The coronary circulation in human septic shock

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ABSTRACT  Reversible myocardial depression, manifested by ventricular dilatation and decreased ejection fraction, is common in human septic shock. A proposed mechanism, based on animal studies, is myocardial ischemia resulting from inadequate coronary blood flow. Coronary flow observations have not been reported for human septic shock. To determine whether myocardial depression in human septic shock is associated with reduced coronary flow, thermodilution coronary sinus catheters were placed in seven patients with septic shock for measurements of coronary flow and myocardial metabolism. Four of the seven patients developed myocardial depression. These patients had coronary flow similar to or higher than that of control subjects and similar to that of the other three patients, who did not develop myocardial depression. None of the patients had net myocardial lactate production. In general, compared with values in control subjects, the oxygen content difference (arterial minus coronary sinus) was narrowed, and the fractional extraction of arterial oxygen was diminished. This pattern of disordered coronary autoregulation is analogous to the pattern of arteriovenous shunting in other organs in patients with septic shock. The preservation of coronary flow, the net myocardial lactate extraction, and the increased availability of oxygen to the myocardium argue against global ischemia as the cause of myocardial depression in human septic shock.

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MYOCARDIAL DEPRESSION within the first several days of human septic shock is characterized by dilatation of the left ventricle, a decrease in left ventricular ejection fraction, and maintenance of normal or increased cardiac index.1, 2 In survivors, these profound changes in ventricular function are transient and the ejection fraction generally returns to normal in 7 to 10 days.1 The pathogenesis of myocardial depression in septic shock is unclear, but in canine preparations of endotoxic shock myocardial depression has been attributed to myocardial hypoperfusion caused by reduced coronary blood flow.3–7

Human coronary blood flow has been studied extensively in normal subjects and in patients with coronary artery disease, by means of nitrous oxide washout, inert gas washout, and thermodilution techniques. The determinants of myocardial lactate metabolism and myocardial oxygen consumption have been characterized. Measurements of coronary blood flow, myocardial lactate metabolism, and myocardial oxygen consumption have been reported in cardiogenic4 but not in septic shock in human beings. The current study was undertaken to determine whether myocardial depression in human septic shock is associated with changes in coronary blood flow and whether such changes could explain the depressed cardiac function.

Methods

Patients. From October 1982 to February 1984, seven patients with septic shock were studied in the Medical Intensive Care Unit of the National Institutes of Health. The diagnosis of septic shock was based on hypotension (mean arterial pressure less than 60 mm Hg), temperature greater than 38°C, and either positive blood cultures or, in some cases, negative blood cultures (attributed to concomitant broad-spectrum antibiotic treatment) in neutropenic, immunocompromised patients with a localized site of infection. All subjects gave informed consent and the study protocol was approved by the institutional committee on human research.

Therapeutic protocol. Each patient was treated by the same group of physicians according to a uniform protocol consisting of (1) initial intravenous fluid resuscitation to attain and then maintain a mean pulmonary capillary wedge pressure of 15 mm Hg, (2) infusion of dopamine at 2 μg/kg/min, followed, if the patient remained hypotensive, by titration of the infusion to attain a mean arterial pressure (MAP) of 60 mm Hg, and (3) if more than 20 μg/kg/min dopamine was required, norepinephrine was added and titrated to an MAP of 60 mm Hg, and dopamine was tapered to 2 μg/kg/min in an effort to preserve renal perfusion.5 All patients received broad-spectrum antibiotic coverage and were given two doses of methylprednisolone.
CUNNING et al.

30 mg/kg, one at the onset of shock and the second 4 to 8 hr later. Respiratory support was given as needed to maintain a normal pH and an arterial oxygen tension greater than 70 mm Hg; all hemodynamic studies were done when arterial oxygen tension and pH were normal. Four patients required mechanical ventilation; the other three received supplemental oxygen. Metabolic variables were checked on several occasions daily, and abnormalities, especially of potassium, phosphate, calcium, magnesium, and glucose, were corrected promptly.

