Reversal of ‘Refractory Septic Shock’ by Infusion of Amrinone and Angiotensin II in an Anthracycline-Treated Patient*

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A 53-year-old granulocytopenic woman with malignant lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, including doxorubicin (Adriamycin) and autologues bone marrow transplantation, presented in the clinical state of “refractory septic shock” caused by Escherichia coli. Despite inotropic treatment with dopamine, dobutamine, and norepinephrine infusion, the patient’s condition did not improve, but during treatment with amrinone and angiotensin II infusion, the septic shock was reversed. The patient was monitored with a pulmonary artery catheter and underwent repeated echocardiographic examinations. Antibiotic treatment with thienamycin and floxacillin was given. The initial reduction in cardiac performance in this patient may be explained by a state of true down-regulation of the myocardial β-receptors. Apparently these β-receptors were bypassed via the enzymatic action of amrinone upon cyclic monoadenosine phosphate. This is, to our knowledge, the first doxorubicin-treated patient with septic shock refractory to conventional vasopressor therapy whose condition reversed by inotropic treatment with amrinone and angiotensin II. This treatment may prove to be an alternative choice for patients developing “refractory septic shock” unresponsive to treatment with norepinephrine, dobutamine, and dopamine.

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Key words: Adriamycin; amrinone; angiotensin II; irreversible septic shock

Under septic conditions, a true down-regulation of the myocardial β-receptors may be induced. Treatment with antineoplastic drugs of the anthracycline type implies a dose-dependent chronic heart failure. The pathophysiologic findings of doxorubicin (Adriamycin)-induced cardiomyopathy are characterized by loss of myofibrils and vacuolization of degenerated myocytes. The combination of cardiomyopathy and bacteremia may induce a state of refractory shock.

In refractory shock, a possible way to increase inotropy is to bypass the β-receptors using enzymatic inhibitors of phosphodiesterase, eg, using amrinone which is a nonglycoside, noncatecholamine drug with both positive inotropic and vasodilator effects. It acts by inhibiting phosphodiesterase F III, the enzyme responsible for the degradation of cyclic adenosine monophosphate, which in turn has multiple actions within myocardial and vascular smooth muscle cells. The effect in treatment of chronic congestive and acute heart failure following cardiac surgery is ascribed to an increased cardiac output and a decrease in right and left filling pressures as well. The most important side effect, however, is the vasodilatory effect of the drug, which may dangerously reduce perfusion pressure of vital organs.

The vasodilatory effects of amrinone, however, can effectively be reversed by angiotensin II, which is a naturally occurring octapeptide with a half-life of only a few minutes, being enzymatically metabolized. It exerts its vasopressor effects by a direct action on specific receptors in arteriolar smooth muscle, on presynaptic receptors in peripheral sympathetic nerves and in the adrenal medulla, and by centrally mediated stimulation of sympathetic nervous system activity.

The purpose of the present report is to describe a patient with anthracycline-induced heart failure who developed “refractory septic shock” that was reversed by treatment with the combination of amrinone and angiotensin II infusion.

CASE REPORT

A 53-year-old woman with a non-Hodgkin’s malignant lymphoma of centrocyte type stage IA, diagnosed in June 1987 and treated with irradiation (mantle field with a total of 40 Gy) plus five series of CHOP (cyclophosphamide, doxorubicin [Adriamycin], vincristine, and prednisolone). A complicating secondary acute myeloid leukemia was diagnosed in December 1991, treated with daunorubicin, cytosine, amascrine, etoposide (VP16), cyclophosphamide, and methotrexate and an autologous bone marrow transplantation June 1992 as rescue to the intensive chemotherapy. Thirty-two days after autologous marrow transplantation, the patient developed cyclophosphamide-cystitis complicated with sepsis caused by Escherichia coli. The patients fulfilled the ACCP/CCCM consensus criteria for sepsis: rectal temperature of 38.9°C, heart rate of 160 beats/min, respiratory rate of 36 breaths/min, PaCO₂ of 31 mm Hg, white blood cell count of 500/cu mm, and six of six blood cultures positive with E. coli. Treatment with thienamycin and floxacillin was started. On day 41 after the transplant, intensive care treatment and controlled

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Table 1—Cardiovascular Parameters During Treatment With Dopamine, Dobutamine, Amrinone, Angiotensin, and Norepinephrine, Day 43 to Day 51

