Hemodynamic Consequences of Desmopressin Administration after Cardiopulmonary Bypass

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Desmopressin acetate is used to reduce blood loss after cardiac surgery. However, there have been reports that hypotension can occur with infusion of desmopressin and that postoperative blood loss is not reduced. In this randomized, double-blinded study, we investigated the effects of desmopressin on hemodynamics, coagulation, and postoperative blood loss in patients undergoing primary elective coronary artery bypass grafting (CABG). After reversal of heparin effect, 20 patients received desmopressin 0.3 $\mu g \cdot kg^{-1}$, infused over 15 min, and 20 patients received a placebo. Desmopressin produced a small but significant decrease in diastolic blood pressure when compared with the placebo (50.8 mmHg vs. 57.6 mmHg for the desmopressin- and placebo-treated groups, respectively; P = 0.0372). A 20% or greater decrease in mean arterial pressure was observed in 7 of 20 patients receiving desmopressin, whereas only one patient in the placebo-treated group experienced a decrease of this magnitude (P = 0.0177). Reductions in arterial pressure were secondary to decreases in systemic vascular resistance (SVR) (mean SVR before and after the drug infusion, 1,006 and 766 dyn $\cdot$ s $\cdot$ cm^{-5}, respectively, for the desmopressin-treated group; and 994 and 1,104 dyn $\cdot$ s $\cdot$ cm^{-5}, respectively, for the placebo-treated group; P = 0.0078). In addition, desmopressin did not reduce postoperative blood loss (mean 24-h mediastinal blood loss, 790 ml vs. 687 ml for the desmopressin- and placebo-treated groups, respectively), improve the postoperative bleeding time (mean times of 8.3 min vs. 9.0 min for the desmopressin- and placebo-treated groups, respectively), or enhance coagulation (mean prothrombin time, 14.2 s vs. 13.5 s and, mean partial thromboplastin time, 46.0 s vs. 45.5 s for desmopressin- and placebo-treated groups, respectively) in patients undergoing primary CABG. The authors conclude that intravenous infusion of desmopressin reduces SVR, often leading to hypotension, and does not reduce postoperative blood loss in patients having uncomplicated CABG. (Key words: Blood, coagulation: desmopressin. Hemodynamics: hypotension; systemic vascular resistance. Surgery, cardiac: coronary artery bypass grafting.)

EXCESSIVE BLEEDING after cardiopulmonary bypass continues to be a significant problem. Bleeding patients are exposed to the risks of reoperation, hemodynamic insta-

bility, and multiple blood transfusions. Factors contributing to bleeding after cardiopulmonary bypass include hemodilution, platelet dysfunction, unneutralized heparin, excessive protamine, and excessive fibrinolysis.[1–4] Although the specific hemostatic defect is complex and multifactorial, platelet dysfunction is a major component. Platelet adhesiveness is impaired progressively by contact with the cardiopulmonary bypass circuit, resulting in partial platelet activation, depletion of alpha-granules, prolonged bleeding time, and significant bleeding. Although platelet function usually returns to normal after discontinuation of cardiopulmonary bypass, a persistent platelet abnormality often is demonstrated in those patients who exhibit excessive bleeding.[2,3,5]

Desmopressin acetate (1-deamino-8-D-arginine vasopressin; DDAVP) is a synthetic polypeptide structurally related to vasopressin. It appears to promote hemostasis by causing a release of von Willebrand factor and Factor VIII:C from the vascular endothelium,[6] thus enhancing platelet adhesiveness to the vascular subendothelium. When given to patients with classic von Willebrand's disease, mild to moderate hemophilia, or uremia, bleeding time shortens and surgical blood loss can be reduced.[7–9]

Czer et al.[10] and Salzman et al.[11] studied the effectiveness of desmopressin used to reduce blood loss and blood product utilization after complicated cardiac surgery. In both studies, a variety of surgical procedures were performed, including valve replacements, reoperations, and procedures requiring prolonged cardiopulmonary bypass. Intravenous desmopressin significantly reduced blood loss and blood product utilization. Since publication of these reports, desmopressin has been used extensively to improve hemostasis for all types of cardiac surgical procedures, including primary elective coronary artery bypass grafting (CABG), a procedure not usually associated with excessive postoperative bleeding. Desmopressin also has been used to reduce blood loss and blood product utilization in patients undergoing major surgical procedures not requiring cardiopulmonary bypass.[12] Deleterious hemodynamic side effects of desmopressin administration were not reported in these studies.

The decision to use desmopressin often is based on a subjective assessment of the presence of abnormal hemostasis and the absence of deleterious side effects. Recently, there have been reports of mild hypotension after intravenous infusion of desmopressin in both uremic and

normal populations.[13-15] In addition, severe hypotension was reported in two patients receiving desmopressin after cardiopulmonary bypass[16] and in an infant undergoing surgery for congenital heart defects.[17]

This study was initiated to determine whether desmopressin infusion after cardiopulmonary bypass for elective primary CABG causes hypotension and, if so, to determine whether this results from a reduction in systemic vascular resistance (SVR). In addition, we examined the effect of desmopressin on postoperative blood loss and coagulation in a population at relatively low risk for excessive bleeding.

