Effects of Noradrenaline and Isoproterenol on Cardiopulmonary Function in a Canine Model of Acute Pulmonary Hypertension*

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The authors investigated acute cardiopulmonary effects of noradrenaline and isoproterenol infusion in a canine model of increased pulmonary vascular resistance (PVR) and decreased cardiac output (CO). In six anesthetized, ventilated dogs, autologous blood clots were injected over approximately two hours to increase right ventricular (RV) afterload and decrease CO. After CO had decreased 40 percent dogs were treated with noradrenaline or isoproterenol in alternate sequence. Both drugs increased stroke volume but only isoproterenol affected CO. Flow increased from 1.3 to 3.0 L/min \( (p < .01) \) with isoproterenol infusion. Corresponding to the increase in CO, RV filling pressure and PVR decreased, from 9 to 5 mm Hg, and from 36 to 16 mm HgL \( ^{-1} \)min \( (p < .01) \) respectively. When a moderate decrease in CO complicates an acute increase in PVR, isoproterenol may be an excellent drug to treat the decrease in flow.

Some patients with acute respiratory failure develop a marked increase in right ventricular (RV) afterload.\(^{1,2}\) The increase in afterload is due to a decrease in effective cross-sectional area of the pulmonary vascular bed explained by active vasoconstriction, interstitial edema, microembolization and vascular obliteration.\(^{1,4}\) The increase in RV afterload increases RV stroke work, reduces cardiac output (CO) and may limit survival in certain critically ill patients.\(^{1,4}\) In another example, pulmonary emboli increase RV afterload and may markedly depress RV performance and CO.\(^{5,7}\)

However, few studies have systematically investigated effects of treatment on ventricular performance when CO is significantly reduced due to acute and/or subacute increase in RV afterload.

Several investigators have recommended isoproterenol for treatment of a low CO complicating an acute increase in RV afterload.\(^{8,9}\) On the other hand, a recent canine study demonstrated that isoproterenol was ineffective in treating shock complicating acute pulmonary emboli.\(^{7}\) In contrast, all dogs given noradrenaline were resuscitated and remained hemodynamically stable during one hour of treatment. In that study, pulmonary vascular resistance (PVR) was increased over approximately 30 min and dogs were treated when mean blood pressure (BP) level had decreased to 70 mm Hg. The study investigated acute effects of treatment in a model of circulatory instability and likely RV hypoperfusion.\(^{11}\) Therefore, we considered the possibility that, in the absence of shock, when resting BP was not so low, isoproterenol might be an excellent drug to treat low CO complicating acute increase in PVR. Accordingly, the current study was designed to compare acute cardiopulmonary effects of therapy with isoproterenol and noradrenaline in hemodynamically stable dogs when CO was reduced secondary to autologous blood clot injection.

**Material and Methods**

Six mongrel dogs (weighing 14 to 22 kg) were anesthetized with pentobarbital (30 mg/kg), intubated, and mechanically ventilated (30 ml/kg) in the supine position with 100 percent \( O_2 \). Anesthesia was maintained by administering fentanyl (2 to 5 mg/kg/hr) and pentobarbital (5 mg/hr). Fluid-filled catheters were placed in the femoral artery and left ventricle (LV) to monitor appropriate pressures. Under pressure monitoring, a thermistor-tipped Swan-Ganz catheter was inserted through an external jugular vein and positioned in a branch of the pulmonary artery. Two other Swan-Ganz catheters were similarly positioned in the RV and one withdrawn into the right atrium for injection of saline solution boluses during CO determinations. Thermal dilution curve was recorded on a separate single channel recorder and analyzed by computer. All catheters were connected to Statham transducers, and outputs were displayed on a 12 channel oscillograph. Transducers were positioned midway between the front and back of the chest. An intravenous catheter for drug and/or volume infusion was placed in an external jugular vein and a 12 FR cannula inserted in a femoral vein for

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Canine Model of Acute Pulmonary Hypertension (Molloy et al)
injection of blood clots.

To induce formation of autologous blood clots, 1000 IU of thrombin was added to 100 to 150 ml of blood which had been withdrawn into a glass beaker. After approximately 30 min, the clot was removed from the beaker and cut into cubes approximately 1 cu mm in size. Clots were placed in a 60 ml, catheter-tipped syringe and suspended in normal saline solution. Initially, normal saline solution was infused, as required, to raise LV end-diastolic pressure (LVEDP) to approximately 5 mm Hg. After ensuring steady state conditions (stable CO, heart rate (HR), RVEDP and pulmonary arterial pressure (PAP) for at least ten min) baseline measurements of CO, HR, PAP, BP, LV pressure and RV pressure were obtained during a five-second apneic period at functional residual capacity.

