Original Article

The Efficacy and Safety of a Pharmacologic Protocol for Maintaining Coronary Artery Bypass Patients at a Higher Mean Arterial Pressure during Cardiopulmonary Bypass

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ABSTRACT

A recent randomized trial of higher versus lower mean arterial pressure (MAP) during cardiopulmonary bypass (CPB) showed that higher MAP on CPB was associated with a lower incidence of overall cardiac and neurologic morbidity and mortality in coronary artery bypass graft surgery (CABG) patients. Cardiopulmonary bypass MAP was controlled pharmacologically while CPB flow was held constant for any given period. The objective of the present study was to assess the efficacy and safety of this pharmacologic protocol. Two hundred forty-eight patients participated in the study; the mean age was 65.8 ± 9.4 years, 20% were women, and the mean preoperative ejection fraction was 48%. The low-flow corrected CPB MAP attained for the low and high MAP groups was 56.7 ± 5.0 mmHg and 77.7 ± 7.1 mmHg, respectively ($p = 0.0001$). Major cardiac and neurologic outcomes, postoperative blood loss, renal dysfunction, intensive care unit (ICU) stay, and duration of intubation were not found to be significantly associated with any drug in the pharmacologic protocol. These findings support that the pharmacologic protocol used to maintain CABG patients at higher MAP on CPB is both efficacious and safe.

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INTRODUCTION

A recent randomized trial demonstrated that managing patients undergoing coronary artery bypass graft surgery (CABG) at higher mean arterial pressure (MAP) during cardiopulmonary bypass (CPB) was beneficial in terms of reducing the incidence of overall cardiac and neurologic morbidity and mortality (1). In that trial, MAP on CPB was controlled pharmacologically while CPB flow was held constant for any given period. Our objective in the present study was to assess the efficacy and safety of this pharmacologic protocol. To confirm that the intended effect of this protocol was achieved, we examined the pharmacologic requirements for maintaining patients in a higher MAP range on CPB. To evaluate the impact of intra-operative medication utilization strategies on outcomes, cardiac and neurologic events, postoperative blood loss, renal dysfunction, length of stay in the intensive care unit (ICU), and number of hours intubated, were examined in the context of the pharmacologic protocol.

MATERIALS AND METHODS

Two hundred forty-eight patients undergoing primary CABG without concurrent other surgery (e.g., valve replacement) were enrolled in a randomized clinical trial comparing a low target MAP of 50 to 60 mmHg to a higher MAP range of 80 to 100 mmHg on CPB; all patients provided written consent as per institutional review board and National Institutes of Health guidelines. A standard anesthetic protocol was followed for induction, intra-operative ischemia, and blood pressure management (1). All intra-operative data, such as insertion of arterial line, induction, intubation, pulmonary artery catheter insertion, skin incision, sternotomy, mammary take-down (if any), pleural entry (if any), pericardical incision, heparinization, aortic cannulation, right atrial cannulation, and all drug administrations were recorded and time stamped as they occurred using a computerized system that was developed for this trial (2).

ANESTHETIC PROTOCOL

Pre-medication was morphine sulfate (0.1 mg/kg) subcutaneously and lorezapam (0.04 mg/kg) orally 1.5 hours prior to induction. Sedation prior to induction included midazolam (1 mg) intravenous bolus and fentanyl (50 μg) intravenously as required. Anesthesia induction was accomplished using thiopental (1 to 2 mg/kg) and fentanyl (25 μg/kg). Pancuronium (0.1 mg/kg) was used for muscle relaxation and intubation. Following intubation, fentanyl bolus (1 to 5 μg/kg, to a total of 50 to 70 μg/kg) or midazolam (1 mg) was used for evidence of light anesthesia (e.g., tachycardia, tearing, hypertension), and phenylephrine boluses (0.5 to 1 mg) were utilized for hypotension. During the pre- and post-CPB periods, isoflurane was also used to maintain anesthesia.

Intra-operative ischemia was determined by continuous electrocardiogram (ECG) and was considered significant if ST deviation exceeded 1 mm. In the absence of hemodynamic changes, a nitroglycerin infusion (0.3 to 1 μg/kg/min) was used to treat ischemia. For ischemia with an increase in MAP greater than 20% of baseline, fentanyl (5 μg/kg), nitroglycerin (0.3 to 1 μg/kg/min), or sodium nitroprusside (50 mg/250 ml) were used. When the patient's heart rate was greater than 80 beats per minute, esmolol (0.1 mg/kg) was administered. In the setting of MAP that was less than 20% of baseline, ischemic ECG changes were minimized using phenylephrine (1.5 μg/kg).