Materials and Methods

After approval was obtained from the Human Investigation Committee at the University of Virginia Health Sciences Center, all patients admitted to the same attending surgeon for elective primary CABG were approached to enter a randomized, placebo-controlled, double-blinded study. Criteria for exclusion of patients from the study included anticoagulation with sodium warfarin (Coumadin®; DuPont Pharmaceuticals, Wilmington, DE), treatment with heparin within 24 h of the operation, documented preoperative coagulopathies or platelet disorders, known drug allergy to desmopressin, renal failure, and acute thrombotic events (cerebrovascular accident, pulmonary embolus, deep vein thrombosis) within the past three months. All preoperative medications except aspirin were administered until surgery. Aspirin was discontinued 1 week before admission. Forty patients provided written consent to participate in the study.

With a system of sealed envelopes, 20 patients were assigned randomly to receive desmopressin (0.3 $\mu g \cdot kg^{-1}$ of body weight) (Rorer Pharmaceuticals, Fort Washington, PA), and 20 patients received a placebo solution that was identical in appearance to the desmopressin solution. Drug or placebo was prepared in 50 ml saline and administered by infusion pump over 15 min. The surgeon, anesthesiologist, and investigator collecting the experimental data were unaware of which solution was being administered.

ANESTHETIC AND SURGICAL TECHNIQUES

Preoperative medication consisted of intramuscular morphine (0.1 mg $\cdot$ kg^{-1}) and scopolamine (0.4 mg). After insertion of pulmonary and systemic arterial cannulas, general anesthesia was induced with opioid alone or in combination with potent inhalational agents and barbiturates. All patients received anesthetic opioid doses at induction or during cardiopulmonary bypass, and no additional anesthetic agents were administered after rewarming was initiated. The use of vasopressors and vasodilators before cardiopulmonary bypass was left to the discretion of the attending anesthesiologist.

After placement of aortic and atrial purse string sutures, beef lung heparin, 300 units $\cdot$ kg^{-1} (Upjohn, Kalamazoo, MI), was injected directly into the right atrium. A partial aortic occlusion clamp was then positioned and the proximal vein graft anastomoses completed. The right atrial appendage and aorta were cannulated and cardiopulmonary bypass initiated. Pump prime consisted of 2.5 l Plasma-Lyte® (Travenol Laboratories, Deerfield, IL) with 3,000 units heparin added for each liter of priming solution. Pump flows were adjusted to maintain a cardiac index of 2.2–2.5 l $\cdot$ min^{-1} $\cdot$ m^{-2}. COBE membrane oxygenators (model S100A; Arvada, CO) or Shiley bubble oxygenators (EXCEL® model; Irvine, CA) were used for all operations. Patients were cooled to esophageal temperatures of 25–30° C. Cardioplegic solution consisted of iced Plegisol®, with 5 mEq potassium chloride and 5 mEq sodium bicarbonate added to each liter. The distal saphenous vein and internal mammary artery anastomoses were completed after the cardioplegic solution was infused. The patients then were warmed to rectal temperatures of 35–36° C. After cardiac reperfusion, the heart was defibrillated if sinus rhythm did not resume spontaneously. Epicardial pacing leads were used as needed for sinus bradycardia or atrioventricular conduction disturbances. Cardiopulmonary bypass was discontinued and the aortic and venous cannulae removed. Protamine sulfate (DuPont) was administered immediately after removal of the aortic cannula, the dosage calculated by using a protamine titration technique (Hemochron® protamine dose assay worksheet; International Technidyne, Edison, NJ). After all the protamine was given, there was a 5-min wait to allow for resolution of any hemodynamic alterations that might have been caused by the protamine. The desmopressin or placebo solution was then infused at a constant rate over 15 min with the use of an infusion pump. Fifteen minutes after drug infusion was complete, additional protamine was administered if indicated by a prolonged activated clotting time ACT.

All available blood from the cardiopulmonary bypass circuit and autotransfusion system reservoir was washed with normal saline, centrifuged to a hematocrit of approximately 60%, and made available for reinfusion during sternal closure. Intravenous fluids were administered to maintain the pulmonary artery diastolic pressure between 10 and 15 mmHg. Lactated Ringer's solution was used unless scavenged autologous blood was available. Transfusion of bank blood was not initiated during the desmopressin infusion. The amount and nature of intravenous fluid administered during the desmopressin infusion were recorded.

Administration of inotropic drugs was left to the discretion of the attending surgeon and anesthesiologist. When the decision to use an inotropic agent was made, the infusion was started before administration of protamine sulfate. The dose was adjusted only if the systolic blood pressure exceeded 130 mmHg, at which time the inotropic drug was discontinued. Vasodilator therapy was not initiated unless the systolic blood pressure exceeded 130 mmHg and the inotropic infusion had been discontinued.

