Myocardial and Body Metabolism in Fatal Cardiogenic Shock after Valvular Replacement

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SUMMARY
Cellular energy substrates and metabolites, electrolytes, oxygenation, and acid-base balance, in arterial and coronary sinus blood of seven adult patients who died after valvular replacements, were studied and compared with these measurements from five patients having aortic replacement who survived. Six of the patients were in New York Heart Association class IV. All but one died within 24 hr of acute circulatory failure, with excessive bleeding being a contributing factor. Plasma potassium and osmolality remained higher in the first postoperative hours in nonsurvivors. Ketone bodies, growth hormone, and lactate levels rose precipitously as shock became severe. Increased arterial blood osmolality and potassium, plus a still-rising lactate concentration, were evident 2 hr after operation in patients who died in the next 24 hr. Low cardiac output, hyperosmolality, and the degree of lactic acidosis were the only early changes predicting the fatal outcome.

Additional Indexing Words: Energy metabolism Postoperative mortality Lactic acidosis Open-heart surgery

INABILITY of the myocardium to maintain sufficient contractility for a satisfactory circulation is the most frequent cause of death after open-heart operations. Acute failure, or low output syndrome, causes deficient perfusion of body tissues. Profound effects on cellular oxygenation, energy metabolism, acid-base balance, and electrolyte patterns occur in the end stages of shock, including that of the cardiogenic type.1 We had the opportunity to follow these metabolic changes until death in seven critically ill patients who died after valvular surgery. They were the nonsurvivors from a group of 85 patients2–7 in whom we have studied the myocardial and whole-body metabolic response during and after whole-body perfusion for repair of acquired and congenital lesions. The data from analysis of arterial and coronary sinus blood, and from cardiac output, from these nonsurvivors are compared with those from five patients who survived aortic valve replacement. Our purpose was to ascertain whether changes in metabolism could be detected early in postoperative shock, and possibly lead to better and successful treatment.

Methods

Information on Patients
Clinical details on the seven patients and their operative courses are shown in table 1. All were in New York Heart Association functional class IV, except patient 6 who was in class III. All had
been taking digitalis, and all but one, diuretics. All therapeutic manipulations possible and available to us were used postoperatively, including mechanical ventilation via endotracheal tube, digitalis (when indicated), isoproterenol by drip, and adjustment of blood volume as allowed by monitoring of right atrial, left atrial, and arterial pressures. Despite these combinations of treatment, the downhill course continued with ventricular fibrillation being the usual terminal event, after a prolonged period of severely depressed cardiac output. A fresh left ventricular infarct was found at autopsy in two instances.

The group used for comparison consisted of five patients surviving aortic valve replacement.2 No significant differences were found in previous similar studies between patients having aortic replacement and those more seriously ill patients having double valve replacements,5 or those in other studies having similar hormonal determinations.7

**Management in the Operating Room**

Anesthesia and supportive care were as previously reported.2 Perfusing flow averaged 2.4 liters/min/m² at 30°C except for patient 7 (36°C). In all cases involving aortic valve replacement direct perfusion of both coronary arteries was done, except in patient 2 in whom the right coronary artery was not able to be cannulated. The priming solution for the vertical sheet oxygenator was two-thirds acid-citrate-dextrose (ACD) blood diluted with 5% dextrose in 0.45% NaCl and tris(hydroxymethyl)aminomethane (THAM). All valve prostheses were of the Starr-Edwards type.

**Protocol**

Arterial blood was drawn before induction of anesthesia, with the patient breathing air. After thoracotomy, a small catheter was inserted deep into the coronary sinus, initially via the right atrium and after the onset of perfusion through the wall of the coronary sinus. Serial samples were taken simultaneously of arterial and coronary venous blood throughout perfusion and operation, and postoperatively for 3 days. The fractional concentration of O₂ in inspired gas (F₀₂) was 0.4–0.5 during anesthesia, 0.98 during perfusion, and 0.4–1.0 from the ventilator after operation.

Biochemical analyses of blood were performed as previously outlined,2 for electrolytes (Na, K, and Ca), osmolality, and energy-producing substrates: glucose, nonesterified fatty acids (NEFA), total ketone bodies, lactate, and pyruvate. Blood gases were determined by electrodes at 37°C, and temperature corrections were made when body temperature was below