In preparation for CPB, an activated clotting time of greater than 480 seconds was achieved and maintained using heparin (300 units/kg). Flow rates were set at 1.6 L/min/m^2 during cooling and 2.4 L/min/m^2 during warming. Blood gases were managed under the alpha-stat protocol (3). Antegrade and retrograde cold blood cardioplegia were used ($[K^+]$=28 meq/L).

The hemodynamic management protocol was the same for both randomization groups (i.e., the low MAP range and high MAP range). For CPB MAP above the target range, a sodium nitroprusside infusion (50 mg/250 ml) was used. For CPB MAP below the target range, phenylephrine boluses (0.5 to 1.0 mg) were used, and phenylephrine infusion (10 mg/250 ml) was used if necessary. If phenylephrine failed to increase the MAP sufficiently, infusion of norepinephrine (8 mg/250 ml) was used first, then metaraminol (200 mg/250 ml) was employed.

Standard techniques including atrio-ventricular pacing and administration of vasoactive or inotropic drugs alone or in combination were used to effect separation from CPB. Post-CPB, protamine was used to reverse heparinization. After separation from CPB, all patients were managed in the operating room and in the ICU according to standard postoperative guidelines which included complete invasive monitoring as well as careful attention to heart rate, rhythm, urine output, and arterial blood gas measurements. Systemic systolic arterial pressure was maintained between 105 and 125 mmHg with a minimum cardiac output of 3.0 L/min. Standard pharmacologic preparations including parentally administered dopamine, epinephrine, isoproterenol, norepinephrine, and dobutamine were utilized for hemodynamic manipulation. Temporary indwelling epicardial atrial and ventricular pacing wires were utilized for chronotropic support, as necessary, to maintain a heart rate above 55 beats per minute.

DEFINITION OF HEMODYNAMIC PERFORMANCE

Evaluation of hemodynamic performance during CPB is complicated by the use of low flow episodes, which involve flow rates of 500 ml/min transiently. Such episodes are technically required by the surgeons during certain critical aspects of the surgery. These episodes drastically reduce the MAP (i.e., down to 10 to 20 mmHg) for short periods of time. The intra-operative MAP target was not raised in order to compensate for these low flow episodes. Because low flow episodes lower the observed mean MAP, a correction factor that took into account the number and duration of low flows was applied to the mean MAP

(see Appendix 1). Blood pressure during CPB was therefore reported in two ways: the mean of MAPs recorded during CPB and the mean CPB MAP corrected for low flow episodes.

POSTOPERATIVE SURVEILLANCE

Cardiac examinations were performed at baseline, immediately postoperatively and on postoperative days one, two, and six, and again at six months postoperatively by the study cardiologist, who was blinded to the intra-operative management. Neurologic examinations were performed at baseline, 24 to 48 hours postoperatively, on postoperative day six, and at six months postoperatively by the study neurologist, who was also blinded to the intra-operative course.

OUTCOME DETERMINATIONS

Major outcomes included cardiac and neurologic morbidity and mortality. Cardiac complications were myocardial infarction, pulmonary edema, adult respiratory distress syndrome, low flow state or cardiogenic shock, and cardiopulmonary arrest. Two cardiologists blinded to the assigned blood pressure range made the final determination of cardiac complications. Definite stroke was the principal neurologic complication, as determined by the study neurologist. Stroke included the new onset of a localized and persistent neurologic deficit (e.g., paresis, plegia, aphasia, hemianopsia, or cortical blindness). Other sequelae were identified from data collected prospectively by either the study cardiologist or research assistant. Postoperative blood loss was determined by the amount of blood drained from the mediastinal and pleural chest tubes recorded at six, 12, and 24 hours. Hours intubated were the number of hours during which the endotracheal tube was in place, starting from when the patient arrived in the ICU; likewise, the ICU stay was the number of hours the patient spent in the ICU, from admission to discharge. A clinically significant impairment of postoperative renal function was defined as a sustained increase of 0.4 mg/dL or greater in serum creatinine value; measurements were recorded at admission to the hospital, immediately postoperatively, and at postoperative days one, two, five, and seven.

