Hemodynamic Effects of Amrinone in a Canine Model of Massive Pulmonary Embolism*

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Amrinone, an inotrope with vasodilatory properties, is of potential use in managing the right ventricular failure and pulmonary vasoconstriction induced by massive pulmonary embolism (PE). Therefore, to determine the hemodynamic effects of amrinone in a canine model of massive PE, autologous blood clot was infused into ten dogs (eight treated and two control animals) in an amount sufficient to decrease mean systemic arterial pressure (MAP) by at least 25 percent. This resulted in an increase in mean pulmonary artery pressure (MPAP) from 13.4 ± 3.7 mm Hg to 44.4 ± 4.8 mm Hg (p < 0.01), a decrease in MAP from 122 ± 9.5 mm Hg to 35.6 ± 9.8 mm Hg (p < 0.01), and a decrease in cardiac output from 2.73 ± 0.83 L/min to 1.22 ± 0.61 L/min (p < 0.01). Amrinone was administered in an initial bolus of 0.75 mg/kg followed by an infusion of 7.5 μg/kg/min, which resulted in significant hemodynamic improvement in all subjects, with a fall in MPAP to 35.3 ± 5.1 mm Hg (p < 0.01), an increase in MAP to 98.1 ± 31.1 mm Hg (p < 0.01), and an increase in cardiac output to 2.01 ± 0.7 L/min (not significant) at 5 min. Cardiac output continued to increase to 2.56 ± 0.16 L/min (p < 0.01) at 35 min. We conclude that amrinone alleviated pulmonary hypertension, systemic hypotension, and low cardiac output in a canine model of massive PE. (Chest 1992; 102:274-78)

PE = pulmonary embolism; PVR = pulmonary vascular resistance; rt-PA = recombinant tissue-type plasminogen activator; SVR = systemic vascular resistance

Pulmonary embolism (PE) is the third most common cardiovascular illness (after acute ischemic syndromes and stroke), and accounts for more than 100,000 hospitalizations per year in the United States. Among patients with massive PE, estimates of the 1-h mortality are as high as 70 percent. Patients die of PE because of right ventricular failure, frequently manifested by hypotension, signs of right ventricular overload, and low cardiac output. Amrinone, a nonglycoside, noncatecholamine cardiotonic agent, has demonstrated both potent inotropic and vasodilatory properties in many in vitro and in vivo preparations. Therefore, we studied the hemodynamic effects of amrinone in a canine model of massive PE.

METHODS

Eight heartworm-free dogs were anesthetized with intravenous pentobarbital sodium. All animals were intubated and ventilated on a Harvard respirator. In the initial design the animals were maintained on room air; however, mild to moderate hypoxemia was observed (nadir Po2 values of 55 mm Hg, 59 mm Hg, and 59 mm Hg in the first three animals). To eliminate the potential pulmonary vasoconstrictive effects of hypoxemia, we instituted supplemental oxygen therapy for the remaining five treated animals and the two control animals. There were no statistical differences in the response to embolism or to therapy with amrinone between the animals receiving supplemental oxygen and those maintained on room air.

All animals underwent placement of right femoral arterial catheters, right internal jugular 7F Sorenson pulmonary artery catheters, and 8F left internal jugular lines. Nonheparinized saline was used to maintain line patency. Autologous blood clot was prepared by mixing 100 ml of the animal's blood with 1,000 units of thrombin (Thrombostat; Parke-Davis, Morris Plains, NJ) in a glass beaker; the mixture was allowed to stabilize for at least 60 min.

Hemodynamic measurements were recorded on an eight-channel physiologic recorder (Dynagraph Recorder model R612; Sensormedics, Yorba Linda, Calif). Measurements included mean systemic arterial pressure, heart rate, central venous pressure, pulmonary artery pressures, and pulmonary artery capillary wedge pressure. Systemic vascular resistance (SVR) in dynes/cm² was calculated as follows: (mean arterial pressure − central venous pressure)/cardiac output × 80. Pulmonary vascular resistance (PVR) in dynes/cm² was calculated as follows: (mean pulmonary artery pressure − pulmonary capillary wedge pressure)/cardiac output × 80. Cardiac output was determined by thermodilution with computations on an American Edwards COM 1 cardiac output computer (Baxter Healthcare, Santa Ana, Calif).

Statistical significance was determined by analysis of variance with repeated measures by Newman-Keuls. A probability value of less than 0.05 was considered significant.

