laboratory and animal investigations

Norepinephrine and Phenylephrine Effects on Right Ventricular Function in Experimental Canine Pulmonary Embolism*

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In a canine model of pulmonary embolism (PE) produced by infusion of autologous blood clots, mean arterial blood pressure (MAP) decreased to 73 ± 4 mm Hg while cardiac output (CO) decreased to less than 50 percent of baseline. Intravenous infusion of phenylephrine (PHEN) and norepinephrine (NE) restored MAP to somewhat above baseline values. However, only NE restored CO to control levels. The right ventricular myocardial blood flow increased 15 percent in the PE group with PHEN and 229 percent with NE at equipressor concentrations. The right ventricular myocardial oxygen consumption (RVMO₂) was not significantly different between PE and PE + PHEN while PE + NE increased RVMO₂ by 144 percent to 20.2 ± 1.8 ml/min/100 g. The RV output was not adequately restored with PE, but when RV contractility was augmented with NE, RV output was restored to baseline. Right ventricular minute work increased 100 percent with NE and was maintained with a 100 percent increase in oxygen consumption. Calculated pulmonary vascular resistance (PVR) was decreased during PE by 36 percent with PE + PHEN while PVR in NE-treated dogs decreased by 59 percent. In NE-treated animals, systemic vascular resistance (SVR) was restored to control levels while in PHEN-treated animals SVR increased about 75 percent from baseline. We conclude that the salutary effects of NE on RV output are due to both α and β receptor stimulation, which increased contractility, RVMBF, and RVMO₂, and decreased both PVR and SVR. In the PHEN-treated dogs, our indices of minute work, RVMBF, and RVMO₂ suggest that coronary auto-regulation was intact; however, there was no apparent benefit to RV output. This study suggests that in the clinical setting of acute PE, the judicious use of NE, rather than PHEN, may be more beneficial in restoring RV function and systemic hemodynamics. (Chest 1991; 100:796-801)

MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; NE = norepinephrine; PHEN = phenylephrine; PVR = pulmonary vascular resistance; RVEDP = right ventricular end-diastolic pressure; RVMBF = right ventricular myocardial blood flow; RVMO₂ = right ventricular myocardial oxygen consumption; RVMO₂ = right ventricular myocardial vascular resistance; RVP = right ventricular peak pressure; SVR = systemic vascular resistance

Low cardiac output (CO) complicating acute pulmonary embolism is due to increased right ventricular (RV) afterload and the consequent reduction in RV pump performance. In acute pulmonary embolism (PE), a reduction in effective cross-sectional area of the pulmonary vascular bed results in increased RV pressure, wall stress, and oxygen consumption.1,2 Recommended therapeutic strategies to improve cardiac and circulatory function in acute PE include volume augmentation, adrenergic mediators, and fibrinolytic therapy.3-6

Previous studies suggest that augmentation of RV myocardial perfusion by pharmacologic means may improve RV performance under conditions of pressure-load induced RV failure. Improved CO has been demonstrated using norepinephrine (NE) and phenylephrine (PHEN) in several types of experimental models of acute PE.3,6,7 However, these studies have not differentiated the relative contribution of a pure vasopressor versus a combination of vasopressor and inotrope on the improved RV output. Since both PHEN and NE are vasopressors (α agonists), the improved RV performance in acute PE may be due only to increased perfusion pressure and flow to the coronary bed. However, NE has inotropic (β₂) as well as vasoconstrictor (α) activity.3 Thus, NE has the potential to increase coronary blood flow by increasing cardiac contractility, as well as by raising perfusion pressure. The increased contractile performance with NE however, may not be appropriate in the clinical

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Experimental Canine Pulmonary Embolism (Hirsch et al)
setting due to the added stress to the right ventricle.

The present study was designed to separate the relative contributions of NE and PHEN to the improved systemic hemodynamics, as well as the hemodynamics and oxygen consumption of the RV free wall in an acute canine model of PE.