Coronary sinus and great cardiac vein blood flows. Within 6 hr of the onset of shock, each patient had an Elecath Baim thermodilution coronary sinus catheter advanced from the right internal jugular vein into the coronary sinus and positioned with its tip in the great cardiac vein under fluoroscopic guidance. Correct catheter placement was confirmed by contrast dye injection, pressure waveforms, and oximetric study of sampled coronary sinus blood. Coronary sinus blood flow and great cardiac vein blood flow were measured according to a previously validated technique. For each flow determination, body temperature was recorded from the catheter thermistors, and then heparinized normal saline solution at room temperature was injected through the distal lumen for 20 to 30 sec at a constant rate of 50 ml/min with a Medrad Mark IV injector. During the injection, temperatures were recorded from the great cardiac vein, coronary sinus, and injectate thermistors with a Hewlett-Packard 7760A multichannel recorder. Each determination was performed three times, with triplicate measurements never differing by more than 10%. Flow determinations were performed every 12 hr for 1 to 3 days. Before each determination, correct catheter position was reconfirmed radiographically. Concomitantly, arterial blood samples were obtained through an indwelling radial or femoral arterial cannula and coronary sinus blood samples were drawn through the coronary sinus catheter. Oxygen content of each sample was determined with a Radiometer hemoximeter and a Corning 178 blood gas analyzer; plasma lactate measurements were performed spectrophotometrically with a Dupont AutoAnalyzer.

An indwelling, flow-directed, balloon-tipped thermodilution, pulmonary arterial catheter was inserted in each patient; concomitant with coronary blood flow determinations, measurements were made of central venous pressure, pulmonary arterial pressures, pulmonary capillary wedge pressure, and cardiac output by the thermodilution technique.

Radionuclide scans. Serial radionuclide cineangiographic studies were done on each patient. The first study was done within 6 hr of the onset of shock and follow-up studies were done every 1 to 2 days thereafter. These electrocardiographically gated cardiac scintigraphic examinations were done in the intensive care unit with a portable Elscint gamma camera. Patients received an injection of stannous pyrophosphate, and 30 min later received 0.3 mCi/kg technetium-99m to accomplish labeling of erythrocytes in vivo. With the patient supine, the camera was positioned in a 35 degree left anterior oblique orientation with a 15 degree caudal tilt. Left ventricular and background regions of interest were labeled, and background-corrected left ventricular time-activity curves were generated from the image sequence.

Calculations. Coronary sinus and great cardiac vein blood flows were calculated from the formula: flow (ml/min) = F1 × 1.19 × 1.05 × (T-M - T-R)/(T-B - T-M), where F1 is inflow rate (ml/min), 1.19 is specific heat constant (based on the thermal properties of normal saline), 1.05 = calibration constant, T-M = temperature (°C) at coronary sinus (or great cardiac vein) thermistor, T1 = temperature of influse, and T-R = temperature of blood.

Radionuclide left ventricular ejection fraction was calculated as EF = (EDC - ESC)/(EDC - Bkgd), where EDC = end-diastolic counts, ESC = end-systolic counts, and Bkgd = background counts.

Oxygen content was calculated from the formula: O2 content (ml O2/100 ml) = (1.34 × SO2 × 0.01 × Hb) + 0.0031 × PO2, where SO2 = percent oxygen saturation, Hb = hemoglobin content (g/dl), and PO2 = partial pressure of oxygen (mm Hg).

Oxygen extraction percentage was calculated as (C02 - C02o) × 100/C02o, where C02 = arterial oxygen content and C02o = coronary sinus oxygen content.

Lactate extraction percentage was calculated as (lacta - lactao) × 100/lactao, where lacta = arterial lactate (mmol/liter) and lactao = coronary sinus lactate (mmol/liter).

Myocardial oxygen consumption was calculated as MVO2 (ml O2/min) = (C02 - C02o) × CSBF, where (C02 - C02o) = arterial minus coronary sinus oxygen content difference (ml O2/100 ml) and CSBF = coronary sinus blood flow (ml/min).

