Amrinone Therapy for Severe Pulmonary Hypertension and Biventricular Failure After Complicated Valvular Heart Surgery

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We report two cases in which amrinone was used effectively, in addition to the conventional sympathomimetic drug, for the emergence from cardiopulmonary bypass following complicated valvular heart surgery in patients who had severe pulmonary hypertension and biventricular failure. Amrinone was used in combination with isoproterenol in one and dopamine in the other case. The clinical changes were brought about by a 21.5 percent and 53.5 percent decrease in pulmonary blood pressure and pulmonary vascular resistance, respectively. Concomitantly, the mean systemic blood pressure was increased by 50 percent, whereas heart rate decreased by 17.5 percent. This report demonstrates that amrinone can be life-saving in patients with biventricular failure and severe pulmonary hypertension not responding to conventional β-adrenergic and vasodilator drug therapy. (Chest 1993; 104:1618-20)

Amrinone is a recent addition to the positive inotropic drug list. It is a nonglycosidic, nonsympathomimetic drug belonging to the bipyrine group. The drug functions by selectively inhibiting phosphodiesterase enzyme-fraction 3 and thereby increasing myocardial adenosine 3',5'-cyclic monophosphate (cAMP), which leads to the increased cellular calcium transport and therefore, the cardiotoxic effect. The above mechanism also leads to increased calcium uptake into the sarcoplasmic reticulum, thus decreasing calcium available for contraction in the vessels and producing vasodilation.1 By the same token, it enhances relaxation in the cardiac muscle and exerts a lusitropic effect (facilitates diastole). Thus, amrinone is classified as an "inodilator."

Goenen et al9 reported beneficial effect of amrinone after open heart surgery in five patients with low cardiac output syndrome, but it is to be noted that their patients had a mean aortic BP of 82±7 mm Hg and none of them was moribund. Another case report has documented that amrinone was useful in two patients with cardiogenic shock after coronary artery bypass graft surgery.1 We report herein two cases in which patients were moribund secondary to severe pulmonary hypertension and biventricular failure during emergence from cardiopulmonary bypass (CPB) after complicated valvular heart surgery in which amrinone was used effectively in addition to the conventional sympathomimetic drug therapy.

CASE REPORTS

CASE 1

A 25-year-old male patient with a history of rheumatic mitral valve regurgitation and stenosis, aortic valve stenosis, and pulmonary hypertension with patent ductus arteriosus (PDA) presented for valvular replacements and closure of PDA. Chest radiograph showed a cardiothoracic ratio of 0.65 and multiple Kerley B lines. Cardiac catheterization revealed a Qs/Qw ratio of 2.1 and grade 2 left ventricular function. The aortic valve area was 1.0 cm² while the mitral valve area was 2.1 cm². Angiography demonstrated a very large PDA measuring 15 mm. Standard cardiac anesthesia of sufentanil, pancuronium, and midazolam was used.

Aortic and mitral valve replacements and PDA closure were performed. Cardiopulmonary bypass was initially terminated without the requirement of inotropic support or vasodilators. However, aortic leakage was recognized and CPB was reestablished within 5 min. After 40 min of vigorous effort to repair the tear in the aortic root, the patient was separated from the CPB (second attempt) with the aid of isoproterenol (5 to 8 µg/min, titrated to heart rate <110 bpm) and nitroglycerin infusion (5 µg/min). However, the bleeding from the aortic root was still not surgically controllable and a decision was made to perform a Bentall procedure, which is a procedure for complete replacement of the aortic valve and ascending aorta. Total CPB time was 192 min and the aortic cross clamp time was 120 min. The patient was separated from the CPB (third attempt) with the titration of isoproterenol and nitroglycerin.