Following baseline measurements, small volumes (1 to 2 ml) of clotted blood were injected, via the femoral catheter, into the venous circulation. Clots were injected in increments over approximately two hours until CO had fallen approximately 40 percent. Arterial blood gas levels were frequently sampled and pH level maintained above 7.25 by treatment of metabolic acidosis with intravenous sodium bicarbonate (range 10 to 40 mEq). The partial pressure of carbon dioxide was maintained between 30 and 40 mm Hg by adjusting the ventilatory rate.

When CO had been reduced to approximately 60 percent of baseline and hemodynamic parameters were stable on consecutive measurements 10 min apart, heparin (100 IU/kg) was administered intravenously. Pilot experiments indicated that this approach results in a preparation that is hemodynamically stable for at least one hour. After a further 10 min period with dogs in a steady state for approximately 20 min, control measurements were obtained. Subsequently, dogs were treated alternatively with either noradrenaline or isoproterenol. The rate of infusion of either drug was increased until one of the following end points was reached: 1) mean BP increased or decreased approximately 30 percent; 2) HR increased 30 percent; or 3) CO approximately doubled. When one of these end points was reached, dogs were maintained in a steady state for 10 min and measurements repeated.

Subsequently, the drug was discontinued and, approximately 15 min after measured variables had returned to control values, a second set of control measurements was obtained. After taking these measurements, to confirm preparation stability, a third set of control measurements was obtained. Subsequently, the alternate drug was infused to the same end points described above and, after documenting steady state conditions for 10 min, measurements were obtained. The drug was discontinued and final measurements were obtained 15 min after measured variables had returned to control conditions.

Resistance was calculated according to the equations: systemic vascular resistance (SVR) = (BP-RVEDP)/CO (mm Hg L-1.min-1) and PVR = (PAP-LVEDP)/CO (mm Hg L-1.min-1).

To determine effects of initial embolization, data were tested for significance using Student's paired t-test. Subsequently, to determine acute cardiopulmonary effects of the drugs, measured variables obtained in the four control periods were tested for significance using analysis of variance. If there were no significant differences, then effects of each drug were assessed by comparing values obtained during infusion with the mean of values obtained before and after drug infusion (paired t-test).

### Results

The hemodynamic effects of blood clot embolization are shown in Table 1. Blood clot embolization increased mean PAP from 11 to 47 mm Hg (p<.01) and PVR from 3 to 35 mm Hg L-1.min-1 (p<.01). Corresponding to this increase in RV afterload, CO fell 43 percent (p<.01), from 2.3 to 1.3 L.min-1 and mean SV fell 62 percent (p<.01), from 21 to 8 ml. RVEDP increased from 2 to 9 mm Hg (p<.01) and there was a 45 percent increase (p<.025) in SVR, from 49 to 72 mm Hg L-1.min. The fall in LV filling pressure from 5 to 4 mm Hg was not significant, and mean BP level decreased 12 percent (p<.05).

Measurements obtained during the four control periods were compared using analysis of variance and there was no significant difference. This confirmed the stability of the preparation for the duration of the experiments.

Table 2 illustrates the acute cardiopulmonary effects of infusion for both drugs. As indicated, the reported control values reflect the mean of values obtained before and after drug infusion. Compared to control measurements, isoproterenol infusion more than doubled CO, from 1.3 to 3.0 L.min-1 (p<.01). Heart rate only increased 23 percent (p<.01), so stroke volume (SV) almost doubled, from 8 to 15 ml/beat (p<.01). There was a small increase in mean PAP from 44 to 49 mm Hg (p<.05) and a 53 percent decrease in PVR, from 34 to 16 mm Hg L-1.min (p<.01). Associated with this fall in PVR, SVR fell 67 percent, from 70 to 23 mm Hg L-1.min (p<.01), and mean BP level fell 24 percent, from 93 to 71 mm Hg (p<.01). There was a large decrease in RVEDP and a smaller decrease in LVEDP with isoproterenol infusion.

In contrast to the effects of isoproterenol infusion, CO did not increase with noradrenaline infusion. As per experimental design, mean BP level rose 30 percent from 90 to 117 mm Hg (p<.01). Associated with the decrease in HR (p<.01), there was a 50 percent increase in SV (p<.01), from 8 to 12 ml. Mean PAP, PVR, right and left ventricular filling pressures remained constant after noradrenaline infusion, and SVR increased 23 percent (p<.025).