Systemic vascular resistance was calculated from the formula: SVR (dyne-sec-cm-5) = (MAP - CVP) × 80/CO, where MAP = mean arterial pressure (mm Hg), CVP = central venous pressure (mm Hg), and CO = thermodilution cardiac output (liters/min).

Statistical analysis. All comparisons were made with a two-tailed Student's t test. A p value of < .05 is considered significant.

Results

The coronary circulation was studied in seven male patients whose clinical characteristics are summarized in table 1. Patients ranged in age from 15 to 66 years, and their underlying illnesses included aplastic ane-

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Underlying disease</th>
<th>Blood cultures</th>
<th>Outcome of shock episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>Aplastic anemia</td>
<td>Pseudomonas aeruginosa</td>
<td>Died on day 2</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>Lymphoblastic lymphoma</td>
<td>Escherichia coli</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>Diffuse histiocytic lymphoma</td>
<td>Candida albicans</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>Testicular carcinoma</td>
<td>Pseudomonas aeruginosa and</td>
<td>Died on day 26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Candida albicans</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>Acquired immunodeficiency syndrome</td>
<td>Negative</td>
<td>Died on day 20</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>Acquired immunodeficiency syndrome</td>
<td>Negative</td>
<td>Died on day 16</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>Diffuse histiocytic lymphoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
mia, malignant neoplasms, and acquired immunodeficiency syndrome. None of the patients had a history of angina pectoris, heart failure, or myocardial infarction, nor did any patient develop ischemic electrocardiographic changes during the study. All patients had fever and hypotension on presentation. Four of the seven had elevated levels of circulating activated complement, including a positive C5a determined by neutrophil aggregation. Four of the seven had blood cultures positive for bacterial and/or fungal pathogens; three of the seven had localized culture-positive infections, with negative blood cultures attributable to concomitant systemic antibiotic therapy.

One patient died on the second day so that only three sets of hemodynamic and metabolic determinations were obtained. Each of the remaining patients had five or six sets of determinations over 48 or 60 hr. In general, coronary flow and myocardial metabolic variables in each patient showed little variation over time. Accordingly, for each of the seven patients, multiple sets of determinations were averaged to obtain the representative values shown in Table 2. The table also shows overall mean values for the seven patients as a group and control values from previous studies. These patients with septic shock, compared with controls, had a decreased oxygen content difference (arterial minus coronary sinus) (p < .001), a decreased arterial oxygen extraction percentage (p < .01), and an elevated coronary sinus oxygen saturation (p < .05). Myocardial oxygen consumption, normalized for the double product, systolic blood pressure times heart rate, did not differ between patients and control subjects.

In figure 1, coronary sinus blood flow and great cardiac vein blood flow in seven patients with septic shock are compared with flows previously reported in subjects with normal coronary arteries, at rest and during pacing, which were obtained by the same thermodilution technique used in this study. Because coronary sinus blood flow and great cardiac vein blood flow increase with increasing heart rate, flows are normalized for heart rate by stratifications of less than 100 and greater than 100 beats/min. The serial heart rate, coronary sinus blood flow, and great cardiac vein blood flow determinations were averaged to obtain representative values for each patient, and the mean values for the patients in each stratum were then averaged to obtain the mean (± SE) shown in the figure. No significant differences were noted in coronary sinus blood flow or great cardiac vein blood flow at heart rates below 100 beats/min. At heart rates above 100 beats/min, however, patients with septic shock had higher coronary sinus blood flow (p < .01) and higher great cardiac vein blood flow (p < .02) than paced normal subjects. Coronary sinus blood flow as a frac-