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**Table 1**

<table>
<thead>
<tr>
<th>No.</th>
<th>Patient Data</th>
<th>Age</th>
<th>Sex</th>
<th>Wt.</th>
<th>Surface area (m²)</th>
<th>Operation</th>
<th>Perfusion time (min)</th>
<th>Survival postop (hr)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>52</td>
<td>F</td>
<td>124</td>
<td>1.46</td>
<td>Aortic &amp; mitral replacement</td>
<td>121</td>
<td>23</td>
<td>LV infarct postop</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>56</td>
<td>M</td>
<td>118</td>
<td>1.60</td>
<td>Aortic &amp; mitral replacement</td>
<td>137</td>
<td>10</td>
<td>Heavy bleeding, tamponade</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>44</td>
<td>M</td>
<td>132</td>
<td>1.68</td>
<td>Aortic &amp; mitral replacement</td>
<td>132</td>
<td>30</td>
<td>Pulmonary edema 1 day postop</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>19</td>
<td>M</td>
<td>113</td>
<td>1.59</td>
<td>Aortic &amp; mitral replacement</td>
<td>141</td>
<td>30</td>
<td>Ventricular arrhythmias postop</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>68</td>
<td>F</td>
<td>110</td>
<td>1.56</td>
<td>Mitral replacement</td>
<td>80</td>
<td>11</td>
<td>Two previous closed commissurotomy; heavy bleeding postop</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>54</td>
<td>M</td>
<td>156</td>
<td>1.30</td>
<td>Aortic replacement &amp; tubular aortic graft</td>
<td>123</td>
<td>18</td>
<td>Dissecting aneurysm postop</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>75</td>
<td>F</td>
<td>76</td>
<td>1.28</td>
<td>Aortic replacement &amp; tubular aortic graft</td>
<td>94</td>
<td>24</td>
<td>Ventricular infarct; LV infarct postop</td>
</tr>
</tbody>
</table>

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Figures 1 and 2

**Figure 1**
Plasma sodium was lower during operation, and hyperosmolality was present preterminally in nonsurvivors.

Abbreviations for all figures: NEFA = nonesterified fatty acids; IRI = immunoreactive insulin; GIK = glucose-insulin-potassium.

**Figure 2**
Cardiac index was markedly low early after operation; growth hormone increased steeply before death.

36°C. Oxygen content of hemoglobin was calculated from oxygen saturation. Plasma immunoreactive insulin (IRI) and growth hormone concentrations were measured by double antibody...
Cardiac output was obtained by dye dilution, with injection of indocyanine green via a left atrial catheter and blood sampling from a catheter in the thoracic aorta.

Analyses of paired data were performed by the Student t-test in the nonsurvivor group, comparing arterial to coronary sinus levels at each sample time and subsequent arterial levels to the control taken before anesthesia. Comparisons between arterial levels in the nonsurvivor and survivor groups were also made (unpaired data) using the t-test. Only differences significant at the 5% level, or greater, are reported.

Results

Mean concentrations of variables in arterial and coronary sinus blood, plus cardiac index, for both groups are shown in figures 1–5, with identification of significant arterial-coronary sinus differences.

Nonsurvivor Group

Mean arterial $P_{\text{O}_2}$ ($P_{\text{aO}_2}$) remained above the preanesthetic level all of day 1, while oxygen content was below control early in perfusion from hemodilution. Arterial $P_{\text{CO}_2}$ ($P_{\text{aCO}_2}$) was below and pH above control during perfusion; buffer base was below control 2 hr postoperatively. Plasma sodium fell during perfusion, because of dilution. Plasma osmolality, potassium, and calcium became elevated above control on beginning perfusion and remained so through the morning of day 2, instead of decreasing shortly after the end of operation as in the other group. Blood glucose increased before perfusion without any being infused; the high level in the priming solution caused elevated blood levels through the remainder of day 1. IRI increased from the end of perfusion through the end of operation. NEFA were higher than control before and during perfusion but fell shortly after perfusion. Ketone bodies were elevated before and during perfusion and became extremely high preterminally. Growth hormone had two periods of increase: at the end of operation, and then an even higher one preterminally on the next morning. Cardiac index was lower 2 hr postoperatively than before perfusion. Lactate increased steadily from preperfusion, with a marked elevation before death. Pyruvate similarly was above control at all subsequent sample times.

Comparison Between Survivor and Nonsurvivor Groups

Table 2 focuses on pertinent findings from the end of operation through the next morning, when the last preterminal sample was taken. No differences in arterial oxygenation or acid-base balance were found. Coronary sinus oxygen tension was lower in nonsurvivors during perfusion and from the end of operation through the next morning. Similarly oxygen content was lower in coronary sinus blood of nonsurvivors from the end of perfusion through 2 hr postoperatively. Cardiac index in nonsurvivors was lower, and growth hormone, lactate, and osmolality higher, on the morning of day 2. Plasma potassium was higher in nonsurvivors from the end of operation through the next morning.

![Figure 3](https://circ.ahajournals.org/)

Figure 3

* Ketone bodies were elevated at all times, and highest preterminally; NEFA were not different between groups postoperatively.
Blood glucose level was higher in nonsurvivors early postoperatively, and both blood glucose and IRI fell by the next morning.