STATISTICAL ANALYSIS

T-tests were used to analyze difference in total drug amounts between the two randomization groups. An analysis was completed for total dose (mg/kg) and for dose corrected for time on CPB (mg/kg/min); the results were the same unless otherwise reported.

Major outcomes—cardiac morbidity, neurologic morbidity, and mortality—were analyzed with respect to drugs used for hemodynamic management on CPB using logistic regression. To assess whether the pattern of drugs administered to the two randomization groups (i.e., low MAP group, high MAP group) on CPB had an impact on postoperative bleeding, renal dysfunction, number of hours in the intensive care unit, and duration of intubation, each of these factors was analyzed using general linear models in SAS[a]. Using general linear models, basic demographic and clinical factors were evaluated as predictors of blood loss and renal dysfunction at 24 hours. Both the logistic regressions and general linear models were done using the entire cohort, included all protocol drugs in dose per kilogram, and controlled for randomization group.

RESULTS

THE TARGET MAP

Detailed demographic and clinical information has been reported previously (1). However, in brief, the mean age overall was 65.8 ± 9.4 years and 20% of the patients were female. The mean angiographically determined ejection fraction prior to surgery was 48%. Forty-three percent of patients had a myocardial infarction prior to surgery. Fifty percent of patients had hypertension; 20%, diabetes; 8%, congestive heart failure; 25%, unstable angina. Overall, 13% had left main coronary artery disease. The two MAP groups did not differ in nearly all demographic and clinical aspects. The only preoperative clinical characteristics that differed between the two MAP groups were that patients in the high MAP group were more likely to be angina-free preoperatively, while those in the low MAP group were more often taking nitrates preoperatively.

Pre-CPB pharmacologic management was identical for the two MAP groups. Mean pre-medication doses for both groups were lorezapam (0.031 mg/kg) and morphine sulfate (0.091 mg/kg). Prior to CPB, patients received on average 2.05 mg/kg of thiopental, 40.1 µg/kg of fentanyl, 0.16 mg/kg of pancuronium, and 0.077 mg/kg of midazolam. Mean pre-CPB phenylephrine was 5 µg/kg. Five percent of patients received nitroglycerin in the pre-CPB period. The mean MAP was 81 ± 7.7 mmHg for the low MAP group and 81 ± 7.1 mmHg for the high MAP group, and mean cardiac output was 3.9 L/min for both groups. Mean pre-CPB hematocrit was 35.9%. Patients received an average of 327 units/kg of heparin prior to initiation of CPB.

REQUIREMENTS FOR ACHIEVING THE TWO GROUPS (I.E., LOW AND HIGH)

Table 1 shows various characteristics of the CPB period for the two randomization groups. CBP was divided into four periods of interest: initiation of CPB to cooling, cooling to warming, warming to cross-clamp removal, and cross-clamp removal to termination of CPB. Blood and bladder temperatures (not shown) and flows rates during CPB did not differ between the groups. Venous saturation was significantly higher in three periods in the low MAP group. The principal difference between the two groups was in the number of low flows, with more low flow episodes in the high MAP group in the warming to cross-clamp off period and in the period from removal of the cross-clamp to the end of CPB. Proximal anastomoses were constructed in the period after cross clamp removal.

ANESTHETIC AND VASOACTIVE DRUGS

Prior to CPB, the patients in the two randomization groups

a SAS System for Windows, Version 6.11, Cary, NC

Table 1: Cardiopulmonary bypass: pressures, flows, and temperatures for the two randomization groups

