vasopressin levels were appropriately elevated in the vasopressin group compared with the placebo group ($p < 0.05$), as demonstrated by the time points in Figure 2. Peak norepinephrine doses were significantly higher in the placebo group than in the vasopressin group (7.3 ± 3.5 versus 4.6 ± 2.5 µg/min, p = 0.03), as was the duration of catecholamine use (11 ± 7 versus 5 ± 6 hours, p = 0.03) (Fig 3) and the number of hypotensive episodes (4 ± 2 versus 1 ± 1, $p < 0.01$). The vasopressin group also had significantly shorter intubation time (1.0 ± 0.4 versus 1.4 ± 0.5 days, p = 0.02) and length of ICU stay (1.2 ± 0.4 versus 2.1 ± 1.4 days, p = 0.03).

The hemodynamic responses of the 6 patients excluded from the study are shown in Figure 4. These results were segregated and are shared as an addendum because the courses of these 6 patients suggest the central role of AVP in the post-CPB period. Two patients initially randomized to placebo could not be weaned

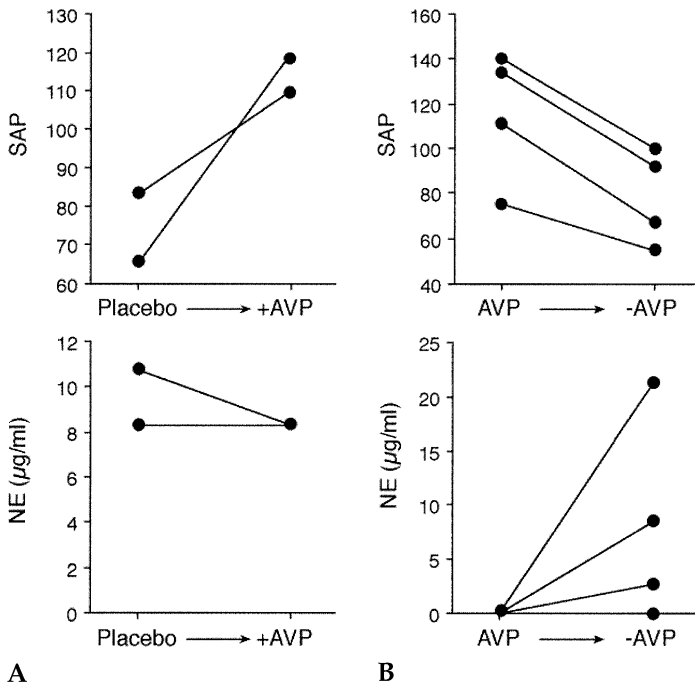

*Fig 4. Hemodynamic response and pressor administration in patients removed from protocol. (A) Placebo changed to open-label vasopressin (+AVP); time course 15 minutes. (B) Vasopressin discontinued prematurely (−AVP); time course 4 hours. (*AVP = *arginine vasopressin;* NE = *norepinephrine;* SAP = *systolic arterial pressure [mm Hg].)*

from CPB because of intractable vasodilatory shock (systolic arterial pressure less than 80 mm Hg despite a cardiac output of more than 5 L/min and norepinephrine administration more than 8 μg/min). Open-label vasopressin (0.03 to 0.1 U/h) was administered and with no other changes in management, systolic arterial pressure rose to more than 100 mm Hg within 15 minutes and both patients were successfully weaned from bypass (Fig 4A). No episodes of intractable vasodilatory shock were observed in the vasopressin group.

In 4 patients randomized to vasopressin, the study drug was discontinued prematurely, during the first 6 hours, and outside the terms of the protocol (eg, due to loss of central venous access). Hypotension followed the premature discontinuation of vasopressin and this response suggests the likely pressor action of the hormone (Fig 4B). No episodes of hypotension were noted upon discontinuation of the study drug within the terms of the protocol.

Two complications occurred in each group: acute renal insufficiency and right heart failure in the vasopressin group and acute renal insufficiency and a lethal hemorrhage in the normal saline group. No instances of postoperative myocardial infarction, hepatic insufficiency, intestinal infarction, limb digit ischemia, or stroke were noted in either group.