Lactate rose steadily postoperatively in nonsurvivors, while it fell in survivors.
Table 2

Differences Between Groups: Mean Levels and Significance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>End of operation</th>
<th>2 hr postop</th>
<th>Morning of day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index (liters/min/m²)</td>
<td>Survivors</td>
<td>NS</td>
<td>2.18</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Nonsurvivors</td>
<td></td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td>Osmolality (mOsm/kg H₂O)</td>
<td>Survivors</td>
<td>NS</td>
<td></td>
<td>280</td>
</tr>
<tr>
<td></td>
<td>Nonsurvivors</td>
<td></td>
<td></td>
<td>301</td>
</tr>
<tr>
<td>K (mEq/liter)</td>
<td>Survivors</td>
<td>3.64</td>
<td>P &lt; 0.05</td>
<td>3.73</td>
</tr>
<tr>
<td></td>
<td>Nonsurvivors</td>
<td>4.44</td>
<td></td>
<td>4.47</td>
</tr>
<tr>
<td>Na (mEq/liter)</td>
<td>Survivors</td>
<td>138</td>
<td>P &lt; 0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonsurvivors</td>
<td>133</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/100 ml)</td>
<td>Survivors</td>
<td>NS</td>
<td>153</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Nonsurvivors</td>
<td></td>
<td>243</td>
<td></td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>Survivors</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonsurvivors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ketones (mg/ml)</td>
<td>Survivors</td>
<td>14.7</td>
<td>P &lt; 0.05</td>
<td>13.2</td>
</tr>
<tr>
<td></td>
<td>Nonsurvivors</td>
<td>24.9</td>
<td></td>
<td>25.1</td>
</tr>
<tr>
<td>Lactate (mmole/liter)</td>
<td>Survivors</td>
<td>NS</td>
<td>3.33</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Nonsurvivors</td>
<td></td>
<td>5.84</td>
<td></td>
</tr>
<tr>
<td>Pco₂ (mm Hg)</td>
<td>Survivors</td>
<td>25.2</td>
<td>P &lt; 0.05</td>
<td>25.2</td>
</tr>
<tr>
<td></td>
<td>Nonsurvivors</td>
<td>18.4</td>
<td></td>
<td>17.5</td>
</tr>
<tr>
<td>Growth hormone (ng/ml)</td>
<td>Survivors</td>
<td>NS</td>
<td>7.7</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Nonsurvivors</td>
<td></td>
<td>48.8</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NEFA = nonesterified fatty acids; Pco₂ = tension of oxygen in coronary sinus; NS = not significant; P < 0.05.

Sodium remained lower in nonsurvivors, compared to the level before anesthestia, through the end of operation. Blood glucose was higher in nonsurvivors 2 hr postoperatively, with no differences in IRI between groups. Before perfusion NEFA were more elevated in the survivor group than in nonsurvivors. Total ketone bodies remained higher in nonsurvivors from the end of operation through the final sampling on the next morning.

Blood Loss

Mean volume of drainage from chest tubes from the end of operation until midnight for the nonsurviving patients was 2,280 ml, while blood replacement averaged 3,230 ml for that period. In comparison, mean volume of chest drainage in the aortic valve replacement group for the same period was 850 ml.

Discussion

Several factors contributed to the fatal outcome. These patients were critically ill, in advanced stages of their disease. In every case but one, more than replacement of one valve was required, with five of the perfusions lasting over 2 hr. The hearts were grossly enlarged with reduced contractility. Cardiac index before perfusion averaged below 2 liters/min, and the sizeable increase in index seen with stronger hearts after valve replacement did not occur. The mean index 2 hr after operation, of 1.2 liters/min, revealed the severity of cardiogenic depression present early in the interval between operation and death. All resuscitative measures were ineffective, and ventricular arrhythmias were prominent in the final hours.

Though death was attributed to myocardial and circulatory failure, an additional critical factor was excessive bleeding. During and after these longer perfusions more blood than usual had to be transfused in the operating room. Impaired coagulation of blood continued postoperatively. Reopening of the thoracotomy was necessary in one patient and acute tamponade occurred in another, so that tamponade may have been primarily responsible for the demise of these two patients. The mean volume of chest drainage for the first 10 hr was four times that during 24 hr after multivalvular replacement in another series.¹¹

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With the circulation precarious from poor myocardial contractility, the adverse effects on
the heart of large amounts of ACD blood, and retension of blood in the pericardium, probably served to tip the scale against survival.

