Anesthesiology 2004; 101:1136–44

Effects of Different Catecholamines on the Dynamics of Volume Expansion of Crystalloid Infusion

Luiz A. Vane, M.D., Ph.D., Donald S. Prough, M.D.,* Michael A. Kinsky, M.D.,† Chad A. Williams,‡ James J. Grady, Dr. P.H.,§ George C. Kramer, Ph.D.**

Background: **The authors studied the influence of α, β, and dopaminergic catecholamines on blood volume expansion in conscious normovolemic sheep before, during, and after a bolus infusion of a crystalloid.**

Methods: **A 0.9% NaCl bolus (24 ml/kg in 20 min) was infused in four paired experiments each: no drug, dopamine infusion (50 $\mu g \cdot kg^{-1} \cdot min^{-1}$), isoproterenol infusion (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and phenylephrine infusion (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Blood volume expansion was calculated by the dilution of blood hemoglobin concentration.**

Results: **Dopamine had little effect on peak blood volume expansion (12.7 ± 0.9 ml/kg) compared with 0.9% NaCl (13.0 ± 2.7 ml/kg); in contrast, isoproterenol augmented blood volume expansion (18.5 ± 1.8 ml/kg), and phenylephrine reduced blood volume expansion (8.9 ± 1.4 ml/kg). Two hours after the 0.9% NaCl bolus, sustained blood volume expansion was greatest in the isoproterenol protocol (12.2 ml/kg), whereas the dopamine protocol (6.8 ml/kg) remained similar to the control protocol (4.1 ml/kg), and the phenylephrine protocol had a net volume loss (−1.9 ml/kg). Some blood volume expansion differences were attributed to changes in renal function as phenylephrine infusion increased urinary output, whereas isoproterenol was associated with antidiuresis. However, dopamine caused diuresis and sustained augmentation of blood volume.**

Conclusion: **Catecholamines can alter the intravascular volume expansion of fluid therapy. β-Receptor (isoproterenol) stimulation augmented blood volume expansion, whereas α (phenylephrine) stimulation reduced blood volume expansion. Combined dopaminergic, β, and possibly α stimulation with dopamine augmented blood volume expansion and cardiac output while inducing diuresis.**

FLUID infusions to augment blood volume (BV) are a mainstay of anesthesia practice. Fluid therapy is used for immediate correction of hypovolemia in emergency departments or for support of blood pressure and cardiac output (CO) in operating rooms and intensive care units. The primary goal of fluid therapy is volume expansion and restoration and maintenance of adequate tissue perfusion and delivery of oxygen. Infusion of crystalloid solutions, most commonly lactated Ringer's solution or 0.9% "normal" saline (0.9% NaCl), are often the first choice to improve circulatory function in critically ill patients.[1,2]

However, in many clinical scenarios, crystalloid solutions alone are inadequate for providing sufficient perfusion or achieve sufficient perfusion only with excessive volume loading and associated interstitial fluid volume expansion and increased cardiac filling pressures. Only a small proportion of infused crystalloid remains in the circulation at the end of infusion,[3–5] and excessive infusion can produce fluid overload, edema, and impaired hemodynamic status.[2] One consequence of poor vascular retention is a limited ability to increase BV resulting in interstitial edema that when excessive may impair gas exchange, compromise pulmonary and cardiac mechanics, cause paralytic ileus, and exacerbate cerebral edema.[2,6,7]

To avoid or minimize the morbidity of fluid overload and to improve perfusion in patients who do not adequately improve perfusion with fluid infusion alone, inotropic and vasoactive catecholamines are commonly administered with fluid infusion to improve hemodynamic and cardiovascular functions. The clinical objectives for fluid therapy and catecholamine therapy are similar, *i.e.*, increase CO and maintain arterial blood pressure and tissue perfusion without excessive filling pressures or volume overload.[2,8–10] However, despite the common coadministration of fluids and catecholamines, surprisingly little is known about the interactions between fluid infusions and catecholamine infusions. An ideal combination of fluid infusions and catecholamines would provide sufficient vascular retention to augment CO without excessive increases in cardiac filling pressure or edema. Catecholamines could have multiple effects on the vascular retention of volume expanders. Alterations in arteriolar and venous tone and cardiac contractility have direct effects on venous and capillary pressures and thus alter the microvascular balance of pressures and blood-to-tissue fluid balances. Further, catecholamines alter renal blood flow, glomerular filtration pressure, and urinary output (UO), which alter the retention of infused volume.

In the current study, we measured volume expansion and hemodynamics during and after a 0.9% NaCl bolus in conscious splenectomized normovolemic sheep. In six sheep, we performed four paired experiments evaluat-

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

* Professor, † Resident, ‡ Research Assistant, Departments of Anesthesiology and Physiology, § Senior Biostatistician, Office of Biostatistics.

Received from the Departments of Anesthesiology and Physiology and the Office of Biostatistics, University of Texas Medical Branch Galveston, Galveston, Texas. Submitted for publication November 5, 2003. Accepted for publication June 3, 2004. Supported in part by The Department of the Navy, Office of Naval Research (N00014-00-1-0362) and by grant Nos. 8720 and 8450 from Shriners Burns Hospitals, Galveston, Texas. The content does not necessarily reflect the position or policy of the sponsors and no official endorsement should be inferred.

Address correspondence to Dr. Kramer: Resuscitation Research Laboratory, Department of Anesthesiology, OSB 2-51, Galveston, Texas 77555-0801. Address electronic mail to: gkramer@utmb.edu. Reprints will not be available from authors. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

ing four treatment protocols: 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine, 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ isoproterenol, 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ phenylephrine, and no drug or control protocol.

Our goal was to determine whether and how a catecholamine infusion influenced volume expansion and retention of a 24-ml/kg infusion of 0.9% NaCl infused over 20 min. Dopamine was chosen because it is used to augment hemodynamics in critically ill patients, and a 50-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dose in sheep has been found to cause predominantly β adrenergic and dopaminergic effects in preliminary experiments. Phenylephrine and isoproterenol were chosen to evaluate the effects of an α agonist and a β agonist, respectively.