HEMODYNAMIC MEASUREMENTS

Before induction of anesthesia, the following hemodynamic parameters were recorded; heart rate; systolic (SBP), diastolic (DBP), mean arterial (MAP), and pulmonary artery blood pressures; mean central venous pressure (CVP); mean pulmonary artery occluded pressure (PAOP); and the average of three thermodilution cardiac output determinations (Gould Spectromed® disposable transducer T4812AD-R, [Washington, D.C.]; used with either Marquette Electronics monitor 7010R-A [Marquette, IN] or Hewlett-Packard pressure modules with a Hewlett-Packard Model 7758B recorder [Waltham, MA], calibrated against a mercury column). These measurements were repeated immediately before starting the desmopressin or placebo infusion (baseline measurement), then 5, 10, 15, and 30 min later. All measurements were made during the expiratory pause phase of the ventilator cycle. SVR and pulmonary vascular resistance (PVR) were calculated at each time point. Hypotension was defined arbitrarily as a 20% or greater decrease in MAP from the baseline value. Cardiac output determinations and SVR calculations were available to the anesthesiologist responsible for the patient's care.

HEMATOLOGIC MEASUREMENTS

Laboratory values obtained the day before surgery included a complete blood count (CBC) and platelet count (H1 automated blood analysis machine; Technicon, NY), prothrombin time (PT), and partial thromboplastin time (PTT) (X2 automated coagulation analyzer; Organon Teknika, Durham, NC). Preoperative blood samples were obtained by venipuncture. A bleeding time was performed using the Simplate II® template (Organon Teknika) during insertion of the invasive monitors. After arterial cannulation, blood samples were drawn from the catheter by discarding the first 10 ml aspirate before the specimen was collected. ACT was measured using the Hemochron 400® (International Technidyne) before induction of anesthesia. The CBC, platelet count, PT, PTT, and ACT were repeated 5 min after administration of protamine (before starting the desmopressin or placebo infusion). The patients then were transported to the intensive care

unit (approximately 60–90 min after completion of cardiopulmonary bypass), where the final set of blood samples was drawn and another bleeding time was performed.

Mediastinal tube drainage was measured 6, 12, and 24 h postoperatively, or until the tubes were removed. All blood products administered after discontinuation of cardiopulmonary bypass were recorded. The investigators made no attempt to alter or influence blood product transfusion practices during the study.

STATISTICAL ANALYSIS

Contingency analysis with chi-squared testing and General Linear Models analysis of variance (ANOVA) with pairwise comparisons by Sheffé's test were used to determine whether significant differences between desmopressin- and placebo-treated groups existed at specific times. Repeated measures ANOVA was used to determine whether significant hemodynamic differences existed between the desmopressin- and placebo-treated groups during the drug infusion. Sheffé's F test was used to determine whether repeated variables changed significantly from the baseline value during the study period. Two-factor ANOVA was used to determine whether differences between the desmopressin- and placebo-treated groups were attributable to the use of inotropic agents or to the administration of desmopressin. Data were considered statistically significant for P values less than 0.05. Values are reported as mean ± standard error of the mean (SEM).

Results

Preoperative characteristics of the desmopressin- and placebo-treated groups are described in table 1. There were no differences in age, sex, height, weight, body sur-

TABLE 1. Comparison of the Two Patient Groups Preoperatively

Characteristics	Desmopressin (n = 20)	Placebo (n = 20)
Age (yr)	59.9 ± 2.4	59.6 ± 2.5
Height (cm)	173.0 ± 2.0	170.8 ± 2.0
Weight (kg)	81.3 ± 3.2	78.9 ± 3.2
Body surface area (m²)	1.95 ± 0.04	1.91 ± 0.04
CPB time (min)	50.8 ± 3.19	50.7 ± 2.4
Men/women	17/3	17/3
Preoperative medications	Patients	Patients
Aspirin	14	16
Calcium channel blockers	16	15
Nitrates	16	16
β-Blockers	3	6
Captopril	1	1
Digoxin	2	3

Values are means ± SEM.
There were no statistical differences between desmopressin and placebo groups preoperatively.

TABLE 2. Hemodynamic Variables Preoperatively and before Desmopressin Infusion

	Desmopressin	Placebo
Preoperative		
Heart rate (beats per min)	69.0 ± 3.1	67.8 ± 3.0
Mean arterial pressure (mmHg)	90.2 ± 3.7	94.2 ± 2.0
Mean pulmonary artery pressure (mmHg)	18.3 ± 1.2	19.2 ± 2.0
Central venous pressure (mmHg)	7.5 ± 0.8	7.6 ± 0.7
Pulmonary occluded pressure (mmHg)	11.9 ± 1.0	12.4 ± 0.9
Cardiac output (l·min⁻¹)	5.1 ± 0.3	5.0 ± 0.3
SVR (dynes·s·cm⁻⁵)	1,389 ± 103	1,487 ± 100
PVR (dynes·s·cm⁻⁵)	101 ± 18	120 ± 28
Before desmopressin (baseline)		
Heart rate (beats per min)	91.1 ± 2.5	94.1 ± 3.0
Mean arterial pressure (mmHg)	69.6 ± 2.8	69.3 ± 1.9
Mean pulmonary artery pressure (mmHg)	18.5 ± 0.8	20.6 ± 0.9
Central venous pressure (mmHg)	9.8 ± 0.7	8.9 ± 0.5
Pulmonary artery occluded pressure (mmHg)	12.0 ± 0.6	12.3 ± 0.6
Cardiac output (l·min⁻¹)	5.2 ± 0.3	5.0 ± 0.2
SVR (dynes·s·cm⁻⁵)	1,006 ± 96	994 ± 44
PVR (dynes·s·cm⁻⁵)	103 ± 10	140 ± 14*