During the subcutaneous chest closure there was a sudden deterioration in the hemodynamic parameters (Table 1). BP dropped precipitously to 46/28 mm Hg, while pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PCWP) rose. A presumptive diagnosis of cardiac tamponade was made and the chest was reexplored surgically with no improvement. Hemodynamic values continued to deteriorate despite isoproterenol infusion (10 µg/min). A bolus of amrinone 1.5 mg/kg IV and an infusion of 25 µg/kg/min was administered in addition to the isoproterenol

<table>
<thead>
<tr>
<th>Time</th>
<th>HR, bpm</th>
<th>BP, mm Hg</th>
<th>PAP, mm Hg</th>
<th>PCWP, mm Hg</th>
<th>CVP, mm Hg</th>
<th>CI, L/min/m²</th>
<th>PVR, dyne/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>70</td>
<td>98/56</td>
<td>90/52</td>
<td>20</td>
<td>5</td>
<td>2.7</td>
<td>1,019</td>
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<td>Pre-CPB</td>
<td>70</td>
<td>90/46</td>
<td>80/40</td>
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<td>5</td>
<td>2.6</td>
<td>930</td>
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<td>64/40</td>
<td>54/35</td>
<td>12</td>
<td>7</td>
<td>2.1</td>
<td>859</td>
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<tr>
<td>After second CPB</td>
<td>84</td>
<td>70/42</td>
<td>56/40</td>
<td>12</td>
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<td>2.6</td>
<td>788</td>
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<tr>
<td>After third CPB</td>
<td>80</td>
<td>80/46</td>
<td>50/20</td>
<td>14</td>
<td>9</td>
<td>2.6</td>
<td>379</td>
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<td>46/28</td>
<td>68/42</td>
<td>22</td>
<td>18</td>
<td>1.8</td>
<td>981</td>
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<td>After amrinone (5-10 min)</td>
<td>82</td>
<td>96/56</td>
<td>54/34</td>
<td>14</td>
<td>14</td>
<td>2.8</td>
<td>587</td>
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<tr>
<td>ICU</td>
<td>88</td>
<td>86/40</td>
<td>50/30</td>
<td>12</td>
<td>10</td>
<td>3.1</td>
<td>490</td>
</tr>
</tbody>
</table>

*HR = heart rate; BP = blood pressure; PAP = pulmonary arterial pressure; CVP = central venous pressure; CI = cardiac index; PVR = pulmonary vascular resistance; CPB = cardiopulmonary bypass.
infusion. Both systemic and pulmonary BP improved significantly within 5 to 10 min. In the course of 6 h operation the urine output was 1,300 ml. The patient was extubated on the fourth day and discharged home on the 11th day.

**Case 2**

A 37-year-old, 110-kg woman with known chronic obstructive pulmonary disease presented with acute severe dyspnea and pleuritic chest pain. Pulmonary angiogram detected pulmonary hypertension but no evidence of pulmonary embolism. Echocardiography demonstrated grade 2 left ventricular function, and left ventricular hypertrophy with severe mitral and moderate tricuspid valve regurgitation. Cardiac catheterization revealed normal coronary vessels, large V wave, and left ventricular end-diastolic pressure of 30 mm Hg. A diagnosis of mitral valve prolapse with acute rupture of the posterior leaflet of mitral valve, and biventricular heart failure was made and the patient was scheduled for urgent mitral valvuloplasty. Standard cardiac anesthesia of sufentanil, pancuronium, and midazolam was used.

The patient underwent CPB for mitral valve repair. Due to the severe valvular damage and continuous leakage, a posterior leaflet quadrangular resection, dissection of papillary muscle, and reconstruction of the valve with sutures (Sorset) was carried out. Eventually a 30-mm Carpenter-Edwards mitral ring was inserted. The first attempt to come off CPB was unsuccessful because of right ventricular failure. After an additional 10 min of reperfusion under CPB, a second attempt was made to come off CPB with dopamine (up to 5 μg/kg/min) and nitroglycerin infusion (5 μg/min). However, the hemodynamic values continued to deteriorate (Table 2). Nitroglycerin therapy was discontinued and a bolus of amrinone 1 mg/kg IV and an infusion of 25 μg/kg/min was given in addition to the dopamine infusion. This led to marked improvement in the hemodynamic parameters within 5 to 10 min. Total time for CPB was 130 min and aortic cross clamp was 97 min. Urinary output was 850 ml during the 4-h operation. The hemodynamics were acceptable with a small V wave and the patient was transferred to the cardiac ICU with 25 μg/kg/min amrinone and 3 μg/kg/min dopamine infusions.

