The Cardiopulmonary and Renal Hemodynamic Effects of Norepinephrine in Canine Pulmonary Embolism*

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Autologous blood clot was injected into six dogs to produce a graded decrease in cardiac output (CO). The effects of an infusion of norepinephrine, titrated to specific end points, were recorded before embolization and at two levels of pulmonary hypertension. Simultaneous measurements of systemic and renal hemodynamics were made. Sequential blood clot injection increased (p<.01) pulmonary vascular resistance (PVR) from 1.3 to 13 to 33 mm Hg.L-1.min and reduced CO 45 percent and 75 percent (p<.01). Norepinephrine increased both stroke volume and CO (p<.01) in each condition and did not increase PVR. Since the biventricular filling pressures remained constant or fell slightly with norepinephrine, the increase in CO is best explained by an improvement in pump performance. There was no deterioration in renal blood flow or creatinine clearance with norepinephrine. The data suggested that in this model of right ventricular dysfunction, norepinephrine consistently improved myocardial performance without provoking further vasoconstriction in either the pulmonary or renal circulations. (Chest 1989; 95:1333-37)

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There are several clinical conditions in which a decrease in cardiac output (CO) accompanies an acute increase in pulmonary vascular resistance (PVR). Certain patients with adult respiratory distress syndrome (ARDS), for example, develop right ventricular (RV) dysfunction secondary to an increase in RV afterload.1 Pulmonary emboli may also result in hypotension and shock secondary to increased PVR and RV failure.2 In both conditions, the increase in PVR decreases CO and increases RV wall stress and O2 consumption.3,4 In this setting, if mean blood pressure (BP) is critically reduced because of a low CO, RV blood flow and thus myocardial O2 delivery may be compromised. Under experimental conditions, such changes have resulted in RV ischemia and a further deterioration in performance.5 A recent canine study compared volume expansion, isoproterenol, and norepinephrine (NE) in treatment of shock due to acute pulmonary emboli.6 Only NE was successful in restoring hemodynamic stability. While NE was effective in this study, the shock was rapidly induced and the blood pressure was low (71 mm Hg) and falling at the point of treatment. The improvement in hemodynamic status with NE is explained by a direct inotropic effect and/or by improved RV function secondary to increased BP and increased RV perfusion. Therefore, it is conceivable that depending on the level of PVR, its rate of increase, and the resting BP, the acute cardiopulmonary effects of NE could vary. Since NE may increase systemic vascular tone, its use could result in an increase in renal vascular resistance and a deterioration in renal function. Alternatively, despite direct pressor effects, if CO and stroke volume increased with NE, renal function may improve. Previous studies have not, to our knowledge, investigated effects of increased PVR and NE therapy on renal performance. Accordingly, the current study was designed to investigate the cardiopulmonary and renal hemodynamic effects of NE as PVR progressively increased after the injection of autologous blood clot.

Materials and Methods
Six adult mongrel dogs (21 to 31 kg) were anesthetized with pentobarbital (30 mg/kg) and ventilated (Vt 15 ml/kg, FIO2 1.0) in the supine position. Cutdowns were performed over jugular and femoral sites. A 7 F Swan-Ganz catheter was introduced via the left external jugular vein and guided into the pulmonary artery wedge position under continuous pressure monitoring. Similarly, fluid-filled Swan-Ganz catheters were positioned in the right atrium and right ventricle. Through the right femoral artery, an 8 F pigtail catheter was advanced into the left ventricle (LV). A large-bore,

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CO = cardiac output; PVR = pulmonary vascular resistance; NE = norepinephrine; PAP = pulmonary artery pressure; PCWP = pulmonary artery wedge pressure; RVP = right ventricular pressure; LVDP = left ventricular end-diastolic pressure; RBF = renal blood flow.
low-compliance catheter was inserted into the left femoral artery and positioned in the aorta for blood sampling and BP recording. The left femoral vein was used to insert a 12 F cannula for IV fluids and for the injection of clot.

Blood was withdrawn, 150 to 200 ml, put into a glass container, and mixed with thrombin 3,000 to 5,000 units. The formed clot was allowed to stabilize for 30 to 45 min and then dissection into approximately 1 ml fragments. These were suspended in normal saline solution and drawn into a large syringe for injection.

The animal was then placed in the left decubitus position and the right flank incised. Through a retroperitoneal approach, the right ureter was identified and cannulated. The right renal artery was exposed, gently teased of its adventitia and fitted with a Carolina Instruments flow probe. The probe had previously been calibrated using an excised renal artery and an infusion pump. The output from the flow probe was recorded continuously on a two-channel recorder. All pressure lines were connected to Statham transducers, which were leveled at mid-chest. The transducer outputs were recorded on a 12-channel Electronics for Medicine (E for M) oscillograph.