Comment

Exogenous vasopressin is a uniquely effective vasopressor in vasodilatory shock states [3, 5, 6]. In contrast, exogenous vasopressin has little vasopressor effect in normal subjects at high doses [7, 8], and patients with the syndrome of inappropriate antidiuretic hormone are normotensive [7, 11]. In states of arterial underfilling such as acute volume depletion or decompensated congestive heart failure, endogenous vasopressin acts as a potent vasopressor as evidenced by marked hypotension upon administration of a vasopressin receptor (V_1) antagonist [12, 13]. However, despite this increased sensitivity to vasopressin, exogenous vasopressin does not significantly raise blood pressure in these states because the levels of endogenous hormone are already elevated (receptor occupancy is high). We have discovered that a variety of vasodilatory shock states with high cardiac output (eg, septic shock, late phase of hemorrhagic shock, and post-CPB shock) are characterized by a defect in the baroreflex-mediated secretion of vasopressin and by a deficiency in the hormone. The administration of vasopressin in these states results in a hypersensitive vasopressor response [3, 5, 14, 15]. The mechanism of vasopressin is unique among vasoconstrictors in that vasopressin both increases cytosolic calcium levels through an inositol trisphosphate second messenger system and antagonizes the vasodilatory mechanisms of shock [3, 5].

The decreased pressor action of catecholamines in vasodilatory shock likely reflects the pathologic activation of vasodilator mechanisms [16, 17]. Increased plasma levels of nitric oxide and atrial natriuretic peptide occur in a variety of vasodilatory shock states. Also, the use of inodilators such as β-agonists (eg, dobutamine) and phosphodiesterase inhibitors (eg, milrinone) in cardiac surgery are often contributory to vasodilation after CPB [2, 18, 19]. Most importantly, K^+_{ATP} channels on vascular smooth muscle are opened in vasodilatory shock by cellular acidosis/hypoxia. These open channels cause vascular smooth muscle cells to hyperpolarize, thereby

closing the voltage-gated calcium channels that mediate catecholamine-induced vasoconstriction [20, 21]. This process may explain why clinically used vasoconstrictors, which are all catecholamine based, are less effective in vasodilatory shock. Vasopressin inhibits the following vasodilator mechanisms: (1) it blocks K^+_{ATP} channels on vascular smooth muscle, allowing endogenous and exogenous catecholamines to become effective; (2) vasopressin blunts the rise in cGMP due to nitric oxide and atrial natriuretic peptide; and (3) vasopressin blunts the rise in cAMP due to β-adrenergic stimulation [3, 20–23].

Thus vasopressin appears to possess ideal properties for vasodilatory shock prophylaxis: it can be administered at doses without effect in hemodynamically stable subjects [8], but is rendered a potent vasopressor in the setting of vasodilatory shock complicated by vasopressin deficiency, as seen in post-CPB vasodilatory shock [5, 6]. In the present study, vasopressin administered before CPB did not increase pre-CPB blood pressure or pulmonary artery diastolic pressure compared with placebo, suggesting no deleterious effect on left ventricular function. Nonetheless, the consequences of vasodilation after CBP were diminished by prophylactic AVP administration in our patients at risk for this complication. Vasopressin significantly reduced the number of hypotensive episodes, the peak norepinephrine dose used to maintain arterial pressure off CPB, and the duration of catecholamine vasopressor use compared with the placebo group. These results were associated with earlier extubation and a shorter ICU length of stay for the vasopressin group.

Prophylactic vasopressin appears to be of benefit in a population of heart surgery patients at risk for vasodilatory shock-related to CPB. Before being widely accepted as a standard of care, larger studies are needed. However, this study demonstrates that because of the unique characteristics of vasopressin, the prophylaxis of hypotension in shock states characterized by vasopressin deficiency (ie, prolonged sepsis and hemorrhagic shock) is possible [14]. Further investigations will be needed to assess the general utility of vasopressin prophylaxis in other clinical scenarios in which patients are at risk for vasodilatory shock.

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