Materials and Methods

The protocol and experimental procedures were reviewed and approved by the Animal Care and Use Committee of the University of Texas Medical Branch at Galveston, Texas, with adherence to the *Guide for Care and Use of Laboratory Animals*.[11]

Animals and Surgical Preparation

Six adult female Merino sheep weighing 29–35 kg (mean, 31.8 ± 2.9 kg) were anesthetized with halothane and surgically prepared with chronic instrumentation in a sterile operating environment. The sheep were orotracheally intubated and mechanically ventilated with 1.5–2.5% halothane anesthesia. Vascular catheters were inserted in the right and left femoral arteries and veins and advanced into the abdominal aorta and the inferior vena cava, respectively. A continuous CO pulmonary arterial catheter (Vigilance System; Baxter Healthcare, Irvine, CA) was introduced through the right common jugular vein and positioned in the pulmonary artery. All catheters were filled with 1,000 U/ml heparin sodium solution and secured to the fleece on the back of the animal. A splenectomy was performed through a left lateral subcostal incision. All catheters were exteriorized, and surgical incisions were sutured closed in two layers. The animals were awakened after surgery and allowed 1 week to recover from surgical procedures. Analgesia consisted of 0.3 mg intramuscular buprenorphine to minimize postsurgical pain. Animals were maintained in large metal cages with free access to food and water. The day after surgery, catheters were connected to pressure transducers (Baxter Pressure Monitoring Kit; Baxter Healthcare) with continuous flushing devices (0.9% saline containing 3.0 U/ml heparin) and connected to a Hewlett-Packard Monitor model 78901 A (Hewlett-Packard, Andover, MA) for continuous hemodynamic monitoring to condition the sheep to the experimental setup. Twenty-four hours before the experiment, the sheep's food and water were removed, and a urinary bladder catheter (14 French; Sherwood Medical, St. Louis, MO) was placed.

Experimental Protocols

Four different experimental protocols were performed randomly in each sheep with a minimum 2-day recovery period between each experiment. Responses to an 0.9% NaCl bolus of 24-ml/kg infused over 20 min were evaluated during a continuous infusion of catecholamine. The four protocols were 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine, 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ isoproterenol, 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ phenylephrine, and control. Performing multiple experiments on the same animal allows the use of more discriminating paired statistical tests. In general, our doses are high and the physiologic responses are large. The focus was on the responses to different adrenergic and dopaminergic catecholamines and did not examine dose–response effects. After a 30-min baseline period to determine the precatecholamine hemodynamics, a continuous catecholamine infusion was started. Thirty minutes after the catecholamine infusion was started, we started a 20-min bolus infusion of 0.9% NaCl. For a time reference, we defined T0 as the start of the 0.9% NaCl infusion, and thus T20 represents 20 min later and the end of the 20-min bolus infusion, and T180 is 180 min after the start of the bolus and the experiment end. The control experiments were performed identically to treatment protocols except for the catecholamine infusion.

Measurements and Data Collection

Hemodynamic data included heart rate, mean arterial blood pressure (MAP), mean pulmonary arterial pressure, central venous pressure, and CO. All were continuously monitored and recorded at specific time points during the baseline period and the catecholamine infusion before the 0.9% NaCl bolus, during the 0.9% NaCl bolus, and for 3 h after the 0.9% NaCl bolus. These variables plus hematocrit, hemoglobin, and UO were recorded three times during the baseline period. After starting the catecholamine infusion but before the 0.9% NaCl bolus, the variables were measured at 5, 15, 20, 28, and 30 min. At this time, the 0.9% NaCl bolus was started (T0), and measurements were taken at T5, T10, T15, T18, and T20. After the 0.9% NaCl bolus ended, variable measurements continued for 180 min. Variables were measured every 2 min during the first 10 min, every 5 min during the next 50 min, and every 15 min during the last 120 min. At each time point, a sample of arterial blood was drawn and analyzed for hemoglobin and hematocrit. Small arterial blood samples were carefully taken in 1-ml syringes previously heparinized using a technique shown to be reliable in collecting arterial blood without dilution. To assure the acquisition of fresh circulating blood without saline dilution from the transducer flush system, sample removal was preceded by a continuous blood withdrawal of 5 ml blood from the catheter. After the sample was taken, the 5 ml blood was returned to the animal.

Total hemoglobin concentration was measured in duplicate using a 482 CO-Oximeter (Instrumentation Laboratory System, Lexington, MA), and the mean value was used in subsequent calculations. From the same sample, blood was centrifuged in capillary tubes for 5 min, and hematocrit was measured in duplicate and the mean value was recorded.

Calculated Variables

Blood volume changes over time were calculated from the estimated baseline BV of 65 ml/kg for normal sheep, and changes in the blood hemoglobin concentration during the experiment at specific times (t) as

$$BV_t = 65 \times \text{hemoglobin}_t/\text{hemoglobin}_o ,$$

where BV_t and hemoglobin_t are the BV and the hemoglobin concentrations at t, and hemoglobin_o is the baseline hemoglobin concentration as previously described.[12]

Vascular resistance was calculated using the following formula:

$$\text{Systemic Vascular Resistance: (SVR)} = (\text{MAP} - \text{CVP})/\text{CO} \times 80,$$

with units expressed in dyn $\cdot$ s^{-1} $\cdot$ cm^{-5}.

Statistical Analysis

Results are displayed as the mean ± SE of the mean. Results from the statistical tests are shown in the figure legends. Statistical comparisons (paired *t* tests) were performed to distinguish between all treatment pairs for selected *a priori* determined time points: the final baseline measurement and the four postbolus time points at 20, 60, 120, and 180 min, after starting the 20-min bolus (T20, T60, T120, and T180). To avoid reporting spurious findings or overinterpretation of the data, we defined a significant group difference as two or more consecutive postinfusion time points being significant at the 0.05 α level. Significant differences between protocols are designated with the symbol >, while no significant difference between protocols is designated with the ≈ symbol. Comparative statistics were also performed to determine whether each variable was altered from its preinfusion (T0) level.