Cardiac outputs were obtained by the thermodilution technique and reported as the mean of four consecutive values. Five-milliliter aliquots of room temperature saline solution were injected through the right atrial catheter, recorded by the pulmonary artery catheter thermistor tip, and analyzed by computer (Columbus Instruments). Hemodynamic measurements, which included CO, BP, pulmonary artery pressure (PAP), PA wedge pressure (PCWP), right ventricular pressure (RVP), left ventricular end-diastolic pressure (LVEDP), and heart rate (HR) were recorded at functional residual capacity during a 5- to 8 min period. Samples of arterial blood were collected for immediate analysis of PCO2, Pco2, and pH. Urine collections were performed over repeated 5-min periods, during which blood was obtained for serum creatinine determination.

Blood gases and pH were measured with a model 165/2 blood gas analyzer (Corning) immediately after collection. The oxygen electrode was calibrated with blood exposed to oxygen tensions from 20 to 700 mm Hg on a tonometer, and measured values were corrected using the tonometer factor. Stroke volume (SV) was calculated according to the formula SV = CO/HR, pulmonary vascular resistance (PVR, mm Hg L.min-1) = (PAP – LVEDP)/CO, and systemic vascular resistance (SVR, mm Hg L.min-1) was calculated as (BP – RVP)/CO. The urine collections were analyzed for volume per minute and creatinine concentrations. Creatinine clearance was calculated from simultaneous urine/serum determinations using the formula: creatinine clearance = (urate creatinine × urine volume/min)/plasma (creatinine). Renal vascular resistance was calculated using the formula RBF/BP.

After phlebotomy, Gentran 75 (6 percent) was infused to raise the LVEDP to 8 mm Hg ± 2. Thereafter, normal saline solution was infused at a rate of approximately 50 ml/hr. Ventilator settings were altered as required throughout the experiment to maintain a PaCO2 of 30 to 35 mm Hg. Sodium bicarbonate in 10 mEq boluses was administered as required to maintain pH 7.30 to 7.40. Additional pentobarbital (1 to 2 mg/kg) was infused over approximately 2-min periods as required to maintain apnea. There was a transient decrease in BP with the anesthetic which recovered after approximately 1 min. All measurements were performed at least 8 min after any IV medication or ventilator change. When hemodynamic (CO, BF, HR, PCWP) stability had been present for 15 minutes, baseline measurements were performed (BL1, condition 1). NE was then infused in a concentration of 100 μg/ml at a rate of 5 ml/hr and titrated upward until an increase of 30 percent was noted in the BP. The restriction of BP elevation was arbitrary but within frequently applied clinical guidelines. Once this goal was achieved, the animals were allowed to stabilize for a further 10 to 15 min before measurements were repeated (NE1). To control for time, measurements were repeated approximately 15 min after NE had been discontinued and after steady-state conditions had been present for at least 5 min (BL5). Autologous clot was then injected until CO was reduced 45 percent (BL3, condition 2), and then 75 percent (BL5, condition 3) in a stepwise fashion. The goal of 45 percent was chosen to achieve moderate RV and PA hypertension. The 75 percent reduction has been determined, in pilot experiments, to be the maximum stable reduction possible in this preparation. To reach the above end points (45 percent and 75 percent decrease in CO), clot was injected over approximately 90-min intervals. Measurements were performed before (BL3 and BL5), during (NE2 and NE3), and after (BL4 and BL6) NE infusion. In each condition, NE was infused at a rate titrated either to match the BP elevation in condition 1 or to double the value at baseline (BL3 and BL5). Heparin (100 μg/kg) was administered after the initial injection of clot to inhibit further clot formation. At the end of the protocol, the animal was killed with KCl.

To confirm preparation stability and to assess effects of time, control measurements before and after NE were compared using Student's paired t test. If significant differences were not detected, values obtained during NE infusion were compared with preceding control measurements.

**RESULTS**

The infusion rate of NE employed in this study varied from 800 to 1,300 μg/h at control (condition 1) to 800 to 2,200 μg/h in conditions 2 and 3. Approx-
mately 33 ml of fragmented clot was required to reduce CO 40 percent. An additional 15 to 30 ml of clot was required to achieve the final reduction of 75 percent. Arterial O₂ saturation remained 100 percent throughout all experiments. Hematocrit did not vary significantly. The cardiopulmonary effects of both emboli and NE are illustrated in Table 1.