Autologous blood clot was injected with a 50-ml syringe through the left internal jugular catheter in an amount sufficient to induce at least a 25 percent reduction in mean systemic arterial pressure. Following embolization, hemodynamic measurements were repeated, and the animals were given a bolus of amrinone, 0.75 mg/kg, intravenously via the proximal port of the Sorenson pulmonary artery catheter. The interval between the completion of embolization and administration of the amrinone bolus ranged from 30 to 108 s, with a mean interval of 62 s. On completion of amrinone bolus...
forms baseline two not output remaining pressure administration nary and amrinone urements bolus measurement mm, E. Squibb, New Brunswick, NJ) in the method described by Dougherty et al.* All animals were euthanized after 35 min. Necropsy was performed to exclude heartworms and to assess the degree of embolization. Two additional animals served as controls and were not given amrinone following infusion of autologous clot infused to the same hemodynamic end points.

Results
Autologous clot was infused in doses ranging from 1.8 to 9 ml/kg (mean, 4.3 ± 2.5 ml/kg). There was a significant decrease in mean systemic arterial pressure (three subjects developed electromechanical dissociation) following clot infusion (Table 1, Fig 1). Within 1 min of amrinone infusion, mean systemic arterial pressure was significantly improved and was not statistically different from baseline at 5 min.

Experimental animals underwent postembolization pulmonary arteriography through the distal port of the Sorenson catheter with use of 10 ml of diatrizoate meglumine and sodium (Renografin-76; E. R. Squibb, New Brunswick, NJ) in the method described by Dougherty et al.* All animals were euthanized after 35 min. Necropsy was performed to exclude heartworms and to assess the degree of embolization. Two additional animals served as controls and were not given amrinone following infusion of autologous clot infused to the same hemodynamic end points.

Cardiac output fell significantly following clot infusion and was unmeasurable in three subjects because the values were less than the sensitivity of the cardiac output computer (<0.05/min). With infusion of amrinone, cardiac output increased progressively and was not significantly different from baseline at 10 min. Cardiac output continued to increase through 35 min.

Heart rate decreased significantly from baseline following clot infusion, but returned to near baseline values at 5 min (Fig 2). Central venous pressure did not change significantly during the protocol, although two animals showed evidence of tricuspid regurgitation following embolization.

Reliable pulmonary capillary wedge pressure waveforms were unobtainable following embolization in all ten animals. Following amrinone administration in the eight treated animals, characteristic pulmonary capil-

TABLE 1—Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Precot Baseline</th>
<th>Premarinone</th>
<th>1 Min</th>
<th>5 Min</th>
<th>10 Min</th>
<th>35 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arterial pressure, mm Hg</td>
<td>122 (± 9.5)</td>
<td>36 (± 9.8)</td>
<td>75 (±31.8)</td>
<td>98 (±31.1)</td>
<td>95 (±31.1)</td>
<td>105.63 (±17)</td>
</tr>
<tr>
<td>Pulmonary arterial pressure, mm Hg</td>
<td>13.4 (±3.7)</td>
<td>44.4 (±4.8)</td>
<td>15.63 (±10.2)</td>
<td>35.3 (±5.1)</td>
<td>31.63 (±5.0)</td>
<td>27.5 (±3)</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>2.73 (±0.63)</td>
<td>1.22 (±0.61)†</td>
<td>1.9 (±1.0)</td>
<td>2.01 (±0.7)</td>
<td>1.88 (±0.5)</td>
<td>2.56 (±.16)</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>143 (± 13.9)</td>
<td>115 (± 23.3)</td>
<td>121.88 (±16.7)</td>
<td>138 (±15.7)</td>
<td>137.88 (±23.6)</td>
<td>144 (±20.0)</td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>0.5 (±0.8)</td>
<td>3.63 (± 4.1)</td>
<td>3.75 (±7.4)‡</td>
<td>2.25 (±2.3)</td>
<td>2.38 (±2.9)</td>
<td>1.38 (±1.8)</td>
</tr>
</tbody>
</table>

*Values are means, with standard deviation in parentheses.
†Unmeasurable in three subjects because values were <0.5 L/min.
‡Two subjects had tricuspid regurgitation.


![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21649/) Changes in (A) mean systemic arterial pressure, (B) mean pulmonary artery pressure, and (C) cardiac output.
lary wedge waveforms returned within 10 min. Systemic vascular resistance fell from a baseline of 3,805 ± 1,333 dynes/s/cm² to 2,555 ± 1,056 dynes/s/cm² (difference not statistically significant). The SVR increased to a peak of 4,167 ± 1,722 dynes/s/cm² at 5 min and then declined to 2,556 ± 611 dynes/s/cm² at 35 min. The PVR increased significantly (p<0.01) from a baseline of 230 ± 139 dynes/s/cm² to 1,517 ± 537 dynes/s/cm² at 1 min after amrinone administration (PVR could not be calculated immediately after amrinone administration due to the inability to obtain an accurate pulmonary capillary wedge pressure). The PVR fell progressively to 526 ± 167 dynes/s/cm² at 35 min, which remained significantly above the baseline value (p<0.05).