Results

All six sheep were in good health for all four paired experiments. No animal demonstrated any adverse reactions during the drug or fluid infusions.

Figure 1 shows the measured hemoglobin and BV calculated from the dilution of hemoglobin. The catecholamine infusions did not produce statistically significant effects on either hemoglobin or calculated BV before beginning fluid infusions. All protocols had a maximum hemoglobin dilution and peak BV expansion at the immediate end of the 0.9% NaCl bolus infusion. Thereafter, BV decreased in all protocols, and each stabilized at a different level of BV.

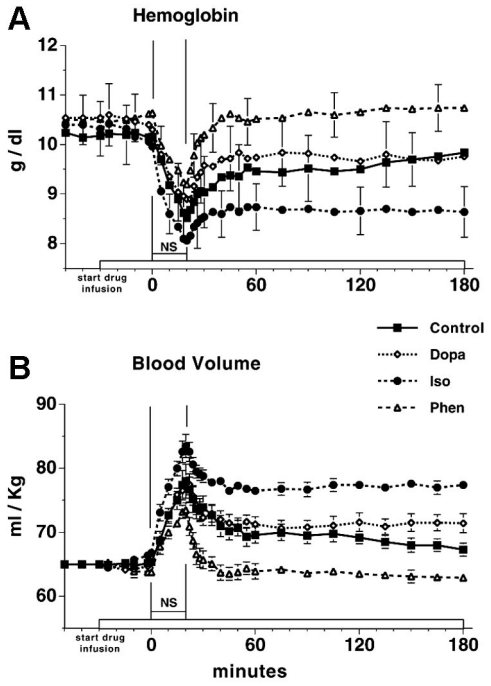

Fig. 1. (*A*) Blood hemoglobin (mean ± SEM) sampled at three baselines periods during a catecholamine infusion and for 3 h after starting a 20-min 0.9% NaCl bolus of 24 ml/kg. Catecholamine protocols are dopamine (Dopa, *open diamonds*), isoproterenol (Iso, *closed circles*), phenylephrine (Phen, *open triangles*), and no-drug control (Control, *closed squares*). NS = normal saline bolus. The symbols > and < represent statistically significant greater or lesser differences, respectively, and ≈ represents that a significant difference was not found. The 0.9% NaCl bolus decreased hemoglobin in all protocols at T20 and in all protocols except the Phen protocol thereafter. Postinfusion protocol differences were Phen > Dopa ≈ Control > Iso. (*B*) Calculated blood volume (mean ± SEM) at three baseline periods during a catecholamine infusion and for 3 h after starting a 20-min 0.9% NaCl bolus of 24 ml/kg. The 0.9% NaCl bolus increased blood volume in all protocols at T20 and in all protocols except the Phen protocol thereafter. Postinfusion protocols differences were Iso > Dopa ≈ Control > Phen.

Figure 2 shows the change in blood volume from baseline levels and the cumulative urinary output. At peak BV expansion, immediately at the end of the 0.9% NaCl bolus infusion of 24 ml/kg, the BV increase was highest in the isoproterenol protocol (18.5 ± 1.8 ml/kg), followed by the dopamine and control protocols (12.7 ± 0.9 and 13.0 ± 2.7 ml/kg), respectively. The phenylephrine protocol showed the lowest increase (8.9 ± 1.4 ml/kg). At the end of the experiment (T180), the isoproterenol protocol had the highest BV expansion (12.4 ± 0.8 ml/kg). The dopamine protocol exhibited less BV expansion (6.4 ± 1.5 ml/kg), which was only slightly higher than the control protocol increase (4.2 ± 1.0 ml/kg) at T120. However, expansion in the control group decreased further to 2.3 ± 1.0 ml/kg by the end of the experiment at T180, whereas the dopamine protocol had sustained

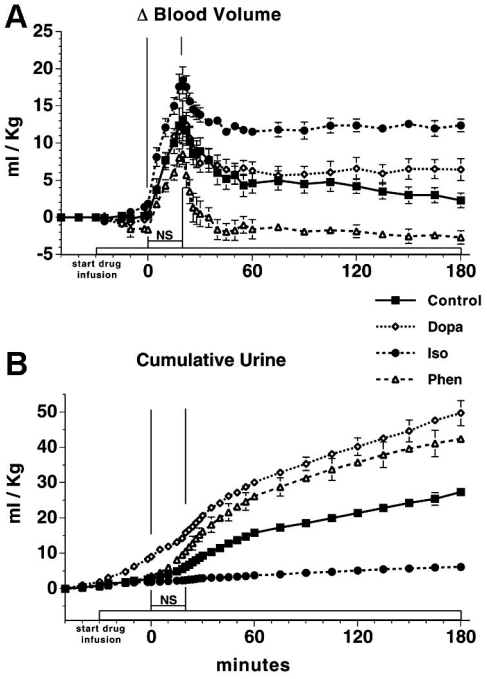

Fig. 2. (*A*) Change in blood volume (mean ± SEM) calculated as the difference in blood volume from the baseline or prebolus measurement. Control = no-drug control; Dopa = dopamine; Iso = isoproterenol; Phen = phenylephrine; NS = normal saline bolus. Statistical comparisons are as described for figure 1. The 0.9% NaCl bolus caused a positive change in blood volume or increase in all protocols at T20 and in all protocols except the Phen protocol thereafter. Postinfusion protocol differences were Iso > Dopa ≈ Control > Phen. (*B*) Cumulative urinary output (mean ± SEM). The 0.9% NaCl bolus caused an increase in cumulative urinary output at T20 for all protocols except the Iso protocol, and thereafter, cumulative urinary output was significantly increased in all protocols. Postinfusion protocol differences in cumulative urinary output were Dopa ≈ Phen > Control > Iso.