	Low MAP mean ± std	High MAP mean ± std	p
MAP during CPB (mm Hg)			
Uncorrected MAP	51.8 ± 5.2	69.5 ± 7.1	0.0001
Initiation to cooling	51.2 ± 7.7	62.5 ± 11.8	0.0001
Cooling to warming	52.6 ± 8.5	72.5 ± 9.8	0.0001
Warming to cross-clamp off	54.9 ± 7.2	78.7 ± 9.9	0.0001
Cross-clamp off to end CPB	50.2 ± 5.6	64.1 ± 9.4	0.0001
Corrected MAP	56.7 ± 5.0	77.7 ± 7.1	0.0001
Initiation to cooling	58.7 ± 10.8	72.6 ± 14.0	0.0001
Cooling to warming	54.9 ± 8.7	76.4 ± 9.4	0.0001
Warming to cross-clamp off	61.9 ± 8.8	91.1 ± 10.3	0.0001
Cross-clamp off to end CPB	57.3 ± 5.8	74.9 ± 10.0	0.0001
Time during CPB			
Initiation to cooling (minutes)	7.3 ± 4.4	6.7 ± 3.2	ns
Cooling to warming (minutes)	34.1 ± 15.0	32.2 ± 14.3	ns
Warming to cross-clamp off (minutes)	11.7 ± 6.0	11.5 ± 5.8	ns
Cross-clamp off to end CPB (minutes)	32.9 ± 11.8	32.4 ± 13.6	ns
Total time	89.4 ± 31.5	84.9 ± 28.3	ns
Flow rates (L/min/m2)			
Initiation to cooling	2.1 ± 0.5	2.1 ± 0.5	ns
Cooling to warming	1.7 ± 0.21	1.7 ± 0.2	ns
Warming to cross-clamp off	1.9 ± 0.3	1.9 ± 0.3	ns
Cross-clamp off to end CPB	2.0 ± 0.3	1.9 ± 0.3	ns
Number of low flows (to 500 ml/min)			
Initiation to cooling	0.88 ± 0.82	0.99 ± 0.95	ns
Cooling to warming	1.27 ± 1.02	1.5 ± 1.38	ns
Warming to cross-clamp off	1.14 ± 0.91	1.69 ± 1.18	<0.0001
Cross-clamp off to end CPB	4.4 ± 2.3	5.0 ± 2.7	<0.05
Venous saturation			
Initiation to cooling	69.9 ± 9.1	66.4 ± 10.0	<0.01
Cooling to warming	70.5 ± 7.1	69.6 ± 7.7	ns
Warming to cross-clamp off	69.9 ± 7.9	66.2 ± 10.7	<0.01
Cross-clamp off to end CPB	66.7 ± 6.8	58.9 ± 7.7	<0.0001

O2 sats were 99% for all; Hct was 20.5

received almost identical doses of fentanyl, midazolam, pancuronium and thiopental. Phenylephrine boluses were used in equal numbers of patients in the high and low MAP group pre-CPB. Nitroglycerin infusion was employed in a small number of patients in both groups.

During CPB, blood pressure was controlled pharmacologically, because flow rates were held constant for body temperature. There was no difference between the randomization groups in the number of patients receiving vasopressors (90% of the low MAP group and 93% of the high MAP group). While nearly equal numbers of patients in the two randomization groups received phenylephrine, which was the first line vasopressor, the high MAP group received twice as much: 0.068 mg/kg versus 0.032 mg/kg (p= 0.0001). Few patients in either group required norepineprine or metaraminol, which were, respectively, the second and third line vasopressors indicated if blood pressure could not be controlled by phenylephrine. Few patients in either group received epinephrine.

Significantly fewer patients in the high MAP group received vasodilators (79% of low MAP group, 48% of high MAP group, p<0.0001). Significantly more patients in the low MAP group received sodium nitroprusside than in the high MAP group (36% versus 4%). However, the mean duration of intravenous sodium nitroprusside, which was 26.8 minutes in the low MAP group and 40.0 minutes in the high MAP group, was not significantly different. While doses of nitroprusside were not recorded on all patients, among a sub-sample of 11 patients where doses were recorded (10 in the low MAP group and 1 in the high MAP group), the mean dose of sodium nitroprusside was 11.5 mg in the low MAP group and 8.0 mg in the high MAP group. Patients in the low MAP group also received more than twice the amount of nitroglycerin, with a mean dose of 16.2 µg/kg versus 7.1 µg/kg for the high MAP group.

In summary, the difference between the groups in terms of pharmacologic management was that the low MAP group required more vasodilators such as nitroglycerin and that both groups responded sufficiently to the first line vasopressor, phenylephrine, but the high MAP group needed twice as much. The average patient managed at the higher MAP range required 15.1 µg/kg of fentanyl, 0.068 mg/kg of midazolam, 0.068 mg/kg of phenylephrine, and 7.1 µg/kg of nitroglycerine on CPB; all other drugs administered were the same as patient managed at lower MAP. The anesthetic agents and vasoactive drugs used for each group during CPB are shown in Table 2.