METHODS

The experimental protocol was approved by the Institutional Animal Care and Use Committee. Twelve male mongrel dogs (19 to 27 kg) were anesthetized with pentobarbital (30 mg/kg), intubated, and mechanically ventilated (tidal volume, 15 to 20 ml/kg) with 100 percent O2. Anesthesia was maintained with intermittent intravenous boluses of pentobarbital (50 to 100 mg) as required. One femoral artery was cannulated for blood pressure monitoring and blood gas and electrolyte sampling. The other femoral artery was cannulated with two small polyethylene catheters for isotope sampling. A large-bore catheter (inner diameter, 3 mm) was inserted into a femoral vein and advanced into the inferior vena cava to the level of the xiphoid process for autologous blood clot infusion. The other femoral vein was cannulated for fluid and drug administration.

A left thoracotomy was performed. After pericardiotomy, a catheter was guided under direct vision into an anterior cardiac vein of the right ventricle. The catheter was used to sample RV coronary venous blood. It has been shown by Gregg et al.11,12 and others13,14 that as much as 85 percent of RV coronary flow is drained by the anterior cardiac veins. Thus, measurement of the difference between the anterior cardiac vein and systemic arterial oxygen contents should give a reasonable estimate of RV oxygen consumption.

A thermistor-tipped Swan-Ganz catheter was placed in the pulmonary artery for CO determination and a Millar microtip microsphere pressure catheter was placed in the right ventricle for pressure recording. A catheter was inserted into the left atrium for pressure monitoring and injection of radioactive microspheres. A Millar microtip pressured transducer was placed in the left ventricle via left atrium for left ventricular (LV) pressure monitoring.

Two hundred milliliters of blood was removed into a beaker and mixed with 2,000 units of thrombin for production of the clot. To maintain isotovolemia, an equal amount of 5 percent dextran was infused into the dogs. The blood was allowed to cure for about 60 minutes until a large, firm clot was formed; it was then cut into 1-cm cubes and suspended in normal saline.

The protocol consisted of three parts, as follows: (1) control; (2) autologous blood clot injection to bring the mean arterial pressure (MAP) 30 to 40 percent below control; and (3) resuscitation with NE or PHEN infusion to bring the MAP back to near control levels. We found, in the course of the experiments, that if the pressure fell below 55 mm Hg during the infusion of the clots, resuscitation procedures were generally not successful. For this reason, we attempted to maintain aortic pressure between 65 and 75 mm Hg. At this level, the preparation remained relatively stable for at least one hour before showing signs of deterioration.

The infusion of NE or PHEN was randomly assigned after all control measurements were made. For each part of the protocol, hemodynamic factors (heart rate, blood pressure, CO, RV pressure, LV pressure, pulmonary artery pressure [PAP], and left atrial pressure) were measured. Arterial and coronary venous blood samples were obtained simultaneously for arterial-venous O2 difference determination. Radioactive microspheres were injected into the left atrium and reference samples were obtained for myocardial blood flow (MBF) measurement. Measurements were made when all measurements were stable for at least 3 to 5 min. In addition, periodic arterial blood gas values were obtained and ventilation adjustment and/or bicarbonate was administered to maintain normal pH. Dextran (5 percent) was infused as needed to maintain isotovolemia. After the experiments, the animals were killed with an overdose of pentobarbital.

The LV pressure was measured using a microtipped pressure catheter. All other vascular pressures were measured with Statham pressure transducers and recorded on a Gould multichannel recorder. Arterial blood gases and electrolytes were measured with an analyzer (Stat Profile).

Myocardial blood flow was measured with gamma-emitting radionuclides.13 Carbon microspheres (15 ± 3 μm) labelled with 14C, 35S, 85Sr, and 153Sn were injected into the left atrium. At the end of the experiment, the heart was excised and frozen to facilitate transmural sampling. Full-thickness myocardial samples were obtained from the LV free wall, interventricular septum, and the entire right ventricle. The LV and septal samples were cut into thirds and the RV samples into halves transmurally to yield regional sections weighing at least 1.0 g each. The tissue and reference blood samples were weighed and analyzed for radioactivity with a scintillation counter. Isotope separation was accomplished by standard techniques of gamma spectroscopy. Values for regional MBF were then calculated. Values for regional MBF were averaged to yield a value for mean transmural MBF. The myocardial oxygen consumption (MVO2) was calculated from the RV transmural blood flow and arterial-coronary venous O2 difference using the Fick equation.

Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and RV myocardial vascular resistance (MVR) were calculated using standard formulae. All results are reported as

| Table 1—Hemodynamic Effects of NE and PHEN on PE |
| --- | --- | --- | --- |
|  | Control (n = 12) | PE (n = 12) | PE + PHEN (n = 6) | PE + NE (n = 6) |
| CO, L/min | 2.41 ± 0.34 | 1.00 ± 0.08* | 1.45 ± 0.15* | 2.72 ± 0.40† |
| MAP, mm Hg | 113 ± 6 | 73 ± 4* | 131 ± 3* | 140 ± 5† |
| RVPP, mm Hg | 21 ± 1 | 46 ± 5* | 45 ± 1* | 51.6 ± 6.1* |
| RVEDP, mm Hg | 1 ± 0.3 | 7 ± 0.8* | 6 ± 0.4* | 5 ± 1* |
| RV minute work, mm Hg-g/min | 38.0 ± 3.8 | 40.6 ± 3.3 | 53.8 ± 4.6‡ | 118.3 ± 21.9| |
| MPAP, mm Hg | 16 ± 1 | 41 ± 4* | 38 ± 4* | 43 ± 3* |
| SVR, mm Hg-min/L | 49.2 ± 3.7 | 67.4 ± 6.5‡ | 84.8 ± 4.9‡ | 57.4 ± 8.4‡ |
| PVR, mm Hg-min/L | 9.4 ± 2.8 | 39.0 ± 6.1* | 25.3 ± 4.1* | 16.3 ± 3.3* |
| RVMBF, ml/min/100 g | 58 ± 7 | 79 ± 8§ | 91 ± 13§ | 260 ± 48†† |
| RVMO2, ml/min/100 g | 5.35 ± 0.87 | 8.25 ± 1.14‡ | 9.24 ± 0.94‡ | 20.2 ± 1.80‡† |
| RVMMR, mm Hg-mm/ml | 2.05 ± 0.16 | 0.87 ± 0.09* | 1.49 ± 0.21‡ | 0.59 ± 0.11‡‡ |

*p<0.01 vs control; †p<0.001 vs PE, p<0.001 vs PE + PHEN; ‡p<0.001 vs PE; †p<0.05 vs control; §p<0.001 vs control, p<0.01 vs PE + PHEN; p<0.01 vs PE + PHEN, p<0.01 vs PE; †p<0.05 vs PE + PHEN; **p<0.01 vs PE; p<0.05 vs control, p<0.05 vs PE + PHEN; †‡p<0.001 vs PE, p<0.001 vs control, p<0.001 vs PE + PHEN; ††p<0.001 vs control, p<0.01 vs PE + PHEN.
The results of the study are as follows:

**Results**

The effects of NE and PHEN on the hemodynamics of PE are summarized in Table 1. All dogs had normal cardiopulmonary function with normal pressures and oxygenation prior to the experiment. Each dog served as its own control; there were no statistical differences between NE control and PHEN control or in the PE data between the two groups. Therefore, all control and initial PE data were combined.

**Effects of PE on Hemodynamics**

Infusion of the autologous clot produced a consistent increase in RV peak pressure and mean pulmonary artery pressure (Table 1). Initially, MAP was well maintained, even though CO began to decrease. As CO decreased, SVR increased from 49.2 ± 3.7 to 67.4 ± 6.5 mm Hg-min/L (p<0.05) (Table 1). As the arterial pressure began to decrease, RV end-diastolic pressure (RVEDP) increased from 1 ± 0.3 to 7 ± 0.8 mm Hg (p<0.01) (Table 1). Mean arterial pressure fell by 37 percent to 73 ± 4 mm Hg (Fig 1, Table 1), and CO decreased from 2.53 ± 0.38 to 1.00 ± 0.08 L/min (p<0.01) (Fig 2). Right ventricular peak pressure, mean PAP (MPAP), and PVR were increased more than 100 percent of baseline (Table 1).

Although RV minute work during PE was unchanged from control, RVMBF and RVMVO2 were significantly increased (40 and 35 percent, respec-
generally; Figs 3 and 4), probably due to increases in wall stress. Calculated RVMVR decreased from 2.05 ± 0.16 at baseline to 0.87 ± 0.09 mm Hg-min/ml during PE (p<0.01).