**DISCUSSION**

These two case reports demonstrate the effectiveness of amrinone in combination with β-adrenergic agonist in treating biventricular failure and severe pulmonary hypertension after valvular heart surgery. The two described patients received isoproterenol and dopamine, respectively, in addition to amrinone for biventricular failure associated with pulmonary hypertension during emergence from CPB. Isoproterenol is a potent selective β-receptor agonist while dopamine exerts its positive inotropic effect on the myocardium via the same receptors. The activation of the β-receptor leads to the conversion of the adenylyl cyclase to cAMP. Therefore, when combined with a phosphodiesterase inhibitor (amrinone), this prevents the degradation of cAMP and gives rise to the synergistic effect. This potentiated pharmacologic effect was taken advantage of in the two documented patients. The process whereby cAMP brings about its response is a complex cascade process. Isoproterenol and dobutamine have been shown to stimulate renal secretion of renin while the combination of dobutamine and amrinone leads to a further increase in the level of renin angiotensin aldosterone system, thus suggesting that amrinone also increases the level of renin, but the exact mechanism remains to be studied.

In our two described patients who had severe pulmonary hypertension and biventricular failure, a bolus injection of amrinone (1 to 1.5 mg/kg) and an infusion of 25 μg/kg/min led to an increase of the cardiac index (CI) by 36 percent and 37 percent, respectively. A similar result of 40 percent improvement in CI was obtained when dobutamine and amrinone were administered to a group of nonsurgical heart failure patients, while a 30 percent increase was reported by Hess et al when amrinone was administered alone. However, when amrinone was used at a dose of 0.75 mg/kg, it did not show any beneficial hemodynamic effect in patients with good ventricular function during weaning from CPB. This probably is due to inadequate dosage of amrinone used.

It is well known that heart rate (HR) is a major determinant of myocardial oxygen consumption (MVO2) and myocardial ischemia. Therefore, HR control is an important element in the pharmacologic therapy for the management of ventricular dysfunction. It is to be noted that catecholamine therapy increases HR and thus MVO2 demand, while the phosphodiesterase inhibitors lead to a decrease in MVO2. The above-mentioned pharmacologic effect made it suitable for administration of amrinone to the two documented patients. As indicated in Tables 1 and 2, after the administration of amrinone in addition to the catecholamine infusion, HR decreased by 13 percent and 22 percent and BP increased by about 51 percent and 49 percent, respectively, in our patients. A similar result was reported after the administration of amrinone to two patients who did not respond to adrenergic drugs following CPB in the recovery room.

A study of 12 patients with mitral stenosis and pulmonary hypertension showed that amrinone lowered their mean PAP and pulmonary vascular resistance (PVR) by 10 percent and 40 percent, respectively. This study was carried out under anesthesia prior to surgery. Bolling et al studied 27

**Table 2—Hemodynamic Changes in Case 2**

<table>
<thead>
<tr>
<th>Time</th>
<th>HR, bpm</th>
<th>BE, mm Hg</th>
<th>PAP, mm Hg</th>
<th>CVP, mm Hg</th>
<th>CI, L/min/m²</th>
<th>PVR, dyne/sec/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>100</td>
<td>102/68</td>
<td>78/34</td>
<td>16</td>
<td>1.3</td>
<td>431</td>
</tr>
<tr>
<td>Pre-CPB</td>
<td>105</td>
<td>98/60</td>
<td>50/20</td>
<td>12</td>
<td>2.0</td>
<td>191</td>
</tr>
<tr>
<td>First attempt CPB</td>
<td>104</td>
<td>70/46</td>
<td>50/20</td>
<td>12</td>
<td>1.7</td>
<td>208</td>
</tr>
<tr>
<td>Second attempt CPB</td>
<td>95</td>
<td>88/48</td>
<td>55/23</td>
<td>12</td>
<td>1.7</td>
<td>240</td>
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<tr>
<td>Before amrinone</td>
<td>100</td>
<td>50/25</td>
<td>60/42</td>
<td>14</td>
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<td>285</td>
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<tr>
<td>After amrinone (5-10 min)</td>
<td>78</td>
<td>95/50</td>
<td>40/20</td>
<td>12</td>
<td>2.7</td>
<td>95</td>
</tr>
<tr>
<td>ICU</td>
<td>93</td>
<td>88/45</td>
<td>40/27</td>
<td>10</td>
<td>3.2</td>
<td>51</td>
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</tbody>
</table>