The use of vasopressors is summarized in Table 3. Phenylephrine was the most commonly used vasopressor. The total dose of phenylephrine was not related to CPB time. The total dose administered was divided into a low range (less than

0.02 mg/kg), a medium range (0.02 to 0.08 mg/kg), and a high range (greater than 0.08 mg/kg). We were also interested in the less frequently used second, third, and fourth line vasopressors (i.e., epinephrine, norepinephrine, and aramine), so within each of the dose ranges for phenylephrine, we examined whether phenylephrine was used alone or in conjunction with another vasopressor. Overall, as well as in each randomization group, the proportion of patients receiving phenylephrine plus another vasopressor increased as the phenylephrine dose increased. Specifically, in the low MAP group, 19% (10/52) who received low dose phenylephrine, 23% (12/52) of those receiving medium dose phenylephrine, and 60% (3/5) of those receiving high dose phenylephrine also were administered other vasopressors. In the high MAP group, 17% (4/24) of the patients receiving low dose phenylephrine, 18% (10/57) of those receiving medium dose phenylephrine, and 32% (10/31) of those receiving high dose phenylephrine also were administered other vasopressors. This indicates that the pharmacologic blood pressure management protocol was followed, as the subsequent lines of vasopressors were more likely to be used if phenylephrine alone was not sufficient.

VASOACTIVE DRUGS AND OUTCOMES

Table 4 shows the major neurologic and cardiac outcomes according to the low, medium, and high total dose ranges for phenylephrine as well as whether phenylephrine was used alone or with another vasopressor. Phenylephrine, nitroglycerin, fentanyl, and sodium nitroprusside were specifically examined in relationship to neurologic and cardiac outcomes, since these vasoactive drugs differed significantly between the low and the high MAP group. Major neurologic outcomes were not related to the dose of phenylephrine or the use of other vasopressors, but they were related to high grade atheromatous disease of the descending aorta (Grade IV or V) as assessed by transesopha-geal echocardiogram, as reported previously (4). Major cardiac outcomes were not related to the total dose of phenylephrine, nitroglycerin, and sodium nitroprusside. However, the total dose of fentanyl was a predictor of cardiac events (p=0.0520). The average dose of fentanyl among patients without cardiac complications was 17 μg/kg while among those with cardiac complications, it was 9.9 μg/kg; thus patients without cardiac complications received double the dose of fentanyl. The number of hours intubated and the number of hours in the ICU were not associated with the use of vasopressors on CPB.

Reoperations for bleeding occurred in a total of seven patients and were unrelated to vasoactive drugs. Table 5 shows patients with a total blood loss of greater than 2 L and the average 24 hour postoperative blood loss in each group. The use of preoperative intravenous heparin, duration of CPB, the dose of phenylephrine on CPB, the use of additional heparin on CPB, and the post-CPB activated clotting time were significant in univariate models and were therefore entered into the multivariate model. In the multivariate model, the only significant predictor of postoperative blood loss at 24 hours was the use of additional heparin on CPB (p=0.0242), so that patients who had received additional heparin during CPB were more likely to have blood loss greater than 2 L at 24 hours postoperatively.

Impaired postoperative renal function was not associated with the use of vasopressors. Univariate logistic regression analy-

Table 2: Anesthetic and vasoactive agent use during CPB in the two randomization groups

Drug Name	Low mean ± std (n)	High mean ± std (n)	p
Thiopental (mg/kg)	4.3 ± 2.6 (3)	1.6 ± 0.4 (6)	ns
Fentanyl (μg/kg)	23.1 ± 14.2 (117)	15.1 ± 9.5 (104)	0.0001
Midazolam (mg/kg)	0.089 ± 0.051 (106)	0.068 ± 0.060 (97)	0.009
Pancuronium (mg/kg)	0.11 ± 0.046 (81)	0.11 ± 0.049 (77)	ns
Phenylephrine (mg/kg)	0.032 ± 0.032 (111)	0.068 ± 0.065 (112)	0.0001
Metaraminol (mg/kg)	0.055 ± 0.0 (1)	0.073 ± 0.041 (6)	ns
Epinephrine (μg/kg)	0.47 ± 0.63 (28)	0.49 ± 0.30 (18)	ns
Norepinephrine (μg/kg)	0.36 ± 0.092 (2)	25.1 ± 21.7 (2)	ns
Nitroglycerin (μg/kg)	16.2 ± 33.1 (78)	7.1 ± 6.5 (59)	0.022
Sodium Nitroprusside (min)*	26.8 ± 29.6 (45)	40.0 ± 1.3 (4)	0.0001