**Effects of NE and PHEN on PE**

Infusion of NE or PHEN restored MAP to somewhat greater than baseline (Table 1, Fig 1). Phenylephrine produced a modest but not significant increase in CO from PE. The NE, however, restored CO to control levels (Table 1, Fig 2).

In both treatment groups, RVEDP was reduced modestly from PE values, although remaining significantly above control (Table 1). The RV peak pressure (RVPP) did not change appreciably in either case from PE. The SVR in the PHEN-treated dogs continued to increase from 67.4 ± 6.5 to 84.8 ± 4.8, whereas SVR in the NE-treated animals was actually reduced to near control levels (57.4 ± 8.4), which was significant (p<0.01) when compared to the PHEN dogs. The PVR also was significantly reduced from both the PE and PHEN groups.

The effects of PHEN and NE on RV free wall blood flow and MVo2 are seen in Table 1 and illustrated in Figures 3 and 4. There appears to be a small stepwise increase in MBF and MVo2 during PE and PE + PHEN, which are significantly different from control but not from each other. However, NE increased MBF four times control and almost 3.5 times that of PE and PE + PHEN. The NE increased MVo2 values four times control and about 2.5 times from PE and PE + PHEN values. In the NE dogs, the increase
of RVMO\textsubscript{2}, from PE and PE + PHEN values is directly proportional to the increase in the RV minute work (Table 1). The right ventricle with incipient failure from PE was capable of increasing its minute work (Table 1) more than 100 percent of baseline during NE treatment.

**Discussion**

The production of a canine model of PE from the infusion of autologous blood clots resulted in a model of pulmonary hypertension. In this model, PAP, RVPP, and RVEDP were increased more than 100 percent of baseline, while CO and MAP decreased to almost 50 percent of baseline, suggesting incipient RV failure (Table 1). The PHEN infusion restored the aortic pressure to somewhat above control values (Fig 1); however, other parameters were not significantly changed from PE values with the exception of SVR, which increased 74 percent from baseline and 25 percent from PE. On the other hand, NE, in addition to restoring blood pressure, produced significant improvements in CO, MBF, and MVO\textsubscript{2}.

The RVEDP generally decreased with NE (Table 1), but this change was not within the criteria for significance. Pulmonary vascular resistance decreased from a high of 39.0 ± 6.1 mm Hg-min/L in the PE group to 25.3 ± 4.1 in the PE + PHEN group and decreased further to 16.3 ± 3.3 in the PE + NE group. The NE effect of pulmonary artery resistance reflects the increase in CO with little change in overall pulmonary artery pressure and may signal either reduction in pulmonary vasoconstriction or opening of previously closed channels. In a canine model of pulmonary hypertension, Ducas et al\textsuperscript{16} compared pressure-flow relationships following infusion of NE and a pure \( \beta \)-agonist (isoproterenol). In their model, both NE and isoproterenol increased CO and decreased PVR. They suggested that the effective pulmonary closing pressure may exceed LV filling pressure, thereby maintaining an elevated PVR. They observed that NE increased CO but did not affect pulmonary closing pressure, i.e., closing pressure remained elevated, while pulmonary artery hemodynamics were unchanged. Consequently, PVR was reduced but PAP remained elevated. Our study showed similar results.

Ducas et al\textsuperscript{16} in another study, compared the acute hemodynamic effects of NE and methoxamine in a canine model of glass bead embolism in an attempt to separate inotropic from vasopressor effects on RV function. They found, as did we, that NE significantly increased CO, systemic pressure, and calculated right coronary perfusion pressure. Methoxamine infusion produced a similar increase in systemic arterial pressure and calculated perfusion pressure, but as in our study with PHEN, little change in CO. They concluded, using measurements of perfusion pressure, that NE improved RV pump performance primarily via a direct inotropic effect. In contrast, Vlahakes et al\textsuperscript{1}, in a study of acute RV hypertension produced by banding of the pulmonary artery, demonstrated improvement in RV hemodynamics following infusion of PHEN. They attributed the improvement in hemodynamics following PHEN, including an increased CO, to the improved systemic and coronary perfusion pressure reversing RV ischemia. Neither of the above studies compared the effect of NE and PHEN on RVMBF.