### TABLE 2

Mean coronary and hemodynamic variables in seven patients with septic shock

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Mean ± SE</th>
<th>Normal values</th>
<th>t test comparing patients with normals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>167</td>
<td>72</td>
<td>98</td>
<td>141</td>
<td>116</td>
<td>83</td>
<td>116</td>
<td>113 ± 12</td>
<td>308 ± 81</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Coronary sinus flow (ml/min)</td>
<td>647</td>
<td>79</td>
<td>164</td>
<td>533</td>
<td>287</td>
<td>119</td>
<td>326</td>
<td>143 ± 39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Great cardiac vein flow (ml/min)</td>
<td>347</td>
<td>56</td>
<td>54</td>
<td>188</td>
<td>143</td>
<td>82</td>
<td>132</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial–coronary sinus oxygen content difference (ml O₂/100 ml)</td>
<td>3.83</td>
<td>8.57</td>
<td>8.64</td>
<td>7.48</td>
<td>7.65</td>
<td>9.15</td>
<td>6.90</td>
<td>7.46 ± 0.67</td>
<td>13.3 ± 0.6 (ref. 12)</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Oxygen extraction (%)</td>
<td>31</td>
<td>67</td>
<td>66</td>
<td>56</td>
<td>56</td>
<td>66</td>
<td>48</td>
<td>56 ± 5</td>
<td>71 ± 2 (ref. 12)</td>
<td>p &lt; .01</td>
</tr>
<tr>
<td>Coronary sinus oxygen saturation (%)</td>
<td>58</td>
<td>31</td>
<td>33</td>
<td>31</td>
<td>42</td>
<td>32</td>
<td>41</td>
<td>38 ± 4</td>
<td>29 ± 2 (ref. 13)</td>
<td>p &lt; .05</td>
</tr>
<tr>
<td>Myocardial oxygen consumption</td>
<td>0.152</td>
<td>0.090</td>
<td>0.097</td>
<td>0.246</td>
<td>0.187</td>
<td>0.106</td>
<td>0.215</td>
<td>0.156 ± 0.023</td>
<td>0.165 ± 0.008 (ref. 14)</td>
<td>p = NS</td>
</tr>
<tr>
<td>Systolic BP × HR (ml O₂/mm Hg/beat)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>9.42</td>
<td>3.10</td>
<td>2.95</td>
<td>7.02</td>
<td>5.52</td>
<td>4.94</td>
<td>4.29</td>
<td>5.32 ± 0.87</td>
<td>3.54 ± 0.15 (ref. 15)</td>
<td>p &lt; .01</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn-sec-cm⁻⁵)</td>
<td>146</td>
<td>927</td>
<td>1170</td>
<td>472</td>
<td>468</td>
<td>537</td>
<td>837</td>
<td>651 ± 130</td>
<td>1130 ± 49 (ref. 15)</td>
<td>p &lt; .001</td>
</tr>
</tbody>
</table>
tion of cardiac index (not depicted) did not differ significantly between patients with septic shock and normal subjects at heart rates below 100 beats/min. Coronary sinus blood flow as a fraction of cardiac index has not been reported for normal subjects at heart rates above 100 beats/min.

Four of the seven patients manifested transient myocardial depression. The ejection fraction in each of the four fell below the normal range (45% to 70% in this institution) on the third day of septic shock and subsequently recovered to normal. The other three patients had normal left ventricular ejection fractions throughout the period of observation. For the four patients with myocardial depression, table 3 compares the mean data before the fall in ejection fraction (“Day 1”) with the mean data on the third day of septic shock (“Day 3”). For the four patients as a group there was no significant change with time in any variable except ejection fraction (46 ± 3% before myocardial depression, falling to 37 ± 2% on the third day; p < .05).

Table 4 compares mean hemodynamic and metabolic values of the four patients with myocardial depression with those of the three patients without myocardial depression. A lower ejection fraction (p < .01) in the patients with myocardial depression was the only difference between the groups that had statistical significance. Although the patients without myocardial depression displayed a trend toward higher mean coronary blood flow, their mean heart rate was also correspondingly higher, and the differences were not significant statistically.

Four of the seven patients received norepinephrine in various doses. No significant differences were noted between those patients receiving norepinephrine and those not receiving it in mean coronary blood flow, mean oxygen content difference (arterial minus coronary sinus), or mean arterial oxygen extraction percentage (table 5). Norepinephrine was discontinued during the study in three of the four patients receiving it. When data from these three patients during and after infusion of norepinephrine were compared, no significant changes occurred in mean coronary blood flow, mean oxygen content difference, or mean arterial oxygen extraction percentage.

