Experimental and Clinical Studies on Lactate and Pyruvate as Indicators of the Severity of Acute Circulatory Failure (Shock)

By Max Harry Weil, M.D., Ph.D., and Abdelmonen A. Affifi, Ph.D.

SUMMARY
The increase in lactate (L) and pyruvate (P) content of arterial blood during experimental and clinical shock states and the extent to which such increases serve as measures of oxygen deficit and irreversible injury were investigated on an empirical basis.

A standardized method for production of hemorrhagic shock in the Wistar rat was employed. During a 4-hour bleeding period, oxygen consumption of the rat was reduced to approximately 40% of control value, pH was reduced from 7.39 to 7.08, and a concurrent increase in L from 0.80 to 6.06 mM and in P from 0.07 to 0.18 mM were observed. Cumulative oxygen debt correlated with log L (r = 0.50; P < 0.0005) and both were significantly related to survival. Correlation of cumulative oxygen debt and survival, both with P and with computed values of the lactate pyruvate ratio (L/P) and excess lactate (XL), were of no higher magnitude. Partial correlation analysis demonstrated that neither the measurement of P nor the computation of L/P or XL improved predictability.

In 142 patients who presented with clinical manifestation of circulatory shock and of whom 62 survived and 80 died, the best empirical discrimination between survivors and those who died was provided by measurement of L, which failed only 11% of the time. This was confirmed by discriminant function analysis in which the percentage probability of misclassification based on L was 12% whereas this probability increased to 21% with L/P and 19% with XL. The combination of XL and L/P with L failed to improve discrimination. In this series of patients, L served as a sensitive predictor; as L increased from 2.1 to 8.0 mM, the estimated probability of survival decreased from 90 to 10%.

These studies corroborate that L alone serves as a reliable indicator, but neither the measurement of P nor the computation of L/P or XL was shown to improve either the reliability of L as a measure of cumulative oxygen debt or its value as a prognosticator of survival during shock states.

Additional Indexing Words:
Blood pressure  Heart rate  Oxygen consumption  Blood pH
Prognosis for survival  Statistical analysis

The physiologic defect which accounts for the clinical manifestations of circulatory shock is a critical reduction in blood flow.

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The experiments reported were conducted according to the Principles of Animal Care of the National Society for Medical Research.

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and, hence, critical curtailment in the transport of vital nutrients to sustain the metabolic requirements of organs and tissues. When the cardiac output or the distribution of blood flow is inadequate, whether due to a deficit of blood volume, cardiac failure, vascular obstruction, bacterial infection, endocrine malfunction, or anaphylaxis, the delivery of oxygen is curtailed. The severity of oxygen deprivation determines the extensiveness of cellular dysfunction and ischemic injury. Experimentally, the reduction in oxygen consumption during shock is predictably related to survival.¹

In patients, opportunity for hemodynamic and metabolic measurements under controlled conditions prior to onset of shock is rarely available. Unless the normal oxygen requirements for an individual are known prior to the onset of shock, the estimate of oxygen consumption, which is based on repetitive measurements during the shock state, may not indicate the cumulative oxygen deficit. Moreover, the measurement is in itself technically difficult. Current technics of gas collection for measurement of oxygen consumption have limited reliability when applied to patients who are too ill to cooperate. For this reason investigators have sought indirect measurements of oxygen consumption or oxygen deficit. Repetitive measurements of lactate (L) and pyruvate (P) in arterial blood have been of particular interest for this purpose.²-⁴

During periods in which metabolism is sustained by anoxic energy exchange, the metabolic fate of P is temporarily altered. Aerobic oxidation in the tricarboxylic acid cycle is blocked.⁵,⁶ The oxidation of nicotinamide-adenine dinucleotide (NADH₂) to its oxidized form (NAD) is controlled by a lack of oxygen. The buildup of NAD in the presence of lactic dehydrogenase shifts the equilibrium of the reaction to favor lactate accumulation. At the same time, the transformation of NADH₂ to NAD during the conversion of pyruvic to lactic acid allows partial glycosis to proceed without obligatory rejuvenation of NAD by oxygen. Therefore, circulatory anoxia accounts for the accumulation of L, and in part, for the progressive acidosis characteristic of shock.

A series of important studies on the relationship of blood lactic acid concentration and oxygen deficiency has been made by Huckabee.²,⁵,⁷ In studies on human subjects during exercise, the author related oxygen deficit to an excess of lactate (XL), defined as:

\[
XL = (L_t - L_o) - (P_t - P_o) \frac{L_o}{P_o},
\]

where \( L_t \) = lactate at time \( t \), \( L_o \) = normal lactate during the basal state, \( P_t \) = pyruvate at time \( t \), and \( P_o \) = normal pyruvate during the basal state. The estimate of oxygen deficit is based on measurement of both L and P. Huckabee has presented theoretical and empirical justification for this formulation which has more recently been the subject of both theoretical and experimental disagreement.⁸-¹² The purpose of the present work was to provide additional insight by an empirical examination of concurrent changes in L and P and oxygen utilization during experimental and clinical shock states.