**Table 2—Ratios of Pulmonary Artery Systolic Pressure to Systemic Arterial Systolic Pressure**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Baseline</th>
<th>Preamrinone</th>
<th>1 Min</th>
<th>5 Min</th>
<th>10 Min</th>
<th>35 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.13</td>
<td>1.55</td>
<td>1.01</td>
<td>0.34</td>
<td>0.26</td>
<td>0.30</td>
</tr>
<tr>
<td>2</td>
<td>0.18</td>
<td>1.30</td>
<td>0.68</td>
<td>0.57</td>
<td>0.36</td>
<td>0.24</td>
</tr>
<tr>
<td>3</td>
<td>0.14</td>
<td>1.50</td>
<td>0.68</td>
<td>0.40</td>
<td>0.50</td>
<td>0.23</td>
</tr>
<tr>
<td>4</td>
<td>0.10</td>
<td>1.66</td>
<td>0.77</td>
<td>0.72</td>
<td>0.25</td>
<td>0.18</td>
</tr>
<tr>
<td>5</td>
<td>0.17</td>
<td>0.92</td>
<td>0.58</td>
<td>0.35</td>
<td>0.38</td>
<td>0.28</td>
</tr>
<tr>
<td>6</td>
<td>0.19</td>
<td>1.20</td>
<td>0.49</td>
<td>0.30</td>
<td>0.27</td>
<td>0.29</td>
</tr>
<tr>
<td>7</td>
<td>0.12</td>
<td>2.00</td>
<td>0.47</td>
<td>0.23</td>
<td>0.25</td>
<td>0.28</td>
</tr>
<tr>
<td>8</td>
<td>0.17</td>
<td>1.77</td>
<td>0.65</td>
<td>0.49</td>
<td>0.37</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Mean ± SD 0.15 ± 0.03 1.49 ± 0.32 0.69 ± 0.18 0.43 ± 0.16 0.33 ± 0.08 0.25 ± 0.04

P value* 0.01/0.01 0.01/0.01 0.01/0.05 NS/NS NS/NS

*First P value is for difference between ratio and preceding ratio; second is for difference between ratio and baseline ratio. NS = not significant.

**Figure 2.** Changes in (D) heart rate, expressed in beats per minute (BPM), and (E) central venous pressure.

**Figure 3.** Pulmonary angiography reveals intraluminal filling defect distal to the Swan-Ganz catheter.

Using the ratio of pulmonary artery systolic pressure to systemic arterial pressure as an index of the severity of pulmonary dysfunction, we were able to demonstrate the rapid improvement in pulmonary hemodynamics following infusion of amrinone. We observed (Table 2) a marked rise of this ratio from a baseline of 0.15 to 1.49 after autologous blood clot embolization. With infusion of amrinone, this ratio decreased significantly at 1 min to 0.69 and continued to decrease progressively to a value of 0.25 at 35 min. The 35-min ratio of 0.25 was not significantly different from the protocol baseline of 0.15.

The two control subjects not receiving amrinone died within 5 min of reaching the same hemodynamic end points as the experimental subjects. The eight dogs receiving amrinone all survived.

Angiography revealed intraluminal filling defects consistent with clot (Fig 3). Necropsy confirmed the absence of heartworms in all ten subjects and revealed extensive intraluminal clot, which was predominantly in the pulmonary arteries of the lower lobes (Fig 4).

**Discussion**

We demonstrated reversal of systemic hypotension,
pulmonary hypertension, and low cardiac output with the infusion of amrinone in a canine model of PE. The lack of significant change in the central venous pressure and SVR of the group is likely a result of the marked variance in the central venous pressure due to the development of acute tricuspid regurgitation in two animals and electromechanical dissociation in three animals. The inability to measure pulmonary capillary wedge pressure following massive PE has been previously documented and is likely due to pulmonary vasoconstriction and the physical obstruction of intraluminal thrombus.5 Similar canine models used by Fisher et al6 and Reines et al7 (1.7 ml of clot/kg and 1.0 to 1.5 ml of clot/kg, respectively) demonstrated a 30 percent immediate mortality. In our protocol, an average of 4.32 ml of clot/kg was infused. In addition, two animals not given amrinone died within 5 min of reaching the same hemodynamic end points as the experimental subjects. Given the high mortality of the experimental group, the fact that three subjects were in electromechanical dissociation at the time of initiation of amrinone infusion, and the rapid demise of the two control animals, we did not feel that it was ethical to use additional control animals.