Although six of the seven patients had at least one elevated arterial lactate determination (greater than 2.2 mmol/liter), each had net myocardial lactate extraction. Every arterial lactate measurement in every patient was higher than the simultaneously drawn coronary sinus lactate measurement; net myocardial lactate production was never observed (figure 2).

Discussion

This report is the first description of the coronary circulation in human septic shock. The data demonstrate that myocardial depression is not correlated with

FIGURE 1. Mean coronary sinus blood flow (left) and mean cardiac vein blood flow (right) in seven patients with septic shock compared with normal subjects. Flow measurements are stratified into heart rate intervals above and below 100 beats/min. *p < .01; **p < .02 compared with normal subjects.
global reduction in coronary blood flow. Furthermore, coronary perfusion in septic shock is marked by a high coronary sinus oxygen saturation and a low arterial oxygen extraction percentage, abnormalities that also characterize the peripheral vasculature in septic shock.

The determinants of coronary blood flow in the normal human heart have been a subject of extensive study. The myocardium ordinarily maintains nearly complete (70% to 75%) extraction of arterial oxygen, producing coronary sinus oxygen saturations of 25% to 35%. Increases in myocardial oxygen demand, which cannot be met fully by further increases in oxygen extraction, instead are met by changes in coronary blood flow. The vasomotor tone of the coronary circulation is autoregulated so that the availability of oxygen parallels the need for it.

In cardiogenic shock, because arterial oxygen extraction is maximal and coronary blood flow is limited, one would predict that oxygen supply would be inadequate to myocardial demand, resulting in anaerobic metabolism and lactate production. In a study of 18 patients with cardiogenic shock after acute myocardial infarction, coronary blood flow was decreased in all but three patients, despite normal or high myocardial oxygen demand. Myocardial oxygen extraction was above 70% and coronary sinus oxygen tension below 22 mm Hg in most of the patients, and 15 of the 18 patients had net production of lactate by the myocardium. These findings indicate that the myocardial dysfunction of cardiogenic shock is associated with inadequate blood flow to myocardial tissue.

If coronary hypoperfusion were responsible for the myocardial depression observed in human septic shock, one might expect (as in cardiogenic shock) to find inadequate coronary blood flow and net myocardial lactate production. Instead, the findings in these seven patients with septic shock are markedly different. In comparison with control subjects, they manifest an elevated coronary blood flow, particularly at rapid heart rates. The arterial–coronary sinus oxygen content difference is narrowed, the arterial oxygen extraction reduced, and the coronary sinus oxygen tension increased in comparison with those of normal subjects. Myocardial oxygen consumption, normalized for the double product, is normal. The high flow, low vascular resistance, and narrowed oxygen content difference in the coronary circulation in patients with septic shock are analogous to the high cardiac output, low systemic vascular resistance, and narrowed arteriovenous oxygen content difference characteristic of peripheral shunting in the systemic circulation in septic shock. Thus, in septic shock, coronary blood flow is not autoregulated normally, that is, it is not determined purely by myocardial oxygen need.

These findings are consistent with those of some previous animal studies and at variance with others. In pigs given Escherichia coli and studied with radio-

### TABLE 3

Data from four patients who developed transient decreases in radionuclide ejection fraction: mean values before and during myocardial depression