Values are mean ± SEM.
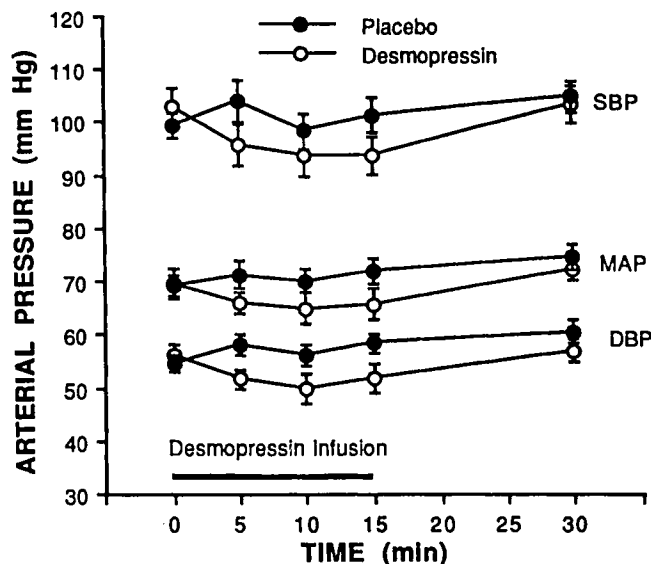* $P < 0.05$. There were no other significant differences between groups.

FIG. 1. The effect of desmopressin on systolic, diastolic, and mean arterial pressures. Values are mean ± SEM. Only the diastolic pressures were significantly different between desmopressin and placebo groups during the drug infusion (repeated-measures ANOVA, $P = 0.0372$). The placebo group's mean diastolic pressure at 15 min was significantly greater than the placebo group mean diastolic pressure at time 0 (Sheffé F test, $P < 0.05$).

face area, time on cardiopulmonary bypass, or preoperative medications. Preoperative and baseline hemodynamic data are presented in table 2. The only significant difference between the desmopressin- and placebo-treated groups was the baseline PVR (103 ± 10 dynes·s·cm⁻⁵ versus 140 ± 14 dyn·s·cm⁻⁵ for the desmopressin- and placebo-treated groups, respectively). All other hemodynamic variables compared favorably. Seventeen patients in each group received opioids as the sole anesthetic agent. Three patients in each group were anesthetized with opioids combined with less than 1 MAC of a potent inhalational agent. All potent inhalational agents were discontinued before rewarming was started.

During drug infusion, the mean systemic diastolic pressure in the desmopressin-treated group was 6–8 mmHg less than that of the placebo-treated group (repeated measures ANOVA, $P = 0.1417, P = 0.0372$, and $P = 0.0831$ for the systolic, diastolic, and mean pressures, respectively; see fig. 1). The only significant change from the baseline measurement occurred at 15 min, when the mean diastolic pressure of the placebo-treated group was increased. Thirty-five percent (7 of 20) of the patients receiving desmopressin met our criteria of hypotension (MAP decrease of 20% or more) at least once during drug infusion (11 episodes). One patient from the placebo-treated group was hypotensive (one episode, $P = 0.0177$;

see fig. 2). Of the 7 patients in the desmopressin-treated group who became hypotensive, 3 were receiving inotropic infusions and 4 were not. The 1 patient in the placebo-
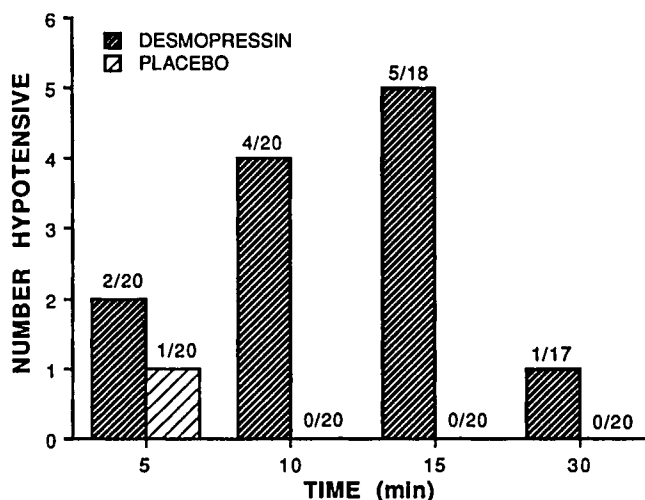

FIG. 2. The number of patients hypotensive at 5, 10, 15, or 30 min. Hypotension was defined as a decrease in mean arterial pressure of 20% or more from the baseline value. Above each column is the number of patients who became hypotensive over the number of patients in that group. Note that in three patients the desmopressin infusion was discontinued before the 30-min measurement because of severe hypotension. More patients became hypotensive (contingency analysis, $P = 0.0177$), and more episodes of hypotension occured ($P = 0.0019$) in those receiving desmopressin.

treated group who became hypotensive was receiving an infusion of an inotropic drug.