*Time of infusion was recorded rather than dose

Table 3: Distribution of patients in the low and high randomization groups according to the amount and type of vasopressor use during CPB

Vasopressor	Low % (n)	High % (n)	All % (n)
None	10% (13)	10% (12)	10% (25)
Phenylephrine (<0.02 mg/kg) only	34% (42)	16% (20)	25% (62)
Phenylephrine (<0.02 mg/kg) plus other pressor	8% (10)	3%(4)	6% (14)
Phenylephrine (0.02 -0.08 mg/kg) only	34% (42)	38% (47)	36% (89)
Phenylephrine (0.02 -0.08 mg/kg) plus other pressor	10% (12)	8% (10)	9% (22)
Phenylephrine (>0.08 mg/kg) only	2% (2)	17% (21)	9% (23)
Phenylephrine (>0.08 mg/kg) plus other pressor	2%(3)	8% (10)	5% (13)

ses indicated that CPB MAP, preoperative history of hypertension, preoperative history of significant peripheral vascular disease (e.g., claudication or history of endarterectomy), the use of prescription diuretics prior to surgery, and blood loss of greater than 2 L at 24 hours postoperatively were associated with a postoperative increase in serum creatinine; these factors were entered into a multivariate logistic regression model. In the multivariate model, only 24 hour postoperative blood loss greater than 2 L was significantly associated with impaired postoperative renal function (p=0.0027).

DISCUSSION

DRUGS AND OUTCOMES

This paper explicitly evaluates the relationship of doses of pharmacologic agents to outcomes to assess the safety of the pharmacologic protocol used to maintain patients in a desired MAP range on CPB. Because the intervention in our trial was pharmacologic in nature, the association of the drugs used with outcomes must be examined.

High dose fentanyl has been associated with better cardiac outcome as compared to other anesthetics (5,6,7) as well as renal outcome (8). A study of high dose fentanyl (mean dose 62.4 μg/kg, range 50-89 μg/kg) (9) showed minor hemodynamic changes (increased heart rate, arterial blood pressure, and systemic vascular resistance with noxious stimulation), but another study examining three levels of fentanyl dosing (30 μg/kg loading dose + 0.3 μg/kg/min infusion, 40 μg/kg loading dose + 0.4 μg/kg/min infusion, and 50 μg/kg loading dose + 0.5 μg/kg/min infusion) (8) found the high dose to be the best with respect to hemodynamic stability. In a study by Mora and coworkers comparing propofol to fentanyl, enflurane, and thiopental (10), the researchers were specifically examining the ability of drugs to maintain a patient within a specified range. In their study, the target range on CPB was between 40 and 80 mmHg. For MAP less than 40 mmHg, first the amount of anesthesia was decreased, then phenylephrine was administered if the blood pressure did not increase, then norepinephrine was administered as a third line intervention. For MAP greater than 80 mmHg, the anesthesia was increased, and if the maximum dose was reached, sodium nitroprusside was administered. The use of sodium nitroprusside was required for seven of the 22 patients in the group receiving fentanyl because the maximum dose of 150 μg/kg had been reached. Patients in the fentanyl group also required more vasopressor support. Our

Table 4: Major neurologic and cardiac outcomes according to randomization group (low or high) and the amount and type of vasopressor used.

	Major Neurologic Outcomes[1]		Major Cardiac Outcomes[2]	
	Low	High	Low	High
Vasopressor	**% (n)**	**% (n)**	**% (n)**	**% (n)**
None	15% (13)	0% (12)	8% (13)	8% (12)
Phenylephrine (<0.02 mg/kg) only	7% (42)	0% (20)	2% (42)	0% (20)
Phenylephrine (<0.02 mg/kg) plus other pressor	20% (10)	0% (4)	10% (10)	0% (4)
Phenylephrine (0.02 -0.08 mg/kg) only	4% (42)	6% (47)	0% (42)	0% (47)
Phenylephrine (0.02 -0.08 mg/kg) plus other pressor	0% (12)	0% (10)	16% (12)	0% (10)
Phenylephrine (>0.08 mg/kg) only	0% (2)	0% (21)	0% (2)	5% (21)
Phenylephrine (>0.08 mg/kg) plus other pressor	0% (3)	0% (10)	33% (3)	10% (10)

[1]Major neurologic outcomes included major focal deficit, including hemiplegia, hemianopsia, cortical blindness. [2]Major cardiac outcomes include myocardial infarction (q wave), pulmonary edema, acute respiratory distress and shock.