Prior to the blood clot injection, NE increased BP (p<.01), PAP (p<.025), RVEDP (p<.0025), and SVR (p<.05). While the mean CO increased from 4.0 to 4.6 L·min⁻¹, the change did not achieve statistical significance. Because HR decreased, the 30 percent increase in SV was significant (p<.01). No other hemodynamic parameters changed. A comparison of all parameters by paired t test before (BL1) and after (BL2) NE revealed no differences.

The injection of blood clot in condition 2 decreased CO and SV 45 percent and 50 percent, respectively (p<.025), despite an increase in RVEDP (p<.025). BP remained unchanged as SVR rose 80 percent (p<.01). Both PAP and PVR increased dramatically (p<.025). With the administration of NE, BP increased 33 percent (p<.01) was CO and SV rose 15 percent and 40 percent, respectively (p<.01). This increase in flow occurred at constant biventricular filling pressures. Neither PAP nor PVR increased. Comparison of baselines before and after NE infusion revealed no differences, confirming the stability of the preparation over the time interval required.

In condition 3, the additional injection of clot further reduced CO 75 percent from initial control, from 4.0 to 1.1 L·min⁻¹ (p<.01). Both PAP and PVR rose significantly when compared with condition 2 (p<.01). BP fell from a mean of 120 to 73 mm Hg (p<.01) and RVEDP doubled from 5 mm Hg to 10 mm Hg (p<.025).

Ventricular function improved with NE. Despite constant biventricular filling pressure, CO and SV increased 64 percent (p<.05) and 100 percent (p<.01), respectively. BP rose 80 percent with NE (p<.01), and SVR did not significantly change. While PVR decreased with NE when compared with BL5, a significant shift in baseline values (BL5 – BL6) prevented an assessment of direct drug effect. PAP also decreased over time (BL5 to BL6). All other variables were similar, and there were no differences by paired t test.

The mean renovascular effects of blood clot and NE are shown in Table 2. In condition 1, NE increased RVR (p<.05) but did not significantly alter RBF or creatinine clearance. In condition 2, blood clot produced a small increase in RVR and a nonsignificant decrease in RBF. Creatinine clearance remained unchanged. Once again, the infusion of NE increased RVR (p<.05) but did not affect RBF or creatinine clearance.

In condition 3, blood clot led to a major increase in RVR (p<.01) and a decrease in both RBF (p<.01) and creatinine clearance (p<.01). NE increased mean values for RBF, and creatinine clearance, though these changes were not significant owing to wide interanimal variability.

Comparison of baseline values before and after NE in each of the three conditions revealed no significant differences with time.

**Discussion**

This study examined the acute cardiac, pulmonary, and renal effects of NE in a canine model of pulmonary embolism as PVR was progressively increased. NE consistently increased SV both before and after pulmonary hypertension had been established. While the change in CO and SV were somewhat greater as PVR increased, the increase in SV was similar in conditions 1 (C1) and 2 (C2), 30 percent and 40 percent, respectively. There was a small increase in RVEDP in C1 with NE; otherwise, ventricular filling pressures did not significantly change with treatment. While RVEDP increased with embolism, LVEDP did not. In all conditions, pulmonary vascular resistance did not increase with NE. Although RVR rose significantly with each infusion of NE, neither RBF nor creatinine clearance was affected.

These results may support a role for NE when a marked decrease in CO complicates an acute increase in RV afterload. However, since these results were obtained in an anesthetized canine preparation with autologous clot emboli, we emphasize caution in direct clinical extrapolation.

Circulatory instability in the clinical setting of massive or submassive pulmonary embolism is associated with a major increase in mortality, from 6 percent to 30 percent in recent combined trials.⁷ ⁸ The current recommendations for treatment of this low output state vary considerably in the literature⁹ ¹² and,

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<td><strong>Condition</strong></td>
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* = p<.05 compared to preceding baseline.
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for the most part, lack experimental verification. Only a few studies specifically examined RV performance in experimental pulmonary hypertension. Vlahakes et al produced RV hypertension and eventually ischemia by progressively constricting the pulmonary artery. The onset of ischemia and of an acute deterioration in RV function coincided with a critical decrease in BP and the RV perfusing pressure, i.e., BP - RV. The importance of maintaining an adequate gradient for flow was demonstrated when raising the systemic BP from 48 mm Hg to 108 mm Hg with phenylephrine brought about a reversal of the biochemical indices of RV ischemia and greatly improved RV performance. Similarly, Scharf et al recently demonstrated that an increase in RV perfusion pressure due to aortic compression increased RV load tolerance.