Both oxygenation and acid-base balance of the arterial blood remained satisfactory in relatively prolonged cardiogenic shock in patients on ventilators. The extreme degree of extraction of oxygen by one tissue, the myocardium, is evident from the low oxygen content of coronary sinus blood. Little evidence of electrolyte exchanges across the heart was detected. The only consistent finding was a higher coronary sinus content of sodium, possibly due to a loss of water from blood to myocardium. Evidence of water loss from blood to the interstitial space, or of solute entering the plasma, appears in the increased osmolality postoperatively. Patients progressing well in the first 24 hr after operation diurese both water and potassium, and often need extra potassium to avoid or treat ventricular hyperirritability. However, the patient in shock develops hemoconcentration, elevated plasma potassium, high catecholamine levels, and, as in these patients, arrhythmias. Another explanation for the elevated plasma potassium may be the excessive amount in the large volume of whole blood transfused.

The effects of cardiogenic shock on energy metabolism are multiple, with a host of interrelated actions and feedback effects. Diminution of oxygen supply to cells impairs oxidative phosphorylation, and the severe preterminal rise in lactate attests to the high rate of anaerobic metabolism of glucose and glycogen. Patients with an adequate circulation began to reduce their arterial levels of lactate and pyruvate by the end of operation. Those who died within 24 hr continued to increase their arterial lactate levels and to lose pyruvate from the myocardium up to the time of their death.

Blood levels of the catecholamines increase with various stresses, including open-heart surgery. Growth hormone also is released in greater amounts during stress as well as in hypoglycemia, exercise, and fasting. Growth hormone values in these patients in cardiogenic shock became five times normal before death. According to Randle and associates, the body uses for energy predominantly glucose or lipid, depending on glucose intake or hormonal stimulation. The stress hormones stimulate lipid mobilization tending to elevate circulating levels of NEFA. With unavailability of underuse of carbohydrate, ketone bodies are produced in the liver from acetyl coenzyme A that cannot enter the Krebs cycle. The severe ketosis before death shows the high rate of NEFA metabolism in the liver, with ketone bodies produced faster than other tissues could use them. Accumulation of NEFA, unbound to protein, in hypoxic myocardial cells is hypothesized as causing arrhythmias after acute infarction. Certainly our nonsurvivors suffered severe NEFA mobilization and had ventricular arrhythmias in their final hours.

The stress hormones enhance glycogenolysis in the liver and muscles, possibly accounting for the higher blood glucose levels toward the end of operation in nonsurvivors than in survivors. The pancreas was still able to respond with a high rate of IRI release, or the rate of its inactivation may have been slowed. However, on the next morning, after hours of inadequate circulation, both blood glucose and IRI had fallen. The catecholamines inhibit both IRI release and its effects in the cell. By this time glucose and glycogen supplies were likely depleted from the massive production of lactate. Central to the concept of the glucose-fatty acid cycle is that NEFA and ketone bodies inhibit glucose uptake by muscle. During operation the myocardium used NEFA, ketone bodies, and lactate, but a significant arteriovenous difference of glucose was not found. With both blood glucose and IRI reaching low levels in shock, with IRI activity depressed in cardiogenic shock and with the known ability of IRI to decrease mobilization of fat, the administration of additional glucose to these patients, possibly also with insulin, may be an effective method of treatment.
The relative lack of changes in the constituents of blood early in cardiogenic shock that might help in predicting prognosis and in treatment is disappointing. Many findings were similar in patients doing well and those with low output, until just before death. Arterial oxygenation and acid-base balance remained satisfactory as long as sampled. Sodium and calcium levels were not different. Neither were fatty acid, blood glucose, or IRI concentrations of help in this regard. Both growth hormone and total ketone bodies rose severely but only shortly before death. However, a few positive signs did appear early after operation. Plasma potassium remained in normal range. Osmolality remained elevated instead of falling, at the end of operation, in patients who died within 24 hr, indicating a deteriorating circulation. A rising, instead of a falling, lactate concentration without pyruvate change, in the early postoperative hours, reflected the low cardiac output at that time. Both the high lactate and low cardiac output were grave prognostic signs. Serial monitoring of cardiac output is probably the most valuable measurement in anticipating a grave prognosis and in evaluating the effect of therapeutic efforts.

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References
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It is known that, when the vectorcardiogram is observed in a single plane, the greatest accuracy in interpretation is attained by using the horizontal plane. In order to obtain the "color vectorcardiogram," therefore, a vector loop in the horizontal plane was usually employed. In cases in which the amplitude of the deflection in the Y axis was unusually large or unusually small, the sensitivity to the voltage in the Y axis was respectively decreased or increased to such an extent that differences in color of the spots could be readily appreciated.

We think that the use of these procedures, as compared with the use of three-plane vectorcardiograms, can remove the above-mentioned complication in the graphic interpretation, without greatly diminishing the accuracy.

References


Correction