In three patients, the MAP decreased to less than 50 mmHg (49, 46, and 35 mmHg). This occurred after the 10-min measurement in two patients and after the 15-min measurement in the third. Subsequent hemodynamic data were not included in the statistical analysis because vasopressors were administered to all three. All three of these patients were receiving desmopressin ($P = 0.072$). One also was receiving dobutamine. A bolus of phenylephrine (Winthrop Pharmaceuticals, New York, NY) was required for all three and an epinephrine infusion for one to return the MAP to baseline levels.

When compared with the control group, those receiving desmopressin had a lower mean SVR (repeated measures ANOVA, $P = 0.0078$; see fig. 3). The desmopressin-treated group also demonstrated a significant decrease from the baseline value (time 0) at the 10- and 15-min measurements (Sheffé F test, $P < 0.05$ for both times). The values for the control group did not change from baseline. Patients receiving desmopressin had a greater cardiac output than those receiving the placebo (repeated measures ANOVA, $P = 0.0166$, fig. 3); however, values did not change significantly from baseline in either group. There were no differences between groups, and there were no significant changes from the baseline value for the heart rate, central venous pressure, or mean pulmonary artery pressure. At the 30-min measurement, the pulmonary artery occluded pressure was greater in the desmopressin-treated group than in the placebo-treated group, and it was significantly greater than the baseline value (mean values of 14.4 ± 0.7 mmHg and 12.0 ± 0.4 mmHg for the desmopressin-treated and placebo-treated groups, respectively; $P = 0.0037$ for a difference between groups). The two groups had different PVRs (mean values of 103 ± 10 dyn·s·cm^{-5} and 140 ± 14 dyn·s·cm^{-5} for the desmopressin- and placebo-treated groups, respectively; $P = 0.0413$ for a difference between groups) before desmopressin infusion was started. This relationship did not change during the infusion.

The mean volume of scavenged blood transfused during the study period was 335 ml and 330 ml for the desmopressin- and placebo-treated groups, respectively. The mean total volume of intravenous fluid infused (scavenged blood plus lactated Ringer's solution) during the 30-min study period was 1,097 ml for the desmopressin-treated group and 800 ml for the placebo-treated group. These differences were not significant.

In 18 patients, inotropic infusions were started before cardiopulmonary bypass was discontinued. Seventeen of these patients received dobutamine, and 1 patient received epinephrine (at a rate of 0.025 μg·kg^{-1}·min^{-1}; this patient was in the placebo-treated group). Eight of the patients who received dobutamine were in the placebo-

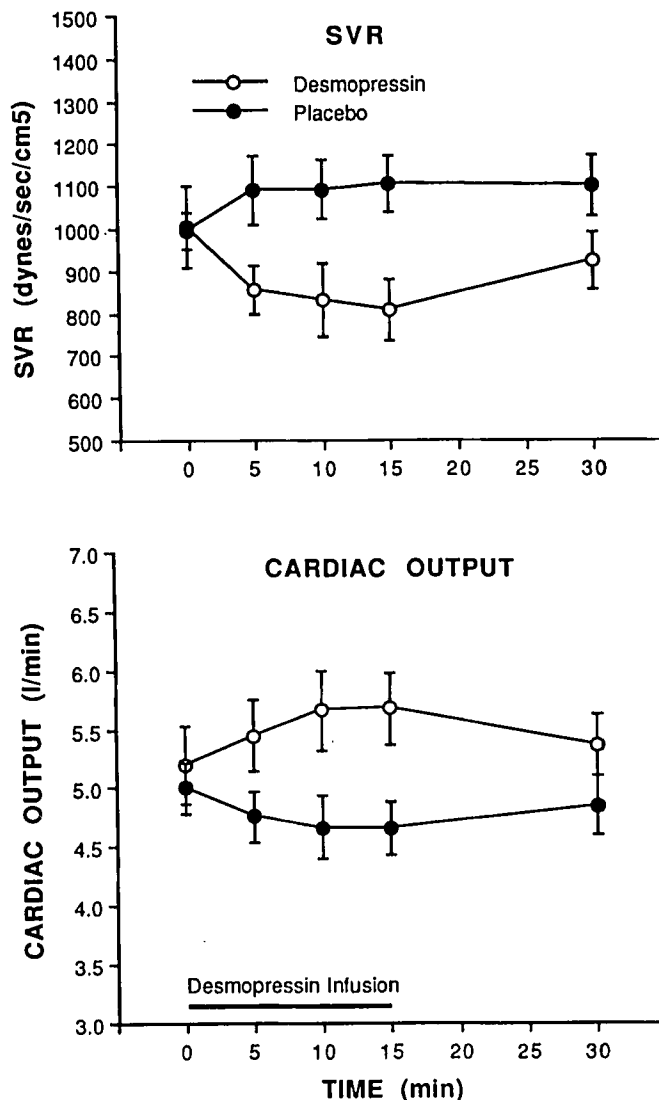

FIG. 3. The effects of desmopressin on systemic vascular resistance and cardiac output. Values are mean ± SEM. The SVR of the desmopressin group was significantly lower than that of the placebo group during the drug infusion (repeated-measures ANOVA, $P = 0.0078$). The desmopressin group also had a greater cardiac output than the placebo group (repeated-measures ANOVA, $P = 0.0166$). Within the desmopressin group, only the systemic vascular resistances at 10 and 15 min were significantly reduced (Sheffé F test after one-factor repeated-measures ANOVA) from the time-0 value. The placebo group exhibited no significant changes with time.