A recent study by Molloy et al investigated treatment of shock in a canine model of pulmonary embolism. They demonstrated that in contrast to treatment with isoproterenol and volume, NE reversed the shock state and dramatically improved RV function. The improvement in ventricular function was explained by a direct increase in contractility and/or by increased contractility secondary to improved BP and increased RV myocardial perfusion.

The studies of Molloy et al and Vlahakes et al investigated effects of therapy in a model of frank circulatory instability. In the current study NE consistently improved ventricular function over a wide range of blood pressure and RV afterloads. Accordingly, current results confirm and extend previous studies and emphasize that at least in this model of increased PVB, beneficial hemodynamic effects of NE are not limited to a hemodynamic subset characterized by frank shock. The greater improvement in RV function with NE in condition 3 may be explained by the higher RV afterload and greater depression in CO and BP prior to treatment. While direct measures of RV ischemia were not obtained, we believe that a direct increase in RV contractility is the predominant explanation for the improvement in RV function. In support of this possibility, in both humans and animals, NE has been shown to cause a direct increase in ventricular contractile force. In addition, via direct peripheral effects, NE may have redistributed the blood centrally and thus increased CO via a Starling effect. In support of this possibility, note that in condition 1, RVEDP increased when CO increased with NE.

A notable finding in this study was the absence of a detectable increase in PVR with NE after pulmonary embolism. Similar results are reported in other canine studies of pulmonary hypertension. Similarly, Fowler et al and Goldring et al showed that in normal humans the rise in PAP seen with NE is related solely to increased flow and left atrial pressure. A recent canine study investigated effects of NE on pulmonary vascular pressure-flow (P-Q) characteristics in embolic pulmonary hypertension. This study confirmed that NE did not adversely affect pulmonary vascular tone; i.e., NE did not affect slope or extrapolated pressure intercept of the P-Q relationship. This lack of independent pulmonary vasoconstriction at therapeutic doses of NE represents a potential advantage in the setting of RV failure.

The use of any drug with significant vasoconstrictor properties warrants concern over detrimental effects on the renal circulation. We believe this study is the first to examine indices of renal function in the setting of acute pulmonary embolism and during treatment with NE. It is important to note, however, that the experimental design precluded specific goals or therapeutic end points within the renal circulation, accounting for a wide interanimal variability. As such, any favorable effects of NE would tend to be minimized. Nonetheless, the responses to NE during control conditions and after the first dose of clot (condition 2), when neither BP nor RBF was significantly reduced, was characterized by parallel increases in RVR and BP without a reduction in RBF. As these changes in RVR can be predicted on the basis of autoregulation alone, it is possible that NE had no direct effect on the renal vasculature. In condition 3, when CO and BP were reduced sufficiently to cause a net decrease in RBF, NE tended to improved perfusion (though the change did not achieve statistical significance). Urine output was restored in two of the three animals that had become anuric. As the changes in creatinine clearance paralleled the changes in net RBF, a major intrarenal redistribution of flow was not seen.

This apparent lack of deleterious effects is not unprecedented. The renovascular effects of NE in previous studies have altered with anesthesia, the rate and duration of the infusion, the concurrent changes in CO and BP, and with the model tested. Berne et al and Berger et al recorded decreases in RBF at relatively high doses of NE (2 µg/kg/min). In each case, barbiturate anesthesia potentiated this increase in RVR. Anderson et al on the other hand, reported an increase in RBF and a net fall in RVR at smaller doses (.1 to .4 µg/kg/min) in awake dogs. Each of these studies used normotensive animals and did not include measurements of CO. In a canine model of hemorrhagic shock and renal hypoperfusion Corday et al produced a further decrease in RBF when NE was infused in hypertensive doses. However, when NE restored BP to baseline levels, RBF increased from 6 percent of control to 50 percent. Once more, CO was not measured. In experimental tamponade, Martins et al showed a slight increase in RBF with NE at an unchanged CO. In a recent study of hypotensive patients with septic shock, Desjars et al reported an
improvement in urine flow and BP with NE. The patients had been treated with volume expansion and were receiving dopamine when NE was given. In keeping with the data then, moderate elevation in BP and the characteristic increase in CO at that dosage in our study would favor preservation of RBF with NE in spite of any independent renal vasoconstriction.

In a canine model of pulmonary embolism and decreased CO, NE, titrated to a moderate increase in BP, produced a significant improvement in ventricular performance without an increase in PVR and without compromising either renal flow or function.

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