Table 5: Blood loss at 24 hours according to randomization group (low or high) and the amount and type of vasopressor used.

	Reoperation for Bleeding		Bleeding >2L		24 hr Blood Loss (ml)	
	Low	High	Low	High	Low	High
Vasopressor	**%**	**%**	**%**	**%**	**mean ± std (n)**	**mean ± std (n)**
None	0%	0%	8%	0%	1016 ± 480 (13)	727 ± 168 (11)
Phenylephrine (<0.02 mg/kg) Only	5%	0%	7%	5%	1010 ± 611 (41)	1014 ± 817 (19)
Phenylephrine (<0.02 mg/kg) plus other pressor	20%	0%	0%	0%	862 ± 373 (10)	658 ± 127 (3)
Phenylephrine (0.02 -0.08 mg/kg) Only	5%	0%	0%	0%	921± 310 (40)	794 ± 298 (44)
Phenylephrine (0.02 -0.08 mg/kg) plus other pressor	0%	10%	8%	20%	867 ± 652 (12)	1198 ± 662 (10)
Phenylephrine (>0.08 mg/kg) Only	0%	0%	50%	9%	2027 ± 67 (2)	935 ± 562 (21)
Phenylephrine (>0.08 mg/kg) plus other pressor	0%	0%	33%	0%	2682 ± 3202 (3)	858 ± 248 (9)
Total	5%	1%	6%	4%	1013 ± 702	885± 500

findings support the high-dose fentanyl studies that demonstrated that a higher dose of fentanyl was associated with fewer cardiac outcomes. While the doses of fentanyl used in our trial were lower than those in the high-dose studies, the patients who received less fentanyl had a higher cardiac outcome rate.

Several studies have examined the use of midazolam during cardiac surgery. A study of midazolam as an adjunct to high-dose fentanyl induction anesthesia (11) showed that there was increased venous pooling and moderate to severe decrease in systemic arterial pressure in the group receiving midazolam. A study comparing lorazepam and midazolam in 52 patients undergoing cardiac surgery (12) found that patients receiving higher doses of midazolam required more phenylephrine to maintain MAP greater than 50 mmHg after rewarming and removal of the cross-clamp, as well as more phenylephrine in the 12 hours following surgery. The authors concluded that a single dose of 0.1 mg/kg of midazolam administered at the start of CPB may exert hypotensive effects into the postoperative period. Unlike these studies, we did not find a relationship between midazolam and any adverse outcome.

A study of the response of cerebral blood flow to phenylephrine infusion during CPB (13) showed that in 10 patients maintained in an alpha-stat protocol (no CO2 correction for temperature), cerebral autoregulation remained despite administration of phenylephrine while the six patients maintained in a pH-stat protocol (CO2 level corrected for temperature) showed increased cerebral blood flow with increased MAP in response to phenylephrine administration. There was no association between phenylephrine and neurologic outcome in our study, perhaps because we used an alpha-stat protocol under which cerebral autoregulation was preserved.

BLOOD LOSS

Many factors have been linked to blood loss after CABG. Extracorporeal blood flow requires anticoagulation with heparin due to activation of platelets, but the exact effect on platelets is not well understood. The amount of heparin required to achieve sufficient anticoagulation, the possibility of either administering too much heparin or not enough protamine to adequately reverse the heparin, and the phenomenon of heparin rebound have all been studied previously (12-18). Heparin rebound is defined as persistent or recurrent anticoagulation after the administration of an appropriate dose of protamine. Factors such as decreased preoperative platelet count, impairment of platelet function, hyperfibrinolysis, consumption of coagulation factors, and changes in red blood cell deformability have also been implicated.