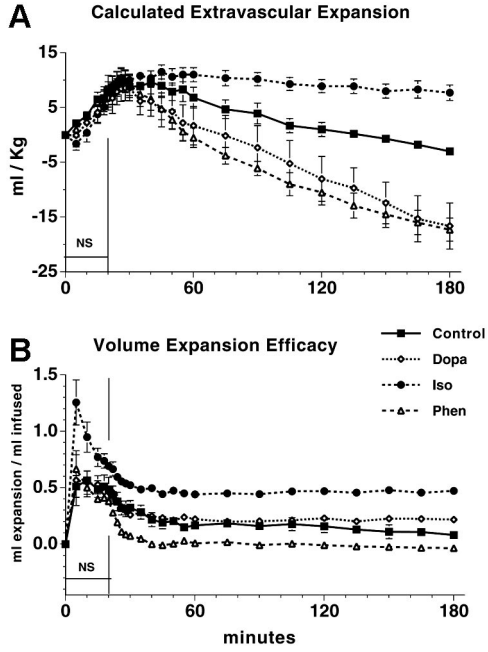

Fig. 3. (*A*) Calculated extravascular expansion calculated as the difference between volume infused minus change in blood volume and cumulative urinary output at each time point. Change in blood volume and cumulative urinary output were both set to zero at the start of infusion. Control = no-drug control; Dopa = dopamine; Iso = isoproterenol; Phen = phenylephrine; NS = normal saline bolus. Statistical comparisons are as described for figure 1. The 0.9% NaCl bolus caused a similar and significant increase at T20 in all protocols except the Dopa protocol. Thereafter, the decreases below baseline in the Dopa and Phen protocols were significant starting at T120, whereas the increased extravascular expansion in the Iso protocol remained significant, and the Control protocol was the same as baseline. Postinfusion protocol differences in extravascular expansion were Iso > Control > Dopa ≈ Phen. (*B*) Calculated volume expansion efficacy (mean ± SEM) as measured by milliliters of blood volume expansion from T0 divided by milliliters infused. Immediately after the 0.9% NaCl bolus at T20, there was no difference between protocols, but from T60 on, postinfusion differences were Iso > Control ≈ Dopa > Phen, and these differences held throughout the entire postinfusion period.

expansion. The phenylephrine protocol had a sustained decrease in BV, with −2.1 ± 0.9 ml/kg below baseline levels at T180.

Some of the differences in BV expansion between the protocols can be accounted for by different renal responses as seen in the plot of cumulative urinary output for all four protocols in figure 2. Only the dopamine protocol significantly influenced and increased UO to 5–7 ml/kg greater than other groups at T0 just before the 0.9% NaCl bolus. The control protocol exhibited a modest diuresis of 6.2 ± 0.8 ml/kg at the end of the 0.9% NaCl bolus, reaching 11.5 ± 2.7 ml/kg at T40, and by T180, UO was 27.4 ± 1.8 ml/kg. Dopamine and phenylephrine infusions enhanced and sustained the diuresis of the 0.9% NaCl bolus. Cumulative UO in the dopamine protocol was nearly double that of the control protocol at most all time periods after the 0.9% NaCl infusion. The phenylephrine infusion had little effect before the 0.9% NaCl bolus but enhanced diuresis after the bolus, similar to the levels of the dopamine protocol. The isoproterenol infusion virtually eliminated diuresis after the 0.9% NaCl bolus.

Figure 3A shows extravascular expansion calculated from the difference between infused volume minus BV expansion and cumulative urinary output. The infused 0.9% NaCl is rapidly transferred to the extravascular space in similar fashion for all protocols during the infusion. Peak extravascular expansion of 7.8 ± 1.5 ml/kg was measured at 10 min after infusion, showing that one third of the infused volume was rapidly transferred to the extravascular space. Thereafter, extravascular expansion was largely maintained in the isoproterenol protocol and decreased slowly in the control protocol, such that extravascular hydration had returned to baseline at T120. Both the dopamine and phenylephrine protocols had rapid decreases in extravascular expansion, with a return to normal hydration around T60, followed by an extravascular contraction in both protocols of ≈17 ml/kg at T180 associated with induced diuresis.

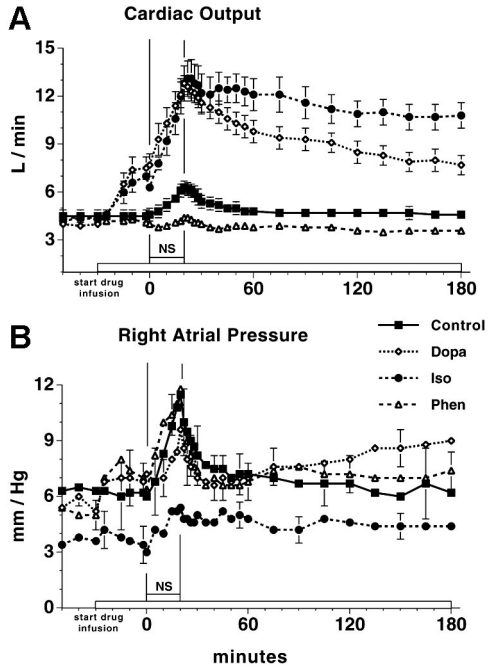

Fig. 4. (*A*) Cardiac output (mean ± SEM). Control = no-drug control; Dopa = dopamine; Iso = isoproterenol; Phen = phenylephrine; NS = normal saline bolus. Statistical comparisons are as described for figure 1. The 0.9% NaCl bolus caused a significant increase in cardiac output of 5 l/min at T20 in the Dopa and Iso protocols, and the Control protocol had a slight increase in cardiac output of 1 l/min, whereas the Phen protocol was the same as baseline. Postinfusion differences in cardiac output were Iso > Dopa > Control > Phen. (*B*) Right atrial pressure (mean ± SEM). The 0.9% NaCl bolus caused a significant increase at T20 in all protocols. Thereafter, right atrial pressure was increased significantly at T120 only in Phen protocol. Postinfusion protocol differences in right atrial pressure were Dopa ≈ Phen > Iso ≈ Control.