<table>
<thead>
<tr>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 5</th>
<th>Patient 7</th>
<th>Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 3</td>
<td>Day 1</td>
<td>Day 3</td>
<td>Day 1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76</td>
<td>67</td>
<td>94</td>
<td>106</td>
</tr>
<tr>
<td>Coronary sinus flow (ml/min)</td>
<td>86</td>
<td>69</td>
<td>143</td>
<td>205</td>
</tr>
<tr>
<td>Great cardiac vein flow (ml/min)</td>
<td>64</td>
<td>44</td>
<td>57</td>
<td>47</td>
</tr>
<tr>
<td>Arterial–coronary sinus oxygen content difference (ml O₂/100 ml)</td>
<td>9.19</td>
<td>8.26</td>
<td>8.74</td>
<td>8.44</td>
</tr>
<tr>
<td>Oxygen extraction (%)</td>
<td>71</td>
<td>66</td>
<td>64</td>
<td>70</td>
</tr>
<tr>
<td>Coronary sinus oxygen saturation (%)</td>
<td>28</td>
<td>32</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Myocardial oxygen consumption</td>
<td>0.077</td>
<td>0.097</td>
<td>0.097</td>
<td>0.099</td>
</tr>
<tr>
<td>Systolic BP × HR (ml O₂/mm Hg/beat)</td>
<td>3</td>
<td>9</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Lactate extraction (%)</td>
<td>52</td>
<td>42</td>
<td>45</td>
<td>38</td>
</tr>
</tbody>
</table>

For change in ejection fraction, p < .05. For changes in other variables, p = NS.
CUNNION et al.

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Mean values in four patients with and three patients without myocardial depression</th>
<th></th>
<th>TABLE 5</th>
<th>Mean values in four patients receiving norepinephrine and in three patients not receiving norepinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With myocardial depression (patients 2, 3, 5, and 7)</td>
<td>Without myocardial depression (patients 1, 4, and 6)</td>
<td>Receiving norepinephrine (patients 1, 2, 5, and 7)</td>
<td>Not receiving norepinephrine (patients 3, 4, and 6)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>101 ± 10</td>
<td>130 ± 25&lt;sup&gt;A&lt;/sup&gt;</td>
<td>118 ± 19</td>
<td>107 ± 17</td>
</tr>
<tr>
<td>Coronary sinus flow (ml/min)</td>
<td>214 ± 57</td>
<td>433 ± 160&lt;sup&gt;A&lt;/sup&gt;</td>
<td>335 ± 117</td>
<td>272 ± 131</td>
</tr>
<tr>
<td>Great cardiac vein flow (ml/min)</td>
<td>96 ± 24</td>
<td>206 ± 77&lt;sup&gt;A&lt;/sup&gt;</td>
<td>169 ± 62</td>
<td>108 ± 41</td>
</tr>
<tr>
<td>Arterial-coronary sinus oxygen content difference (ml O₂/100 ml)</td>
<td>7.94 ± 0.41</td>
<td>6.82 ± 1.57</td>
<td>6.74 ± 1.03</td>
<td>8.42 ± 0.49</td>
</tr>
<tr>
<td>Oxygen extraction (%)</td>
<td>59 ± 4</td>
<td>51 ± 10</td>
<td>51 ± 8</td>
<td>63 ± 3</td>
</tr>
<tr>
<td>Coronary sinus oxygen saturation (%)</td>
<td>37 ± 3</td>
<td>40 ± 9</td>
<td>43 ± 6</td>
<td>32 ± 1</td>
</tr>
<tr>
<td>Myocardial oxygen consumption (ml O₂/100 mm Hg/min)</td>
<td>0.147 ± 0.032</td>
<td>0.168 ± 0.041</td>
<td>0.161 ± 0.027</td>
<td>0.150 ± 0.048</td>
</tr>
<tr>
<td>Systolic BP × HR</td>
<td></td>
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</tr>
<tr>
<td>Lactate extraction (%)</td>
<td>13 ± 3</td>
<td>19 ± 7</td>
<td>11 ± 4</td>
<td>22 ± 5</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>42 ± 2</td>
<td>55 ± 2&lt;sup&gt;B&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>A</sup>The numerically higher coronary flows in the patients without myocardial depression are attributable to their higher mean heart rates (see text), and the differences are not significant statistically.