Although the mode of action of amrinone is not completely understood, it appears that both inhibition of phosphodiesterase fraction III and alterations in calcium transport are operative in its inotropic and vasodilatory properties.8,9 The ability of amrinone to increase cardiac index, increase left ventricular dP/dT max, and decrease both SVR and PVR in dogs anesthetized with enflurane was demonstrated by Makela and Kapur.10 Takeda et al11 demonstrated substantial increases in coronary flow without changes in myocardial oxygen consumption in a canine heart-lung preparation that was considered to reflect the activity of amrinone as a coronary vasodilator. Hill and Rounds12 demonstrated that amrinone is a rapidly acting pulmonary vasodilator in an isolated rat lung model. Additionally, they demonstrated its ability to inhibit hypoxic and angiotensin II-induced vasoconstriction.

More recently, Prielipp et al13 have shown that amrinone increases cardiac output, decreases pulmonary artery pressures, and thus decreases PVR in patients who underwent coronary artery bypass grafting and were given amrinone in doses similar to those administered in this protocol. Additionally, they noted arterial oxygen desaturation and a decline in PaO2 following amrinone administration at this dose (bolus of 0.75 mg/kg, and infusion of 10 μg/kg/min) and especially at higher doses (bolus of 2.25 mg/kg and infusion of 20 μg/kg/min). This is considered to be secondary to increased pulmonary shunting and should lead to careful observation of arterial saturation and PaO2 when amrinone is used in the setting of PE when significant ventilation perfusion mismatching is present.

In our study, it seems most probable that the early beneficial effects of amrinone were mediated by its vasodilatory, rather than its inotropic, properties, because of the rapid time course over which the hemodynamic improvements occurred and the marked decline in PVR observed. The inotropic activity of amrinone is likely to contribute to the continued response. Angle et al14 demonstrated improvement in cardiac output in a nonlethal canine model of PE without observing changes in filling pressures, which implies improvement in myocardial contractility following administration of norepinephrine.

Decreases in cardiac output in settings in which PE is the sole variable are related directly to the degree of elevation of right ventricular afterload.15-17 Abnormalities of right ventricular function and reduction of left ventricular cavity size among patients with acute PE were confirmed by Come et al18 and were shown to be affected favorably following initiation of a 2 to 6-h infusion of recombinant tissue-type plasminogen activator (rt-PA). This improvement seems to be related to clot dissolution, based on sequential angiographic studies revealing clot lysis.

In addition to echocardiographic studies, Come et al19 also assessed changes in hemodynamic parameters, with one of their indices for the severity of pulmonary dysfunction being the ratio of pulmonary artery systolic pressure to systemic artery systolic pressure. They demonstrated a reduction of this ratio from 0.35 to 0.21 following administration of rt-PA. Their post-rt-PA ratio of 0.21 is similar to our postamrinone ratio of 0.25. These results suggest that a significant portion of the severe pulmonary hypertension we observed was mediated by vasoconstrictive influences.
The early mortality seen in PE patients without prior cardiopulmonary disease is due to marked pulmonary hypertension with resultant impairment of right ventricular function and cardiogenic shock. The ability of the nonhypertrophied right ventricle to adjust to this acute increase in afterload may be a major determinant in surviving the embolic event. In our canine model, the cardiovascular collapse immediately following massive embolism can be alleviated and reversed with the intravenous administration of amrinone.

Clinical hemodynamic improvement has been demonstrated in the later stages of PE with various vasoactive agents, including isoproterenol, hydralazine, and dobutamine. Amrinone may be an optimal agent for use in the clinical setting of increased right ventricular afterload associated with pulmonary vasoconstriction because of its potent and rapidly acting vasodilatory properties in addition to inotropic activity. Anecdotally, amrinone was shown to result in significant hemodynamic improvement within 30 min of administration when given to a patient with severe pulmonary hypertension and congestive heart failure following PE in the postoperative setting.

We caution against direct clinical application of our results. Aside from the differences between the canine model and clinical PE, we also utilized a model that produced 100 percent mortality in order to eliminate the chance of spontaneous hemodynamic recovery and to maximize the possibility of showing drug effect. In summary, we believe our observations demonstrate that amrinone is an effective agent for the reversal of cardiac failure associated with massive canine PE and that it warrants further investigation in the management of hemodynamically significant PE.

It would be of interest to evaluate the effects of amrinone in a less lethal model of PE and also to study its effects when used to augment the effects of anticoagulant and/or thrombolytic therapy. If further animal work substantiates our findings, then the examination of the effects of amrinone clinically in patients with hemodynamic instability due to PE would seem warranted.

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