Selecting a Vasopressor Drug for Vasoplegic Shock After Adult Cardiac Surgery: A Systematic Literature Review

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The choice of vasopressors to treat vasodilatory shock after cardiac surgery is a matter of controversy. We have systematically reviewed the literature and found that the data are insufficient to guide choice of agent. However, we found sufficient evidence that when a target blood pressure can not be achieved with a single agent, addition of another is more likely to help achieve the blood pressure target. We also found that there is no evidence that vasopressors induce organ ischemia. Finally, the lack of high quality data indicate that large multicenter trials are needed in this field.

(Ann Thorac Surg 2007;83:715–23)

Vasodilatory (vasoplegic) shock requiring vasopressor support is a recognized and relatively common complication of cardiopulmonary bypass (CPB) [1]. It is characterized by an adequate or elevated cardiac output, a low mean arterial pressure, and evidence of organ dysfunction, such as oliguria or elevated lactate levels or confusion or coronary ischemia. Such physiologic changes in association with a low blood pressure suggest organ dysfunction secondary to insufficient perfusion pressure in turn secondary to vasodilatation. They lead to the initiation of vasopressor therapy with the aim of restoring vessel tone toward normal and improving the perfusion of vital organs. The underlying mechanisms responsible for the decreased vascular resistance seem related to a systemic inflammatory response to CPB and are only partly understood [2–8]. Several factors are associated with postoperative CPB vasodilatory shock, including chronic heart failure, preoperative use of vasodilators, such as angiotensin-converting enzyme inhibitors and beta-blockers, or postoperative use of amiodarone and phosphodiesterase III inhibitors [9–13].

The syndrome of vasoplegic shock has been reported in approximately 5% to 20% of adult patients after CPB [7]. Such shock is typically of limited severity and may only require low doses of vasopressor support to maintain vital organ perfusion pressure [14]. However, in a smaller percentage of cases, a more severe syndrome develops, which requires high-dose vasopressor therapy [10, 15]. The mortality associated with this condition is considerable [16].

Despite a wide range of available vasopressor agents, no consensus exists on the treatment of hyperdynamic vasodilatory shock postoperative CPB, and there is controversy about the choice of vasopressor to achieve an adequate mean arterial pressure (MAP) [17].

This systematic review of the literature seeks to examine the pharmacological options for vasopressor support in the postoperative CPB patient and to describe and classify the available evidence for the choice of vasopressor drugs after CPB in adults.

Material and Methods

We performed a systematic literature search (January 1980–July 2006) with preset rules. The literature search was performed with MEDLINE and PubMED using the following key words: cardiac surgery, cardiopulmonary bypass, coronary artery bypass grafting, valve surgery, norepinephrine, vasopressin, phenylephrine, methylene blue, dopamine, vasopressor, alpha adrenergic, vasoactive, low systemic vascular resistance, vasoplegia, shock, ischemia, perfusion, and blood flow.

All articles in question were obtained. The bibliographies of articles identified through this methodology were also studied for articles that might have been missed by the electronic reference library methodology. Non-English language papers, animal studies, pediatric studies, and in vitro studies were not included. Papers were selected and graded for quality of evidence according to the methodology of Cook and colleagues [18] (Tables 1, 2). One of authors (ME) performed the literature search, read all the articles, and selected those relevant to the current review.

Particular attention was given to the following issues regarding each agent: (1) the ability of each vasopressor to increase systemic arterial pressure; (2) the effects of

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Published by Elsevier Inc

0003-4975/07/$32.00
doi:10.1016/j.athoracsur.2006.08.041

Table 1. Grading of Levels of Evidence

Level 1	Randomized trials with low α error (< 0.05) and β error (< 0.8)
Level 2	Randomized trials with high α error or low power
Level 3	Non randomized, concurrent cohort studies
Level 4	Nonrandomized, historic cohort studies
Level 5	Case series

each vasopressor on systemic hemodynamics; (3) the effect of each vasopressor on measures of vital organ perfusion and function; (4) the effect of each vasopressor on major clinical outcomes (eg, time spent in the hospital or intensive care unit or need for ventilation or artificial renal support); (5) the effect of each vasopressor on survival; and (6) the presence of any important side effects of each vasopressor.