<sup>B</sup>Comparing ejection fractions, p < .01. For all other comparisons, p = NS.

labeled microsphere techniques, coronary blood flow was increased, coronary vascular resistance decreased, and coronary venous oxygen content increased compared with baseline values. In isolated perfused cat coronary arteries, endotoxin may augment coronary vasodilatation. Canine studies with a variety of intact animal and isolated heart preparations have generated divergent hypotheses as to the roles of coronary hyperperfusion, cardiotoxic and cardiodepressant humoral substances, and myocardial edema in the pathogenesis of myocardial depression. Those canine studies that assert a principal role for coronary hypoperfusion have major differences from the current investigation of human septic shock in that: (1) canine endotoxic shock, unlike human septic shock, is a low cardiac output preparation, (2) the dogs generally were not resuscitated with fluid from arterial hypotension, hence coronary perfusion pressure was reduced, (3) in most studies, the dogs were anesthetized or the hearts were denervated, removing the influence of conscious autonomic mechanisms, and (4) definitions of myocardial depression differ, with cardiac failure in canine endotoxic shock generally manifested within 4 to 6 hr by short-term rises in left ventricular end-diastolic pressures. In general, the findings of the present human study are similar to those of animal studies that demonstrate a high cardiac output and low systemic vascular resistance, i.e., hyperdynamic preparations of septic shock.

All of the patients in this study received dopamine at 2 µg/kg/min, and several received norepinephrine in various doses. The coronary arteries are known to contain dopaminergic receptors, but there is no experimental evidence in human or in canine studies that dopamine, even at low doses, causes increases in coronary blood flow or decreases in coronary resistance beyond those expected from its α- and β-adrenergic effects and the consequent increases in myocardial oxygen demand. The low doses of dopamine administered to these patients with septic shock almost certainly did not influence coronary flow. Although early studies with norepinephrine in anesthetized dogs concluded that it caused coronary vasodilation, more recent studies have established clearly that norepinephrine causes powerful α-mediated coronary vasoconstriction and that it has no intrinsic vasodilator effects on the coronary circulation in conscious animals. Norepinephrine does not produce effects on coronary flow like those observed in these patients with septic shock. In the present study, patients receiving norepinephrine were compared with patients not receiving it, and no differences in coronary flow or metabolism were found. Furthermore, in several pa-
PATHOPHYSIOLOGY AND NATURAL HISTORY—VENTRICULAR PERFORMANCE

FIGURE 2. A total of 35 pairs of simultaneous arterial and coronary sinus lactate determinations were made in seven patients with septic shock. Left. For each patient, the mean arterial lactate and mean coronary lactate are shown as a pair of points. Right. Each of the 35 pairs of determinations is represented by a line. The arterial lactate invariably is higher than the simultaneous coronary sinus lactate.

tients whose norepinephrine infusions were discontinued during the study, these variables were unchanged. Consequently, it is most unlikely that the coronary circulatory abnormalities observed in this study of human septic shock represent a confounding effect of vasopressors.

The abnormally high coronary sinus oxygen content and low oxygen extraction could reflect high flow through dilated capillaries or a defect in oxygen utilization at the cellular level. Alternatively, there could be anatomic redistribution of intramyocardial blood flow, i.e., blood may be shunting from arteriole to venule without reaching all of the capillary beds. Subendocardial hypoperfusion, with redistribution of flow to the epicardial vessels, has been demonstrated in canine septic shock. Global net lactate extraction can obscure regional lactate production in patients with coronary artery disease. The measurements reported here of coronary blood flow, lactate metabolism, and oxygen extraction reflect the global myocardial circulation. The status of the coronary microcirculation and of regional flow distribution in human septic shock will require further investigation of localized areas of myocardium.

An important objective of this study was to correlate changes in ejection fraction with changes in coronary blood flow, myocardial lactate extraction, and myocardial oxygen utilization. No such correlations were found in the four patients with myocardial depression. The persistence of high coronary blood flow, net lactate extraction, excess oxygen availability with submaximal oxygen extraction, and a normal ratio of myocardial oxygen consumption to the double product exclude global myocardial ischemia as the cause of myocardial depression.

In conclusion, the coronary circulation in human septic shock displays abnormalities similar to those of the systemic circulation. The cause of the myocardial depression does not appear to be reduced coronary blood flow, and other possible mechanisms of myocardial dysfunction are being investigated. Recent studies provide evidence that a circulating myocardial depressant substance might be a major factor in myocardial dysfunction during human septic shock.

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