treated group, and the other 9 received desmopressin. The mean dobutamine dose was identical (5.6 μg·kg^{-1}·min^{-1}; range, 3–10 μg·kg^{-1}·min^{-1}) for both the desmopressin- and placebo-treated groups. There were no changes in the dobutamine dose during the 15-min desmopressin infusion. In one patient, who received the placebo, the infusion was discontinued at the 15-min measurement because systolic blood pressure was greater than 130 mmHg. A second patient, who received des-

mopressin, was profoundly hypotensive (MAP less than 50 mmHg) at the 15-min measurement. An epinephrine infusion was started in this patient.

Two-factor ANOVA was used to determine whether the changes in diastolic blood pressure, SVR, or cardiac output were secondary to the infusion of desmopressin, infusion of an inotropic drug, or interaction between the two. Patients receiving inotropic drugs had lower mean diastolic blood pressures and SVRs compared with those not receiving them, but there were no significant changes from the baseline (fig. 4). These effects were independent of the changes produced by desmopressin, and there were

FIG. 4. The effect of inotropic infusions on the diastolic blood pressure and systemic vascular resistance. Values are mean ± SEM. *A significant effect attributable to desmopressin; ‡a significant effect attributable to infusion of an inotropic agent (two-factor ANOVA, $P < 0.05$). Both desmopressin and infusion of inotropic agents reduced the diastolic blood pressure and SVR; however, these effects were independent of each other. There was no significant interaction between the two variables.

no significant interactions between the two variables. Administration of inotropic infusions did not result in significant differences between the desmopressin- and placebo-treated groups or changes from the baseline measurements for the remainder of the hemodynamic variables examined.

HEMATOLOGIC DATA

The coagulation parameters and hematocrit measured preoperatively, after the protamine administration, and on arrival in the intensive care unit are presented in table 3. The preoperative PT was the only variable that was significantly different between the two groups; however, the PT values were within the normal range for both desmopressin- and placebo-treated patients. The amount of protamine required after cardiopulmonary bypass was equivalent in both groups. There was no significant difference in mediastinal tube drainage. Data on use of blood products are presented in table 3. Eleven patients received transfusions of blood bank products; 6 were in the desmopressin-treated group and 5 were in the placebo-treated group. Four patients received a platelet transfusion postoperatively (8 units each); all were in the desmopressin-treated group. Only 6 patients lost more than 1 l into the mediastinal tubes at 24 h; 4 of these patients these patients received desmopressin.

Two patients underwent reoperation. One had myocardial ischemia secondary to internal mammary artery occlusion; this patient received the placebo. The second patient, who received desmopressin, was bleeding from a distal saphenous vein graft anastomosis.

Discussion

The practice of administering desmopressin after cardiac surgery became prevalent after reports by Czer et al.[10] and Salzman et al.[11] demonstrated its effectiveness in reducing postoperative blood loss. The reported success in improving hemostasis, combined with an apparent lack of important side effects, seemed to justify this widespread use. However, there have been reports that hypotension can occur with intravenous infusion of desmopressin after cardiopulmonary bypass[16,17] and that desmopressin does not reduce blood loss or transfusion requirements significantly after uncomplicated cardiac surgery.[18–20] This study was conducted to determine whether administration of desmopressin resulted in hypotension or reduced postoperative blood loss in patients undergoing primary CABG.

Desmopressin infusion was associated with a reduction of the diastolic blood pressure when compared with the placebo-treated group. In addition, 35% of the patients receiving desmopressin experienced at least one 20% or greater decrease in MAP during desmopressin infusion. This represents a potential risk to patients early after cor-
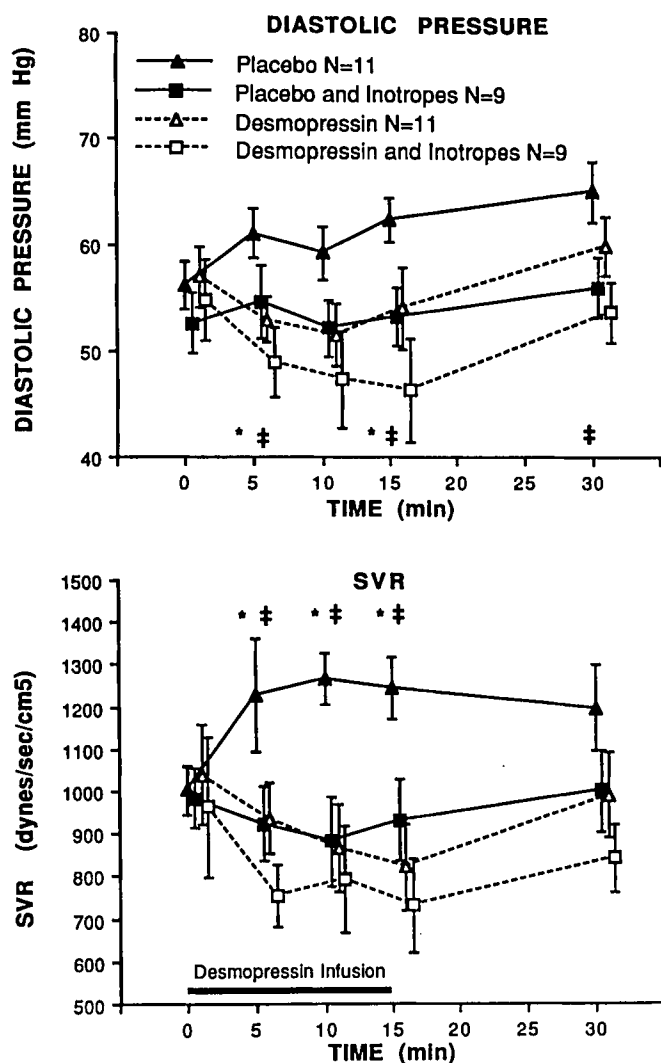
TABLE 3. Coagulation Parameters, Blood Loss, and Blood Product Transfusion