Figure 3B shows volume expansion efficiency (VEE). VEE is calculated as the ratio of BV expansion to infused volume. VEE was generally 0.5 or less even during the infusion, suggesting that nearly half of the infused fluid was rapidly transferred to the extravascular space or excreted as urine during the infusion. Only the isoproterenol protocol had a short-lived enhanced VEE with a value greater than 1.0 during the early infusion period, suggesting augmentation of expansion. However, the sustained VEE values for all protocols between T60 and T180 were less than 1.0 or 0.2 to 0.1 for the control protocol, 0.2 for the dopamine protocol, and 0.5 for the isoproterenol protocol. VEE for the phenylephrine protocol became negative as volume expansion became less than baseline at T60.

Although the direct effect of fluid therapy is volume expansion, the desired clinical effect is to augment CO. Figure 4A shows that the dopamine and isoproterenol infusions had similar effects on CO before the 0.9% NaCl bolus, causing increased levels of 70–90% above baseline or change in CO of 3.8 ± 0.7 and 2.8 ± 0.8 l/min, respectively. Clearly, the β effects of both dopamine and isoproterenol increased CO even before the 0.9% NaCl bolus. However, it is equally clear that the 0.9% NaCl bolus further increased CO approximately 5 l/min in both the dopamine and isoproterenol protocols, which was significantly more than the 1.8 ± 0.4-l/min increase in the control protocol. The phenylephrine infusion abolished CO augmentation because of the 0.9% NaCl bolus.

At the end of the 0.9% NaCl bolus, T20, CO had returned to baseline levels in the control protocol, whereas the phenylephrine protocol exhibited a slightly decreased CO (−0.8 ± 0.1 l/min), which was sustained until the end of the experiment. The isoproterenol protocol showed a sustained high CO with 6.5 ± 0.8 l/min above baseline, and the dopamine protocol had an intermediate position with 3.8 ± 0.6 l/min above baseline at the end of the experiment.

Figure 4B shows the mean right atrial pressures (RAPs) plotted for all protocols. All catecholamine infusions showed only statistically insignificant and variable effects on RAP before the 0.9% NaCl infusion. At T20, the end of the 0.9% NaCl bolus infusion, all protocols exhibited an increase in RAP. The phenylephrine protocol showed the largest RAP increase of +6 mmHg, followed by the control and dopamine protocols with +5 and +4.5 mmHg from baseline, respectively. The isoproterenol protocol showed a small and statistically insignificant effect, with a slight increase or change in RAP of +2 mmHg at T20. At T180, RAP in both the isoproterenol and control protocols had fully returned to baseline levels, whereas the dopamine and phenylephrine protocols at T180 showed a change in RAP of +3.5 and +1 mmHg above baseline, respectively.

Figure 5A shows the changes in MAP. In the control protocol, the 0.9% NaCl bolus caused only a transient increase in MAP of 10–15 mmHg during the bolus, which quickly returned to baseline by T40. The phenylephrine infusion rapidly and dramatically increased MAP by nearly 50 mmHg above baseline before the 0.9% NaCl bolus and over 70 mmHg at the peak expansion of the 0.9% NaCl bolus. The dopamine infusions caused a small increase in MAP before the 0.9% NaCl bolus of ≈10 and ≈30 mmHg at peak expansion, respectively. The isoproterenol protocol exhibited a slightly decreased MAP before the 0.9% NaCl bolus of ≈6 mmHg, but blood pressure returned to baseline at peak expansion.

Figure 5B shows the changes from baseline in SVR. The phenylephrine protocol had a doubling of baseline SVR before the bolus; this level was sustained until the experiment ended. Both the isoproterenol and the dopamine protocols displayed a decreased SVR to ≈40% of baseline. The 0.9% NaCl bolus had only a slight effect. At T60, in the control protocol, SVR returned to baseline levels, whereas the dopamine and isoproterenol protocols continued to display a decreased SVR of ≈50% of baseline. From T60 until T180, SVR in the dopamine protocol approached baseline, whereas the isoproterenol protocol remained reduced at ≈50% of baseline.

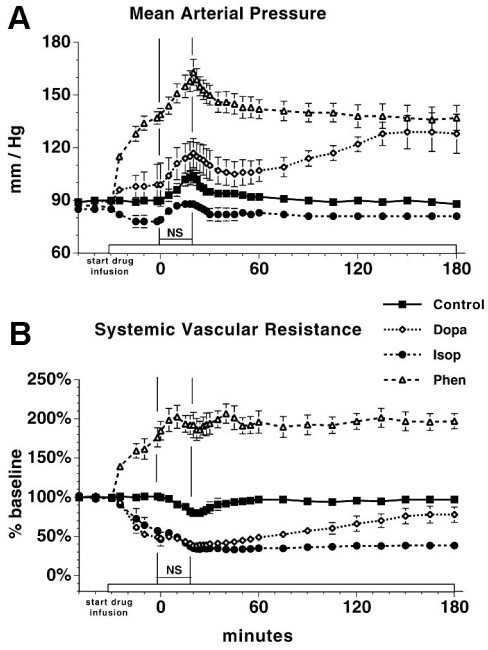

Fig. 5. (*A*) Mean arterial pressure (mean ± SEM). Control = no-drug control; Dopa = dopamine; Iso = isoproterenol; Phen = phenylephrine; NS = normal saline bolus. Statistical comparisons are as described for figure 1. Only the Phen protocol was increased significantly at T0 by the drug alone. The 0.9% NaCl bolus caused a significant increase at T20 in all protocols. After the 0.9% NaCl bolus, the Dopa and Phen protocols continued to increase significantly until the end of the experiment. The Iso and Control protocols were not different than baseline. Postinfusion protocol differences in mean arterial pressure were Phen > Dopa > Control ≈ Iso. (*B*) Systemic vascular resistance (mean ± SEM). The Phen protocol was significantly increased at T0, while the Iso and Dopa protocols decreased significantly by the respective drug before the saline bolus. The 0.9% NaCl bolus caused a significant decrease at T20 in all protocols, except in the Phen protocol. Postinfusion and until the end of the experiment protocol differences in systemic vascular resistance were Phen > Control > Iso > Dopa, except after T120, when Dopa ≈ Control.