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 43</th>
<th>Day 44</th>
<th>Day 45</th>
<th>Day 46</th>
<th>Day 47</th>
<th>Day 49</th>
<th>Day 51</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPM, mm Hg</td>
<td>53</td>
<td>52</td>
<td>70</td>
<td>65</td>
<td>71</td>
<td>60</td>
<td>73</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>5.0</td>
<td>3.1</td>
<td>4.0</td>
<td>4.4</td>
<td>5.1</td>
<td>8.35</td>
<td>6.81</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>11</td>
<td>18</td>
<td>15</td>
<td>14</td>
<td>16</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>HF, beats/min</td>
<td>125</td>
<td>136</td>
<td>130</td>
<td>114</td>
<td>112</td>
<td>120</td>
<td>109</td>
</tr>
<tr>
<td>PAPM, mm Hg</td>
<td>25</td>
<td>26</td>
<td>24</td>
<td>24</td>
<td>30</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>PAWP, mm Hg</td>
<td>17</td>
<td>18</td>
<td>...</td>
<td>16</td>
<td>18</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>PVR, DS/cm²</td>
<td>80</td>
<td>205</td>
<td>...</td>
<td>145</td>
<td>187</td>
<td>172</td>
<td>176</td>
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<tr>
<td>SVR, DS/cm²</td>
<td>700</td>
<td>871</td>
<td>...</td>
<td>925</td>
<td>857</td>
<td>392</td>
<td>599</td>
</tr>
<tr>
<td>Dopamine/dobutamine, µg/kg/min</td>
<td>4/57</td>
<td>4/60</td>
<td>4/60</td>
<td>4/40</td>
<td>4/21</td>
<td>4/17</td>
<td>4/18</td>
</tr>
<tr>
<td>Amrinone/angiotensin II, µg/kg/min</td>
<td>...</td>
<td>10/0.06</td>
<td>10/0.06</td>
<td>10/0.06</td>
<td>10/0.05</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Norepinephrine, µg/min</td>
<td>67</td>
<td>110</td>
<td>28</td>
<td>14</td>
<td>...</td>
<td>...</td>
<td>8</td>
</tr>
</tbody>
</table>

*ABPM=arterial blood pressure mean; CO=cardiac output; CVP=central venous pressure; HF=heart frequency; PAPM=pulmonary artery pressure mean; PAWP=pulmonary artery wedge pressure; PVR=pulmonary vascular resistance; SVR=systemic vascular resistance.

ventilation were necessary due to a persisting “refractory septic shock” despite vasoactive pressor therapy with dopamine, dobutamine, and norepinephrine infusion. The patient was monitored with pulmonary artery catheter from day 43 and treated with infusions of amrinone and angiotensin II from day 44. Her condition improved during the following 8 days, with cardiac performance monitored by pulmonary artery parameters as seen in Table 1. Echocardiographic examination on day 44 and day 47 confirmed the cardiac improvement.

**DISCUSSION**

Refractory septic shock is a clinical entity, comprising signs of severe systemic infection associated with tachypnea, tachycardia, hyperthermia or hypothermia, and finally hypotension for more than 1 h unresponsive to adequate volume resuscitation and vasopressor treatment. During the septic shock, an increased sympathetic nerve activity and a concomitant reduced response of the heart to adrenergic stimulation may occur, explained by adrenergic receptor desensitization to adrenergic agonists. This reduction in receptor sensitivity develops in a sequential order. Initially, uncoupling of the receptor from adenylate cyclase occurs. In a later phase, the decrease in surface receptor population reduces the number of available β-receptors due to internalization of receptors decreasing the total number of β-adrenergic receptors and thus may cause a true down-regulation. Apparently, sepsis of 1 to 2 days’ duration may infer a true down-regulation of the β-receptors induced by catecholamines, endotoxins, tumor necrosis factor, and cytokines.6,7

The present patient failed to sustain a satisfactory cardiac output and appropriate arterial mean blood pressure despite infusion of massive doses of norepinephrine, dopamine, and dobutamine, all exceeding suggested dosages in treatment of shock.8 The cardiac toxic reaction following doxorubicin treatment can further attenuate cardiac performance in septic shock. Treatment with amrinone and angiotensin II improved the cardiovascular variables markedly, and after 4 days of treatment, the cardiac output was maintained with usual therapeutic doses of dopamine and dobutamine infusions only.

To our knowledge, this is the first doxorubicin-treated patient with septic shock refractory to conventional vasopressor therapy whose condition was reversed by inotropic therapy with amrinone and angiotensin II. The successful course despite a down-regulation of the β-receptors secondary to treatment with vasopressor drugs or from the influence of endotoxins is explained from the enzymatic action of amrinone on cyclic adenosine monophosphate, an effect that bypasses the β-receptors of the heart. Concomitant treatment with angiotensin II reversed the unfortunate vasodilatory effect in sepsis of amrinone, thus improving cardiac performance.

Although the concomitant infusion of amrinone and angiotensin II reversed the “refractory septic shock” in this patient, further studies are needed to distinguish the effects of the drugs from the pathophysiologic changes due to the progression of the severe septic shock. In general, the stabilization of circulation during a septic shock is highly important to preserve function of vital organs, and early antibiotic treatment is mandatory.

In conclusion, we recommend the infusion of amrinone and angiotensin II as an alternative treatment modality for patients developing refractory shock irreversible to traditional treatment with norepinephrine, dobutamine, and dopamine.

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