	Desmopressin	Placebo
Preoperative		
Hematocrit (%)	42 ± 1	42 ± 1
Platelet count $(1,000 \cdot mm^{-3})$	264 ± 14	263 ± 15
Prothrombin time (s)	11.1 ± 0.1	$10.8 \pm 0.1*$
Partial thromboplastin time (s)	29.4 ± 0.6	29.0 ± 0.8
Activated clotting time (s)	116 ± 5	126 ± 4
Bleeding time (min)	7.0 ± 0.5	5.9 ± 0.4
After protamine (dose in mg)	(145 ± 4)	(158 ± 10)
Hematocrit (%)	26 ± 1	25 ± 1
Platelet count $(1,000 \cdot mm^{-3})$	134 ± 10	140 ± 10
Prothrombin time (s)	14.8 ± 0.3	14.4 ± 0.3
Partial thromboplastin time (s)	45.2 ± 1.9	43.7 ± 2.2
Activated clotting time (s)	134 ± 3	131 ± 3
Arrival in intensive care unit		
Hematocrit (%)	36 ± 1	35 ± 1
Platelet count $(1,000 \cdot mm^{-3})$	162 ± 12	155 ± 9
Prothrombin time (s)	14.2 ± 0.4	13.5 ± 0.2
Partial thromboplastin time (s)	46.0 ± 2.3	45.5 ± 2.0
Activated clotting time (s)	140 ± 3	146 ± 6
Bleeding time (min)	8.3 ± 0.8	9.0 ± 0.7
Mediastinal blood loss $(ml \cdot 24\ h^{-1})$	790 ± 130	687 ± 50

	Units	Patients	Units	Patients
Blood products given				
Packed erythrocytes	12	5	6	3
Fresh frozen plasma	13	4	6	3
Platelets	32	4	0	0
Patients exposed to blood transfusion		6		5

Plus or minus values are mean ± SEM.

* $P < 0.05$. There were no other statistical differences between desmopressin and placebo groups.

onary revascularization, especially if this side effect is not anticipated. Three of the 20 patients receiving desmopressin (15%) experienced hypotension severe enough to necessitate additional vasopressor and fluid therapy. All three of these episodes were remarkably similar in clinical presentation to the two cases of desmopressin-induced hypotension previously reported by D'Alauro and Johns.[16]

The lower diastolic pressure in the desmopressin-treated group was secondary to a reduction of SVR rather than decreased ventricular filling pressures. These observations are consistent with previous experimental results examining the effects of desmopressin on hemodynamics in dogs[21] and on isolated vascular rings.[22] Human studies performed on patients not undergoing cardiac surgery confirm reductions in MAP.[13,14] The effects of desmopressin on other hemodynamic variables in humans was not studied previously.

We used only a single desmopressin dose and rate of infusion (0.3 $\mu g \cdot kg^{-1}$ infused over 15 min). One of our goals was to corroborate previous studies that examined the effect of desmopressin on postoperative hemostasis and blood loss[11,13,18-20]; therefore, we used the same drug-administration protocol. The clinician should not require

larger doses of desmopressin because infusion of 0.3 $\mu g \cdot kg^{-1}$ produces maximal increases in levels of serum Factor VIII and von Willebrand factor,[23] the presumed mechanism by which hemostasis is enhanced. Desmopressin was not infused at a faster rate because of concern that profound hypotension could occur in patients still at risk for myocardial ischemia. This concern appears to have been justified. We did not include a group of patients in whom desmopressin was infused at a slower rate, and we do not know whether slower infusion would result in lesser, clinically insignificant cardiovascular effects.

Because both groups had similar hemodynamic profiles 15 min after infusion was discontinued, it appears that plasma concentrations of desmopressin sufficient to cause vasodilation were achieved only during the drug infusion. Johns[22] reported that desmopressin concentrations needed to produce vascular relaxation *in vitro* are within the range of 7–10 $nmol \cdot l^{-1}$. Human plasma concentrations of desmopressin are reported to be 891 ± 89 $pmol \cdot l^{-1}$ 10 min after an infusion of 0.3 $\mu g \cdot kg^{-1} \cdot 20$ min^{-1}.[13] Because the distribution half-life is only 7.8 min,[24] peak plasma concentrations would be expected to be much higher during drug infusion.