Discussion

These data are the first to examine the interaction between catecholamine infusions and volume dynamics of fluid boluses. They demonstrate potentially important effects of β agonists, α agonists, and combined β and dopaminergic agonists on the intravascular retention of infused fluid. These results are potentially important because of the great frequency with which the interventions of fluid therapy and catecholamines are combined in critically ill patients. As a first attempt, to better define the combined effects of inotropic and vasoactive catecholamines and fluid therapy on volume expansion and cardiovascular function, we infused a 24-ml/kg bolus over 20 min in conscious normovolemic sheep receiving set doses of catecholamines. However, there are multiple issues that this study did not address and that must be addressed in subsequent studies. First, inotropic and vasoactive drugs are not used in normovolemic healthy patients, but rather in patients with a variety of circulatory disorders, such as hypovolemia, sepsis, and cardiac failure. Results would likely be different in such scenarios, but the current study clearly shows that catecholamines not only alter cardiovascular function, but also can alter the effectiveness of fluid infusion to expand vascular volume. Second, we examined only one dose of each catecholamine. This limitation is important not only because β and α effects of catecholamines are dose dependent, but also because the predominant receptors stimulated by dopamine tend to change as the dose increases. Future experiments are needed to define the dose–response effects of each drug on volume expansion.

A common misconception of fluid therapy is that the infusion of a fixed volume of crystalloid initially expands BV by the infused volume and that over time the fluid distributes into the extravascular space, approximately in the ratio of plasma volume to the distribution volume of the infused fluid. The current analysis and calculated VEE show that half or more of the infused 0.9% NaCl in the control protocols leaves the circulation as rapidly as it is infused. Such results are consistent with data from recent studies in human volunteers and patients.[3,13] In the current study, the control protocol showed that within 20 min after the 0.9% NaCl bolus ended, only approximately 20% of the infused volume remained in the vascular space, whereas 30% of the infused volume was extravascular, and 50% was lost *via* UO.

The VEE (milliliters of expansion per milliliters infused) of the 0.9% NaCl bolus in the control protocol decreased to the range of 0.2–0.1 by 180 min. In humans and animals, hypovolemia has been shown to augment the VEE of fluid.[4,5,14,15] Such VEE augmentation results from volume-conserving mechanisms secondary to hormonal and neuronal reductions in urinary loss of volume and the compensatory mechanism of transcapillary refill. Catecholamine concentrations are increased in hypovolemia and may play a dominant role in initiating such volume sparing mechanisms. One purpose of the current study was to define how specific catecholamines in the absence of hypovolemia would alter the volume response to a fluid challenge.

Dopamine and Enhanced BV Expansion

Despite some sustaining of the BV expansion with the 0.9% NaCl control protocol, there was a significantly better expansion in the dopamine protocol *versus* the control protocol at only one time point, T180. Cumulative UO in the control protocol by the end of the study was similar to the total infusion of 24 ml/kg (figure 2). Cumulative UO in the dopamine and phenylephrine protocols were approximately 50% greater than the infused load. Despite the diuresis, the dopamine protocol maintained BV expansion after the 0.9% NaCl bolus. The BV expansion and diuresis were at the expense of significant extravascular contraction.

One mechanism for the sustained and enhanced BV expansion effect of dopamine could be alterations at the microvascular level that reduce capillary pressure, thereby decreasing capillary filtration. However, reduced capillary pressure is difficult to reconcile with the overall reduction in SVR in the dopamine protocol. Reduced arteriolar tone allows an increased transfer of arterial pressure downstream to the capillaries. Also, arterial pressure was significantly higher in the dopamine protocol from T120 through T180 because CO was increased more than SVR was reduced. Further, RAP was similar or greater in the dopamine protocol compared with the control protocol at this time period. All data suggest higher capillary pressures and an expected increased capillary filtration in the dopamine-treated sheep.

One alternate mechanism could be enhanced lymphatic pumping, in that dopamine has been shown to stimulate bovine and canine lymphatics and to enhance pumping.[16] Further, increased lymphatic pumping is believed to play a significant role in the interstitial autotransfusion of fluid and protein that occurs after hypovolemia.[17]

Isoproterenol and Enhanced Volume Expansion

Although the dopamine protocol resulted in a modestly better sustained BV expansion *versus* the control protocol, the isoproterenol protocol had a threefold to fourfold greater BV expansion than the control protocol from T60 through T180. This response seems to be largely the result of the antidiuresis induced by isoproterenol. Isoproterenol induces increases in plasma renin and antidiuresis.[18] The antidiuresis effect on isoproterenol has been described in both sheep and dogs.[18,19] The antidiuresis also resulted in a sustained extravascular expansion, compared with an extravascular contraction present with the other two treatment protocols, and a return to nearly normal extravascular hydration after 0.9% NaCl alone. We cannot exclude a direct effect of vasodilation, based on a study in human volunteers in which subarachnoid block slowed the loss of plasma volume after a crystalloid bolus.[20]

Phenylephrine Rapidly Eliminated Any Sustained Volume Expansion of 0.9% NaCl Bolus

Although the initial BV expansion during the 0.9% NaCl bolus in the phenylephrine protocol was similar to the control protocol, immediately after the infusion, BV rapidly decreased to a level less than baseline. The phenylephrine protocol had a significantly greater diuresis than the control protocol, but one that did not start until the 0.9% NaCl bolus was initiated. Phenylephrine infusions also enhanced diuresis and natriuresis in volunteers when used in a dose to increase diastolic pressure by 25 mmHg.[21] In the current study, it is likely that phenylephrine induced a pressure diuresis. Data suggest that in normal subjects, phenylephrine infusion should exert its effects through the increased release of the atrial natriuretic factor.[21]

Mechanism for Catecholamine Modulation of Volume Expansion

A simplified summary of our findings is that vasodilatation augments or sustains volume expansion and that vasoconstriction impairs volume expansion after a 0.9% NaCl bolus. An initial analysis suggests that these are paradoxical findings.