Despotis and coworkers found that duration of CPB was associated with a greater postoperative blood loss (14). In our univariate analyses, we also found that duration of CPB was a significant factor in postoperative blood loss. There have been numerous reports that high doses of heparin require greater doses of protamine, which may be due to heparin rebound (15-18). The phenomenon of heparin rebound may explain our finding of the use of additional heparin during CPB and blood loss of greater than 2 L at 24 hours postoperatively. Preoperative aspirin therapy (19,20), the use of calcium channel blockers (21,22), and warfarin sodium (21) have been reported as possibly contributing to postoperative bleeding. However, we did not find that preoperative aspirin, warfarin, or calcium channel blockers were associated with blood loss, nor did we identify any other preoperative factor associated with blood loss except the use of preoperative intravenous heparin, which was, as noted above, related to blood loss only in a univariate analysis.

With respect to intra-operative drugs, there was no literature supporting the concept that phenylephrine dose is associated with greater postoperative bleeding. Sodium nitroprusside has been shown to inhibit platelet function in vitro (23). However, a study investigating the effect of sodium nitroprusside on bleeding found no observed clinical effects. Neither phenylephrine nor sodium nitroprusside had an effect on postoperative bleeding in the present study.

RENAL FUNCTION IMPAIRMENT

The definition of renal function impairment varies in the literature (24, 25), and the factors that have been associated with a poor renal outcome vary from study to study. These factors include decompensated congestive heart failure and long periods of low intraoperative MAP (27), decreased cardiac performance (26), age, high BUN, high creatinine, decreased 24 hour urine creatinine clearance, duration of CPB, aortic-cross clamping, and total duration of surgery (27), use of an intraaortic balloon pump, need for deep circulatory arrest, low-output syndrome, advanced age, need for emergency operation, and low urine output during CPB (28). However, others have found that the morbidity and mortality of patients on dialysis undergoing CABG is acceptable (29). It is of interest that Kono et al found that the use of high dose fentanyl as compared to halothane anesthesia was associated with the preservation of renal function and postulated that the deeper anesthesia afforded by fentanyl blocks the vasopressin-catecholamine stress response to surgery (9). However, we found no association between fentanyl dose and postoperative renal function.

The issue of postoperative bleeding with respect to renal function is compelling, as poor renal perfusion secondary to blood loss provides a reasonable explanation for impaired renal function. A study by Heikkinen found that patients who developed acute renal failure had significantly higher postoperative bleeding than those who did not develop acute renal failure (30). We found that blood loss greater than 2 L at 24 hours postoperatively was the only factor in a multivariate analysis that was significantly associated with renal function impairment; it is unclear if the blood loss contributed to factors identified in other studies, such as low-output syndrome. Neither advanced age nor duration of CPB were associated with postoperative renal function in our study, not even in univariate analyses.

CONCLUSION

As shown by the significant difference between the CPB MAP in the low and in the high randomization groups, whether or not the MAP was corrected for low flow episodes, the pharmacologic protocol to achieve our intervention of maintaining patients at different ranges of CPB MAP was effective. Furthermore, no deleterious outcomes were associated with the drugs that were used to maintain patients in the low or the high randomization group. The factors related to postoperative blood loss and renal dysfunction were not associated with the pharmacologic protocol and were consistent with those previously reported in the literature. In conclusion, in addition to our previous finding that the combined rate of major cardiac and neurologic morbidity and mortality was lower in patients maintained at a higher CPB MAP (1), we have found that the pharmacologic protocol that was used to achieve higher pressures was both efficacious and not associated with any deleterious outcome.

APPENDIX 1: MAP CORRECTION FACTOR FOR LOW FLOW EPISODES

Transient low flow episodes during CPB decreased the mean CPB MAP. The problem is analogous to trying to achieve an average speed of 55 miles per hour (MPH) on a car trip. If every stop for gasoline, food, and tolls were included ("low flow" episodes on this trip), the average rate will appear to be well below 55 MPH despite having spent much of the time on the road at that speed. One would have to either drive at an excessive speed or correct for stops in order to reach the target average speed. As it was clearly not reasonable to maintain the patient's CPB MAP at excessive levels to achieve the target range, the following equation was developed to obtain the value for full flow mean CPB MAP. The correction factor, shown in boldface type, is based on 1.5 minutes being the estimated duration of low flow episodes and on the estimated drop in blood pressure to one-third of baseline.

$$CMAP = MAP \pm \mathbf{1.5} * \frac{\mathbf{LOWFLOW * 0.67 * MAP}}{\mathbf{TIME}}$$

where CMAP = corrected MAP
MAP = uncorrected MAP
TIME = time of CPB, in minutes
LOWFLOW = number of low flow episodes

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