In the studies which are the subject of this report, experiments were performed on rats which served as a model of hemorrhagic shock. The relationship between oxygen deficit and the concurrent alterations in the L and P content of arterial blood during shock were examined. As part of this effort, we sought additional understanding of the values derived from the primary measurements of L and P, that is, XL and the lactate-pyruvate ratio (L/P). To test applicability to patients, we then measured arterial L and P concentrations in a large series of patients observed in our shock ward. Data on patients, previously published from our laboratory,⁹ had indicated that survival was competently estimated from XL, but we had not established whether either XL or L/P was a better indicator of survival than L alone.

**Experimental Studies**

**Methods**

A standardized method for production of hemorrhagic shock in the rat has been previously...
LACTATE AND PYRUVATE IN SHOCK

Purina hexachlorophene (pHisoHex) rats were studied. Animals were housed in groups of six in standard cages in an air-conditioned room and supplied ad libitum with Purina laboratory chow and tap water. The rats had been observed in the vivarium for a minimum period of 7 days prior to experimentation and were certified as being in good health by the staff veterinarian. Food, but not water, was withheld for 24 hours prior to the acute experiment.

Animals were sedated by the intraperitoneal injection of paraldehyde, 1 mg/kg, and this was supplemented by local injection of 1 ml of lidocaine in a 1% solution into the femoral area. The rats were then placed on a surgical board in the supine position, and the hind limbs were fixed in full abduction by adhesive strips. The groin area was prepared with surgical detergent, hexachlorophene (pHisoHex) and washed with antiseptic 1:750 benzalkonium (Zephiran) chloride.

Using aseptic technic, the left femoral artery was exposed through a longitudinal incision extending distally for 2.5 cm from the midpoint of the inguinal ligament. The artery was isolated with minimal dissection and cannulated with a polyethylene catheter 22 cm long.* Heparin sodium was injected through the arterial cannula immediately after completion of cannulation in amounts of 100 units/kg of rat weight. An arterial catheter was then filled with 1 ml of physiologic saline containing 5 units of heparin per milliliter and connected to the barrel of a 20-ml plastic syringe which served as a reservoir for bleeding of the animal. The pressure in the reservoir was controlled by a mercury manometer system. A three-way stopcock was employed for intermittent measurement of arterial pressure and for obtaining samples of blood. Arterial pressure was measured by use of a Statham 23 Db pressure transducer in conjunction with a Sanborn multichannel recorder. Pulse rate was computed at hourly intervals from a record of arterial pressure pulses. Pressure in the reservoir was maintained at 35 mm Hg for a period of 240 min. Because of the high resistance in the catheter, there was a gradual decline in the arterial pressure over the period of bleeding of 240 min (fig. 1). The total volume bled into the reservoir at the end of 240 min ranged from 6.4 to 16.8 (mean, 10.7; SEM ± 0.2) ml. Between 240 and 250 min, blood was reinfused by increasing the pressure in the reservoir to 200 mm Hg above that observed during the control period. At 250 min, 20 of the rats received various medications for the purpose of an unrelated experiment and were, therefore, excluded from analysis of survival.

Blood pH, hematocrit, L, and P were measured in samples of arterial blood during the control period and also at intervals of 1 hour. Immediately prior to the withdrawal of blood, the animal received 1 ml of donor blood obtained from an animal of the same colony. Experimental proof of the compatibility of donor blood from animals of the same strain was demonstrated by cross-transfusion of 15 rats which resulted in no adverse effects during the subsequent 7-day period. The pH was analyzed with the use of a radiometer microelectrode system. L and P concentrations in arterial blood were analyzed by the method of Marbach and Weil.18 Animals received a total of approximately 2 ml of heparinized saline by intermittent flush with a tuberculin syringe during the 6-hour period of study. A total of 0.5 mg of protamine sulfate in a 1% solution was injected intra-arterially prior to removal of the catheter. The artery was ligated proximally and distally, and the skin was closed with continuous nylon sutures. The operative site was inspected at regular intervals in the subsequent 24-hour period, and in no instance was further bleeding detected.

For measurement of oxygen consumption, each of the animals was placed in a chamber fashioned from 1-gallon mayonnaise jars. Three 17-gauge needles were fused to the metal cover of the jars to serve for exit of up to three catheters. A Luer opening through the gas-tight metal cover was used for connection of a miniature spirometer. A second Luer Lok connection was used to

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*PE 50 Intramedic, Clay-Adams, Parsippany, New Jersey.