Data on the use of each drug were examined. Evidence-based recommendations were developed where possible.

Results

Our literature search identified 786 articles. Of these, 164 articles were relevant to cardiac surgery. Of these 164 articles, only 56 reported clinical studies of vasopressor drugs in cardiac surgery patients. Of these 56 articles, only 37 assessed these agents in the postoperative CPB period. These 37 articles were used for the current systematic review. The results of our literature search are considered by pharmacological groups and agents.

Catecholamines

Natural and synthetic catecholamines have different hemodynamic effects because of their differential ability to stimulate adrenergic receptors. Accordingly we considered each separately.

Norepinephrine

Norepinephrine increases MAP by stimulation of α1-adrenergic receptors in vascular smooth muscle and β receptors in the kidney causing angiotensin II release [19].

We found 12 studies [17, 20–30] of which only 7 report on its MAP effect, and all found that norepinephrine increases MAP after CPB [22, 23, 25–27, 29, 30]. This increase is typically associated with no change in heart rate, cardiac index, pulmonary capillary wedge pressure, and central venous pressure, but with a significantly greater increase in left ventricular stroke work index [26].

In one study, norepinephrine infusion induced no change in left internal mammary artery graft flows and significantly increased flow through saphenous vein grafts by 21% (n = 21).

Totaro and Raper conducted a small randomized study to compare norepinephrine and epinephrine in patients requiring vasopressor support for the management of vasodilatory shock after CPB (n = 36) [23]. None of 17 patients allocated to the norepinephrine group had acidosis, hyperlactatemia, or a significant decrease in base excess or pH develop. Norepinephrine was associated with a significantly higher base excess and pH (at 1 hour and 6 to 10 hours after starting the infusion) and a lower cardiac index and mixed venous PO2 (at 1 hour after start the infusion) compared with epinephrine. During the norepinephrine study period, cardiac index and limb blood flow, measured using strain gauge plethysmography, did not change significantly compared with the pre-infusion period. Maillet and colleagues [20] also showed that the postoperative use of norepinephrine did not induce hyperlactatemia after cardiac surgery.

Only three studies assessed the effect of norepinephrine infusion on measures of organ perfusion or function. Dunser and colleagues [21] showed that in 63 patients with vasodilatory shock, norepinephrine infusion was not an independent predictor of ischemic skin lesions. Nygren and colleagues [30] conducted small randomized crossover trials to compare norepinephrine and phenylephrine in 10 patients after uncomplicated coronary artery bypass surgery. Norepinephrine infusion did not impair perfusion of the gastrointestinal mucosa. Both norepinephrine and phenylephrine increased splanchnic oxygen extraction and the mixed venous-hepatic vein oxygen saturation gradient significantly. This increase was more pronounced with phenylephrine. Morimatsu and colleagues [17] showed that norepinephrine infusion in patients with hypotensive vasodilatation after CPB did not increase postoperative serum creatinine concentration.

Phenylephrine

Phenylephrine is an α1-selective agonist. It activates β adrenergic receptors only at much higher concentrations [31].

We found only nine studies investigating phenylephrine in postoperative CPB patients [26–28, 30, 32–36]. Six of these investigations described that phenylephrine was effective in increasing MAP [26, 27, 30, 32–36]. As part of one randomized study involving patients who had taken angiotensin-converting enzyme inhibitors, phenylephrine failed to increase MAP in a single individual who then went on to respond to angiotensin II [33]. Two remaining studies did not describe the effect of phenylephrine on MAP [28, 36].

In 1991, DiNardo and colleagues [26] showed that phenylephrine at a dose of 0.87 ± 0.37 μg/kg/min increased MAP by 19 mm Hg (25.3%). These increases are typically accompanied by no changed in heart rate, pulmonary capillary wedge pressure, central venous pressure, and cardiac index [34].

In a small randomized study, phenylephrine infusion to increase MAP by 20% and increased internal mam-

Table 2. Grading of Evidence Statements

Grade A	Supported by at least two level 1 investigations
Grade B	Supported by only one level 1 investigations
Grade C	Supported by level 2 investigation only
Grade D	Supported by at least one level 3 investigation
Grade E	Supported by level 4 or 5 evidence

REVIEWS