Throughout the course of study, arterial O2 tension was always greater than 110 mm Hg; thus, hemoglobin

### Table 1—Hemodynamic Effects of Embolization

<table>
<thead>
<tr>
<th></th>
<th>CO L/min</th>
<th>HR beats/min</th>
<th>SV ml/beat</th>
<th>PAP mm Hg</th>
<th>RVEDP mm Hg</th>
<th>LVEDP mm Hg</th>
<th>BP mm Hg</th>
<th>SVR mm Hg L-1.min</th>
<th>PVR mm Hg L-1.min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.3±0.7</td>
<td>114±34</td>
<td>21±5</td>
<td>11±2</td>
<td>2±2</td>
<td>5±2</td>
<td>108±13</td>
<td>49±15</td>
<td>3±1</td>
</tr>
<tr>
<td>Pre-embolization</td>
<td>1.3±0.4*</td>
<td>170±17*</td>
<td>8±4*</td>
<td>47±5*</td>
<td>9±4†</td>
<td>4±3</td>
<td>96±13‡</td>
<td>72±25†</td>
<td>35±10*</td>
</tr>
</tbody>
</table>

*p<0.01; †p<0.025; ‡p<0.05.
saturation was always 100 percent.

**Discussion**

This study was designed to investigate the acute cardiopulmonary effects of isoproterenol and noradrenaline infusions in a canine model of increased PVR and decreased CO. This study also tested the hypothesis that when a moderate decrease in CO and BP levels complicates an acute increase in PVR, RV function would improve more with isoproterenol than with noradrenaline infusion.

We emphasize that our study is experimental in nature and that an artificial method was used to increase PVR. Further, the study was performed in anesthetized, ventilated dogs, in which a short-term increase in resistance decreased CO; therefore, it is possible that effects of drugs in this preparation would be different from those in the unanesthetized patient.

Repeat injections of pulmonary emboli increased RV afterload and reduced CO and BP levels. In this setting, isoproterenol decreased PVR and increased CO and SV. While PVR and CO remained constant with noradrenaline, SV increased.

Current recommendations for treatment of a low output state accompanying acute pulmonary hypertension vary considerably in the literature and, for the most part, lack experimental verification.

However, a few studies have 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 rapidly deteriorating RF function coincided with marked hypotension and a critical decrease in the RV perfusing pressure, ie, BP-RVP. Under these conditions, phe- nylephrine, a potent vasoconstricting drug without direct inotropic activity, increased systemic BP, coronary blood flow, and dramatically improved RV performance.

A more recent study by Molloy et al. investigated hemodynamic effects of therapy in a canine model of pulmonary embolism and shock. Injection of autologous blood clot over one-half hour resulted in a marked and progressive decrease in CO and BP levels. All dogs treated with noradrenaline therapy were acutely resuscitated and remained hemodynamically stable during one hour of continuous infusion. In contrast, all dogs randomized to isoproterenol infusion continued to deteriorate and died within 10 min. We speculated that isoproterenol failed to increase CO in this hemodynamically unstable model because its direct inotropic effects were offset by peripheral vascular effects which tend to decrease BP and RV perfusion.

Accordingly, we hypothesized that therapy with isoproterenol would be useful in the treatment of RV dysfunction when the increase in RV afterload was lower and when the BP level prior to treatment was higher.

Current results support this hypothesis. In the setting of acute pulmonary hypertension, stable BP and a moderate decrease in CO, isoproterenol infusion markedly improved RV function. Despite a decrease in mean RVEDP, there was a marked increase in CO. While SV almost doubled, there was an increase in heart rate. The improvement in RV function is explained by direct inotropic effects of the drug and by a decrease in PVR. While SVR and BP levels decreased after isoproterenol infusion, the fall in pressure was not so great as to cause RV hypoperfusion and ischemia. The changes in pulmonary and systemic vascular resistances caused by isoproterenol treatment are probably explained by peripheral vascular effects of the drug.

Previously, several investigators have recommended isoproterenol for treatment of acute cor pulmonale. A clinical study reported hemodynamic effects of graded infusion of isoproterenol over 18 hours in one patient with ARDS and pulmonary hypertension. In that patient, therapy with isoproterenol decreased PVR and increased CO.

In the current study, while the increase in CO was greater with isoproterenol infusion, ventricular performance improved with noradrenaline infusion, ie, despite constant RVEDP, SV increased 50 percent with noradrenaline infusion. In contrast to effects of therapy with isoproterenol, BP and SVR increased with infusion of noradrenaline. While it is possible that ventricular performance would have improved more with noradrenaline infusion if the dose had been higher, all dogs reached one of our prospective end points, ie, 30 percent increase in BP.

As discussed above and in contrast to current results, previous studies of acute pulmonary hyperten-
sion have reported marked increases in CO with pressor agents. The different results are explained by the cardiovascular status prior to treatment, ie, marked decrease in CO and circulatory instability versus moderate decrease in flow and stable BP.

In summary, current results suggest that isoproterenol may be the preferred agent for treatment of acute pulmonary embolism without shock. However, it is conceivable that an agent or agents combining α and β adrenergic activity might even be better.

REFERENCES
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