Rich et al\textsuperscript{17} have recently shown in patients with chronic pulmonary hypertension that PHEN worsened RV function, although coronary driving pressure was elevated. Murray and Vatner\textsuperscript{18} report that when the autonomic nervous system is blocked with hexamethonium, an \( \alpha \)-adrenergic blocking agent, RVMBF increases during a controlled elevation of aortic pressure. Indeed, it has been shown that alpha stimulation results in vasoconstriction of coronary vessels,\textsuperscript{19} which seems to be the case in the present experiments with PHEN use as seen from the increase in RVMVR (Table 1). Thus, restoration of driving pressure alone will not completely reflect the state of RV myocardial perfusion.

In our studies, RVMBF and RVMO\textsubscript{2} responded to NE to a much greater extent than to PHEN. This suggests that an inotropic effect produces a greater response than peripheral vasoconstriction to restore not only the hemodynamics, as evidenced by near normal systemic pressure and CO, but also to meet the increased oxygen requirements of the right ventricle. It would appear from our studies and those of Ducas et al\textsuperscript{16} that NE improved RV pump performance through its combination of \( \alpha \) and \( \beta \) properties. The inotropic property of NE directly stimulates myocardial oxygen consumption, and as a result of coronary dilation, increases coronary flow; the vasoconstrictor component increased systemic pressure (perfusion pressure), which may have had an additive effect on flow and oxygen consumption (Table 1, Figs 3 and 4). Right ventricular myocardial flow and MVO\textsubscript{2} may be at their maximum since flow and oxygen consumption of the RV are about four times greater than control and 2.5 times those values during PE and PE + PHEN.

In summary, we have demonstrated that in the experimental setting of clot-induced PE, NE improves RV function by reducing PVR and augmenting contractility, which improves RV output and restores systemic vascular resistance and pressure. In the PHEN-treated dogs, our indices of minute-work, blood flow, and oxygen consumption suggest that coronary autoregulation was intact; however, there was no apparent benefit to RV output.

The data suggest that the increased energy demands
(minute work) of the myocardium, with the use of NE, were met by increased RV coronary blood flow and oxygen consumption. The amount of work performed by the right ventricle under these conditions may be in excess of need, and therefore, lower effective doses of NE may be warranted.

This study, therefore, may be applicable to the clinical setting of acute PE complicated by hypotension, low CO, and RV dysfunction. The RV performance may be restored by the judicious use of NE. The elevation of right coronary perfusion pressure, flow, and MVO₂, as well as improved contractility and reduced pulmonary resistance, makes NE a seemingly appropriate therapy in the supportive management of acute PE. Human studies will be necessary to determine if this is indeed the case.

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REFERENCES
2 Calvin JE, Quinn B. Right ventricular pressure overload during acute lung injury: cardiac mechanics and the pathophysiology of right ventricular systolic dysfunction. J Crit Care 1990; 4:251-65
4 Ghignone MM, Girling L, Prewitt RM. Volume expansion versus norepinephrine in treatment of a low cardiac output complicating an acute increase in right ventricular afterload in dogs. Anesthesiology 1984; 60:132-35
5 Molloy DW, Lee KY, Jones D, Penner B, Prewitt RM. Effects of noradrenaline and isoproterenol on cardiopulmonary function in a canine model of acute pulmonary hypertension. Chest 1985; 88:432-35
7 Angle MR, Molloy DW, Penner B, Jones D, Prewitt MR. The cardiopulmonary and renal hemodynamic effects of norepinephrine in canine pulmonary embolism. Chest 1989; 95:1333-37
9 Gregg DE, Shipley RE, Bidder TG. The anterior cardiac veins: their functional importance in the venous drainage of the right heart. Am J Physiol 1943; 139:732-41
10 Gregg DR, Shipley RE. Studies of the venous drainage of the heart. Am J Physiol 1947; 143:13-25
12 Scheel KW, Williams SE, Parker JB. Coronary sinus pressure has a direct effect on gradient for coronary perfusion. Am J Physiol 1990; 258:H139-44