*See Table 1 for explanation of abbreviations.
†Pulmonary arterial diastolic pressure was used in the calculation of the PVR because of the large V wave. Although pulmonary artery diastolic pressure overestimated left ventricular end-diastolic pressure and the resultant PVR was underestimated, the relative change in PVR remained valid.
patients who did not respond to nitroprusside treatment for reducing pulmonary hypertension prior to cardiac transplantation. These patients were given a bolus of amrinone (0.75 mg/kg) followed by a prolonged continuous infusion (25 µg/kg/min) for 48 h; 89 percent of these patients responded to the therapy evidenced by a decrease in PCWP, right atrial pressure, systemic vascular resistance (SVR), and PVR.* In our two documented patients who had severe pulmonary hypertension and biventricular failure, the administration of amrinone brought about the dramatic change in the pulmonary indices. The PAP decreased by 20 percent and 23 percent while the PVR decreased by about 40 percent and 67 percent, respectively. We are aware that in case 2, because of the initial large V wave, the mean height of the A wave or the diastolic pressure of the PCWP should be used to calculate the PVR. Unfortunately, PCWP was not recorded; therefore, pulmonary arterial diastolic pressure was used in the PVR calculation. This probably underestimates the absolute severity of PVR, but the relative change in PVR remains valid. The resultant lower pulmonary resistance and pressure improved the right ventricular performance and reduced the wall stress of the right side of the heart, thus improving the left ventricular function and systemic BP.

In conclusion, we demonstrated that the addition of amrinone can be life-saving in patients with severe pulmonary hypertension and biventricular failure following complicated valvular heart surgery, not responding to conventional β-adrenergic (isoproterenol or dopamine) and vasodilator (nitroglycerin) drug therapy. A loading dose of amrinone, 1 to 1.5 mg/kg, followed by 25 µg/kg/min infusion increased the mean BP by 49 to 51 percent, CI by 36 to 37 percent, and decreased mean PAP by 20 to 23 percent, PVR by 40 to 67 percent, and HR by 13 to 22 percent in the moribund patients.

REFERENCES
8 Bolling SF, Deeb GM, Crowley DC, Badellino MM, Bove EL. Prolonged amrinone therapy prior to orthotopic cardiac transplantation in patients with pulmonary hypertension. Transplant Proc 1988; 20:753-56

Pneumonitis Complicating Low-dose Methotrexate Therapy for Rheumatoid Arthritis*

Discrepancies Between Lung Biopsy and Bronchoalveolar Lavage Findings

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Two very similar cases of drug-induced pneumonitis complicating treatment of rheumatoid arthritis with low-dose methotrexate are presented. Diagnosis was suggested by clinical history and findings, but the bronchoalveolar lavage showed a high percentage of neutrophils, an unusual feature in methotrexate-induced pneumonitis. Transbronchial lung biopsies (TBB) confirmed the diagnosis by showing interstitial lymphocytic infiltrate with microgranulomas. Although histologic findings are not strictly pathognomonic, when a differential diagnosis has to be made with infectious and rheumatoid lung disease, TBB appears to be of great promise.

(Chest 1993; 104:1620-23)

Case Reports

Case 1

This 69-year-old woman was a nonsmoker and had no history of respiratory disease. In 1967, she developed severe RA which required treatment with salazopyrine, salicylates, and corticosteroids.

In July 1991, treatment with salicylates and corticosteroids was stopped because of slight impairment of renal function and osteoporosis. Starting on July 15, 1991, methotrexate sodium (10 mg/wk) was administered orally with improvement of articular complaints. She received the last dose the day before her admission. From the end of September 1991, she recurrently complained of cough and fever, and these complaints progressively increased until admission on October 31, 1991. She had no articular symptoms. Examination revealed an ill-appearing woman with severe respiratory distress and fever. Dry inspiratory crackles were heard in both lungs. A chest radiograph (Fig 1, top) and computed tomography scan (Fig 1, bottom) showed massive interstitial infiltration of both lungs. Lung function tests showed a severe restrictive ventilatory impairment (Table 1). While she was breathing room air, the PaO2 value was 37.2 mm Hg, PaCO2, 20 mm Hg, and arterial pH, 7.50. The white blood cell count was 4,000/mm3, with 81 percent neutrophils.

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Pneumonitis Complicating Low-dose Methotrexate Therapy (Leduc et al)