Vasodilatation would be expected to reduce the arteriolar tone and allow transfer of a larger component of the arterial pressure downstream to the capillary level. SVR was reduced by nearly 50% before the 0.9% NaCl bolus in the dopamine and isoproterenol protocols and by 70–80% in the isoproterenol protocol compared with the control protocol. The large decrease in SVR and presumably arteriolar tone would logically increase capillary pressure and cause an increased capillary filtration and an increase in loss of vascular volume. Perhaps there is a greater decrease in venous resistance to offset the likely increase in capillary pressure. The blunted response of RAP in the isoproterenol group during bolus infusion is consistent with reduced capillary pressure.

The paradoxical effects of dopamine and isoproterenol on volume expansion could possibly be accounted for by other explanations. It has been suggested that vasodilator catecholamines could augment lymphatic pumping and return interstitial fluid back to the circulation in excess of capillary filtration. Another possibility is that the decrease in SVR results more from an increase in the total number of open capillaries and an increased microvascular surface area than it does from vasodilatation of a fixed number of arterioles. If a fixed number of arterioles dilate, greater pressure is reflected downstream, but if the vasodilatation reflects the opening of several parallel new arterioles, the downstream pressure is dispersed over a greater surface area and capillary pressure could decrease. The increased CO of the dopamine and isoproterenol protocols may not be associated with the increased flow through individual capillaries of the microcirculation but rather an increased number of capillary surface areas. Likewise, the vasoconstriction of the phenylephrine protocol could reduce the microvascular surface area more than the increasing resistance. Vasoconstriction of a fixed number of arterioles would increase arterial pressure but reduce downstream microvascular pressure, unless a greater number of capillaries were actually closed down.

One possible explanation for our findings is that β-agonist stimulation reduces the hydraulic conductivity of the microvascular barrier. Adamson *et al.*[22] showed that hydraulic conductivity of the endothelial barrier of intact individual capillaries was reduced 73% by isoproterenol. This group provided strong evidence that this effect was

modulated by increased cyclic adenosine monophosphate because similar responses were demonstrated with direct cyclic adenosine monophosphate stimulation with forskolin or with phosphodiesterase inhibitors. β Agonists have been shown to block the inflammatory increases in capillary permeability.[22,23] Data from Adamson *et al.* and the current data suggest that hydraulic conductivity may be physiologically regulated.

Study Limitations

The current results must be extrapolated to human studies with caution because sheep and ewes differ from men and women. Sheep seem to have all of the major receptors and innervations of the autonomic nervous system of humans. We found that the cardiovascular response to human doses of catecholamines were similar in kind but of an altered magnitude. We chose high doses of catecholamine infusion that caused larger changes in hemodynamics than clinically desired. How results would vary in magnitude and kind at lower doses is unknown.

Clinical Implications

The primary goal of infusing a volume expander is to expand the plasma volume with the clinically relevant events of sequentially augmenting venous return, CO, adequate tissue perfusion, and oxygen delivery. Ideally, this goal is accomplished without causing or exasperating cardiac ischemia or causing excessive extravascular fluid retention, pulmonary edema, or any of the complications associated with fluid overload. The common approaches to limiting fluid accumulation are the use of hyperosmotic crystalloids, colloid solutions, inotropic support, and diuretics. Dopamine is known to augment CO, renal blood flow, and glomerular filtration rate and to induce diuresis. Our research suggests that dopamine in addition augments volume expansion, reduces interstitial accumulation of fluid, and could reduce the need for further volume therapy.

Bolus infusions of fluid and the specific catecholamines used in the current study have been studied extensively in animals, and their clinical effects on hemodynamics are well described and used for a variety of clinical needs.[10] Despite this extensive background and experience, little has been reported about how catecholamines alter the volume expansion effects of fluid therapy. Fluid infusion is typically the first intervention to improve hemodynamics in critically ill patients, whereas catecholamines are often used when fluid therapy does not provide the desired sustained improvement in hemodynamics. Our data show that β and dopaminergic agonists not only have direct cardiac and vascular effects, but also enhance volume expansion, suggesting that specific pharmacologic agents might be developed for administration before fluid therapy to enhance volume expansion. In the current study, not only is volume expansion augmented by dopamine and isoproterenol, but also there is an increase in CO augmentation of a 0.9% NaCl bolus. The augmentation was fourfold higher compared with the 0.9% NaCl bolus alone. The clinical message is that dopaminergic- and β-agonist stimulation can increase volume expansion and lower volume needs, whereas infusion of α agonists may necessitate increased volume support. However, dopamine may also result in a loss of interstitial volume.

Whether catecholamines can influence volume expansion independently of their cardiac effects or their vasopressor/dilator affects remains to be determined. Another approach to modulating volume expansion might be to consider altering renal function. The strategy of using an antidiuretic (nasal vasopressin) to enhance temporary volume expansion has been suggested as a means to sustain and enhance volume loading after oral hydration, as a pretreatment to prevent orthostatic hypotension of astronauts returning to gravity after space flight.[24]

The current data suggest that pretreatment with dopamine, isoproterenol, another vasodilator, or a cardiac inotrope might be considered before fluid infusion as opposed to after it. An obvious downside of early use of catecholamine therapy is that increased cardiac work may overstress an already compromised myocardium. Because MAP and CO increase with dopamine, cardiac work (MAP $\times$ CO) can be calculated as fivefold higher at peak levels after dopamine and twofold higher with isoproterenol. However, smaller doses of isoproterenol or another β agonist may be an efficient means to augment both volume expansion and cardiovascular function.