The decision to infuse inotropic agents was not controlled by our study protocol. Infusion of inotropic agents (dobutamine in all except one case) decreased the diastolic blood pressure and reduced the SVR when compared with values in those not receiving inotropic agents; however, these effects were independent of the decreases caused by desmopressin. In addition, the process of randomizing patients into drug- and placebo-treated groups resulted in nearly identical utilization of inotropic drugs. The use of inotropic agents was not associated with other differences between the desmopressin- and placebo-treated groups.

Patients in the desmopressin-treated group were given 30% more intravenous volume than the placebo-treated group. Although this difference was not statistically significant, it may account for the higher pulmonary artery occlusion pressures in the desmopressin-treated group 15 min after completion of the infusion. It is possible this additional fluid volume was given in response to systemic vasodilation caused by desmopressin. This could have prevented observation of greater decreases in arterial pressure.

Before desmopressin infusion was started, the two groups had significantly different PVRs. This occurred despite randomization, and we cannot provide an explanation. Although the two populations started with different PVRs, there was no significant change from the baseline values during desmopressin or placebo infusions. Desmopressin did not reduce the mean pulmonary artery pressures. There are no human studies with which to compare these results; however, they are in contrast to *in vitro* experiments that indicate desmopressin is also a potent pulmonary vasodilator.[22]

It has been our practice to administer desmopressin soon after cardiopulmonary bypass[19]; thus, hypotension could occur during a critical period. We did not observe any major complications such as reinstitution of cardiopulmonary bypass, myocardial ischemia leading to cardiac failure, or systemic hypoperfusion resulting from a reduction in diastolic pressure. When the MAP decreased to less than 50 mmHg in three patients receiving desmopressin, the hypotension was treated effectively with phenylephrine alone or in combination with epinephrine.

Derkx *et al.*[15] first observed minor decreases in systolic and diastolic blood pressure with administration of desmopressin to normal humans. He suggested the vasodilation resulted from antagonism with endogenous arginine vasopressin at the smooth muscle V1 receptors that mediate vasoconstriction. Bichet *et al.*[13] suggested an alternative mechanism whereby desmopressin decreases blood pressure through a direct vascular effect mediated by a non-V1 receptor. They observed that carriers of the gene for nephrogenic diabetes insipidus did not exhibit hypotension with desmopressin infusion, whereas normal controls and those with central diabetes insipidus experienced a 10–15% decrease in MAP. They hypothesized that desmopressin exerts its vasodilating effects through a vascular V2 receptor and that this receptor or its transducing mechanism (adenylate cyclase–stimulated cyclic adenosine monophosphate) is defective in blood vessels and kidney tubules of patients with nephrogenic diabetes insipidus.

Experiments performed by Liard[21,25,26] also support the presence of vascular V2 as well as V1 receptors. Although administration of V1 receptor agonists such as arginine vasopressin results in vasoconstriction, selective V2 agonists such as desmopressin produce vasodilation. Vasodilator activity appears to be related to the V2 or antidiuretic activity of the drug. These effects can be blocked by selective V1 and V2 antagonists. In addition, arginine vasopressin, which is a mixed V1 and V2 receptor agonist, produces vasodilation in the presence of a selective V1 antagonist.

Desmopressin did not reduce postoperative blood loss or enhance postoperative coagulation parameters. Two study design limitations make definitive statements about the effect of desmopressin on blood product utilization impossible. First, the sample size was not large enough to allow one to dismiss the possible benefits of desmopressin used after cardiopulmonary bypass. Second, we did not establish strict criteria for postoperative blood product administration. However, desmopressin did not reduce the bleeding time or enhance any of the coagulation tests performed. These findings are in agreement with those of other studies that specifically have examined the hemostatic properties of desmopressin.[18–20] In particular, Hackmann *et al.*[18] examined a large number of patients undergoing primary CABG and did not find any significant benefit from the routine use of desmopressin.

Our results are in contrast to those reported by Salzman *et al.*,[11] possibly because the patient population they studied was quite different from ours. They selected patients having repeat sternotomies, undergoing long cardiopulmonary bypass runs, and having complicated operative procedures. They also specifically excluded patients undergoing primary CABG. Our patients underwent primary sternotomy and had short cardiopulmonary bypass runs; also, CABG was the only procedure performed. The quantity of postoperative bleeding described by Salzman *et al.* was much greater than that experienced by our population. Only six patients in our study (15%) lost more than 1 l of blood into their mediastinal drains in 24 h, whereas the mean 24-h blood loss for the placebo-treated group in Salzman's study was approximately 1 l. These differences could account for the disparate results.

Only 2 of 40 patients required reoperation, too few to allow any conclusions to be drawn regarding a possible reduction in reoperations resulting from administration of desmopressin. There was no evidence that desmo-

pressin induced internal mammary artery spasm, induced vein graft vasoconstriction, or produced a hypercoagulable state.

In conclusion, there appears to be increasing evidence that desmopressin has no benefit in reducing blood loss after primary CABG. Desmopressin does reduce the SVR, often leading to hypotension, and should be used with caution after cardiopulmonary bypass.

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