In summary, vasodilators (isoproterenol, dopamine) augmented BV expansion after a 0.9% NaCl bolus, whereas a vasoconstrictor (phenylephrine) decreased volume retention. Multiple mechanisms for augmented volume expansion of dopamine and isoproterenol are possible, but the most likely are reduced capillary pressure secondary to increased microvascular surface area or augmented lymphatic pumping. It may be possible to optimize cardiac and volume effects with selective β agonists. Optimization of hemodynamics and vascular volume in critically ill patients may require considerations of interactions between pharmacologic and volume therapy.

The authors thank Mary Townsend (Administrative Secretary, University of Texas Medical Branch, Department of Anesthesiology, Galveston, Texas) for preparation and editing of the manuscript.

References

1. American College of Surgeons Committee on Trauma: Chapter 3: Shock, Advanced Trauma Life Support: Program for Physicians, Instructor Manual. Edited by Alexander RH, Proctor HJ. Chicago, American College of Surgeons, 1993, pp 75–94

2. Shoemaker WC, Peitzman AB, Bellamy R, Bellomo R, Bruttig SP, Capone A, Dubick M, Kramer GC, McKenzie E, Pepe PE, Safar P, Schlichtig R, Severinghaus JW, Tsherman SA, Wiklund L: Resuscitation from severe hemorrhage. Crit Care Med 1996; 24:S12–23

3. Lamke L-O, Liljedahl S-O: Plasma volume changes after infusion of various plasma expanders. Resuscitation 1976; 5:93–102

4. Tølløfsrud S, Tønnessen T, Skraastad Ö, Noddeland H: Hypertonic saline and dextran in normovolemic and hypovolemic healthy volunteers increases interstitial and intravascular fluid volumes. Acta Anaesthesiol Scand 1998; 42:145–53

5. Tølløfsrud S, Mathru M, Kramer GC: Hypertonic-hyperoncotic solutions in open-heart surgery. Perfusion 1998; 13:289–96

6. Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, Bistrian BR: Postoperative fluid overload: Not a benign problem. Crit Care Med 1990; 18:728–33

7. Demling R, Harms B, Kramer G, Gunther R: Acute versus chronic hypoproteinemia and posttraumatic pulmonary edema. Surgery 1982; 92:79–86

8. Henderson IS, Beattie TJ, Kennedy AC: Dopamine hydrochloride in oliguric states. Lancet 1980; 18:827–9

9. Kulka PJ, Tryba M: Inotropic support of the critically ill patient: A review of the agents. Drugs 1993; 45:654–67

10. Bellomo R, Cole L, Ronco C: Hemodynamic support and the role of dopamine. Kidney Int 1998; 66:S71–4

11. Institute of Laboratory Animal Resources (U.S.): Guide for the Care and Use of Laboratory Animals. Washington, DC, National Academy Press, 1996

12. Tølløfsrud S, Elgjo GI, Prough DS, Chinkes DL, Williams CA, Kramer GC: The dynamics of vascular volume and fluid shifts of infused lactated Ringer's and hypertonic saline dextran (HSD) in normovolemic sheep. Anesth Analg 2001; 93:823–31

13. Tølløfsrud S, Bjerkelund CE, Kongsgaard U, Noddeland H: Cold and warm infusion of Ringer's acetate in healthy volunteers: The effects on haemodynamic parameters, transcapillary fluid balance, diuresis and atrial peptides. Acta Anaesthesiol Scand 1993; 37:768–73

14. Norberg A, Brauer KI, Prough DS, Gabrielsson J, Hahn RG, Traber DL, Svensen CH: Volume turnover kinetics of fluid shifts in sheep after hemorrhage, fluid infusion, and the combination of hemorrhage and fluid infusion. ANESTHESIOLOGY (In press)

15. Drobin D, Hahn RG: Volume kinetics of Ringer's solution in hypovolemic volunteers. ANESTHESIOLOGY 1999; 90:81–91

16. Dobbins DE, Buehn MJ, Dabney JM: Constriction of canine prenodal lymphatic vessels following the intra-arterial injection of vasoactive agents and hemorrhage. Microcirc Endothelium Lymphatics 1986–1987; 3:297–310

17. Ohhashi T, Kawai Y, Azuma T: The response of lymphatic smooth muscles to vasoactive substances. Pflugers Arch 1978; 375:183–8

18. Kattan AH, Parker JC, Noble AR: Beta-adrenoceptor mediated secretion of active and inactive renin in conscious sheep. Clin Exp Pharmacol Physiol 1990; 17:427–37

19. Zahajszky T, Fejes-Toth G, Filep J: Effect of isoproterenol on renal function. Acta Physiol Hung 1982; 59:197–202

20. Hahn RG: Increased haemodilution in hypotension induced by epidural anaesthesia. Acta Anaesthesiol Scand 1993; 37:357–60

21. Closas J, Genest J, Larochelle P, Cusson J, Gutkowska J, Hamet P, De Lean A, Thibault G, Cantin M: Effects of phenylephrine on atrial natriuretic factor and the renin-aldosterone axis in normal patients and essential hypertensive patients. Arch Mal Coeur Vaiss 1988; 81:75–8

22. Adamson RH, Liu B, Fry GN, Rubin LL, Curry FE: Microvascular permeability and number of tight junctions are modulated by cAMP. Am J Physiol 1998; 274:H1885–94

23. Baluk P, McDonald DM: The beta 2-adrenergic receptor agonist formoterol reduces microvascular leakage by inhibiting endothelial gap formation. Am J Physiol 1994; 266:L461–8

24. Fortney SM: Development of lower body negative pressure as a countermeasure for orthostatic intolerance. J Clin Pharmacol 1991; 31:888–92