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Figure 1

The effect of hemorrhage on mean values of arterial blood pressure, heart rate, arterial blood pH, and on oxygen consumption is demonstrated. After 240 min of hemorrhage, all blood was reinfused.
Table 1

Average Value and Standard Error of Measurements on Animals

<table>
<thead>
<tr>
<th>Measurements</th>
<th>0</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>310</th>
<th>370</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td>124 ± 1.5</td>
<td>97 ± 3.0</td>
<td>74 ± 3.4</td>
<td>50 ± 2.3</td>
<td>36 ± 0.9</td>
<td>93 ± 3.9</td>
<td>82 ± 4.1</td>
</tr>
<tr>
<td>Heart rate (/min)</td>
<td>379 ± 5</td>
<td>347 ± 8</td>
<td>315 ± 7</td>
<td>261 ± 9</td>
<td>244 ± 9</td>
<td>229 ± 11</td>
<td>239 ± 11</td>
</tr>
<tr>
<td>O₂ consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ml/hr</td>
<td>423 ± 10</td>
<td>342 ± 10</td>
<td>285 ± 8</td>
<td>217 ± 11</td>
<td>173 ± 9</td>
<td>229 ± 16</td>
<td>205 ± 16</td>
</tr>
<tr>
<td>ml/kg/hr</td>
<td>1209 ± 34</td>
<td>957 ± 29</td>
<td>812 ± 27</td>
<td>613 ± 34</td>
<td>497 ± 247</td>
<td>655 ± 52</td>
<td>573 ± 47</td>
</tr>
<tr>
<td>pH (units)</td>
<td>7.395 ± 0.007</td>
<td>7.320 ± 0.009</td>
<td>7.262 ± 0.019</td>
<td>7.180 ± 0.022</td>
<td>7.077 ± 0.024</td>
<td>7.145 ± 0.028</td>
<td>7.160 ± 0.021</td>
</tr>
<tr>
<td>Lactate (nm)</td>
<td>0.80 ± 0.04</td>
<td>2.45 ± 0.29</td>
<td>4.18 ± 0.42</td>
<td>5.10 ± 0.47</td>
<td>6.06 ± 0.49</td>
<td>4.37 ± 0.52</td>
<td>4.49 ± 0.56</td>
</tr>
<tr>
<td>Pyruvate (nm)</td>
<td>0.067 ± 0.004</td>
<td>0.150 ± 0.013</td>
<td>0.177 ± 0.012</td>
<td>0.180 ± 0.013</td>
<td>0.181 ± 0.011</td>
<td>0.151 ± 0.016</td>
<td>0.120 ± 0.011</td>
</tr>
<tr>
<td>Log L</td>
<td>-0.13 ± 0.03</td>
<td>0.24 ± 0.08</td>
<td>0.51 ± 0.05</td>
<td>0.62 ± 0.05</td>
<td>0.68 ± 0.05</td>
<td>0.55 ± 0.06</td>
<td>0.56 ± 0.06</td>
</tr>
<tr>
<td>Log P</td>
<td>-1.20 ± 0.02</td>
<td>-0.93 ± 0.06</td>
<td>-0.81 ± 0.03</td>
<td>-0.79 ± 0.03</td>
<td>-0.80 ± 0.03</td>
<td>-0.89 ± 0.05</td>
<td>-0.96 ± 0.04</td>
</tr>
<tr>
<td>L/P</td>
<td>13.3 ± 0.84</td>
<td>17.5 ± 1.49</td>
<td>24.8 ± 2.15</td>
<td>30.0 ± 2.58</td>
<td>34.8 ± 2.42</td>
<td>30.0 ± 2.33</td>
<td>36.1 ± 4.22</td>
</tr>
<tr>
<td>Log L/P</td>
<td>1.07 ± 0.03</td>
<td>1.16 ± 0.05</td>
<td>1.32 ± 0.04</td>
<td>1.41 ± 0.04</td>
<td>1.49 ± 0.03</td>
<td>1.44 ± 0.04</td>
<td>1.53 ± 0.05</td>
</tr>
<tr>
<td>XL (mm)</td>
<td>1.81 ± 0.37</td>
<td>2.71 ± 0.41</td>
<td>3.71 ± 0.42</td>
<td>2.32 ± 0.37</td>
<td>2.74 ± 0.49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Results**

The average value and standard error for each of the measurements obtained at hourly intervals are shown in Table 1.

Arterial pressure. The typical decline in arterial pressure during the 240-min interval of hemorrhage is graphically shown in Figure 1. After restitution, there was a marked increase in the mean arterial pressure, but the increase was substantially less than those which were observed during the control period. A progressive decrease rather than an increase in heart rate occurred during the bleeding period and was followed by a marked increase in heart rate subsequent to the control period. The decline in pulse rate paralleled the decrease in RPP during the hemorrhage. The treatment of these data showed that the relationship between these variables was not linear, but was better described by a polynomial equation. The correlation coefficient for the linear relationship was 0.95, and for the second-order polynomial, it was 0.99. These results are similar to those reported by others.

Computation of the relationship between arterial pressure and heart rate was performed using correlation and regression techniques to obtain the best fit for the data. The correlation coefficient for the relationship between arterial pressure and heart rate was 0.95. The results of the analysis are shown in Table 1. The time required for the arterial pressure and heart rate to return to control values after the bleeding period was approximately 60 min.

The results of the present study show that hemorrhage causes a significant decrease in arterial pressure and an increase in heart rate. The decrease in arterial pressure is due to the decrease in blood volume, which is compensated by an increase in heart rate. The increase in heart rate is due to the increase in sympathetic activity, which is stimulated by the decrease in arterial pressure.

**Discussion**

The results of the present study show that hemorrhage causes a significant decrease in arterial pressure and an increase in heart rate. The decrease in arterial pressure is due to the decrease in blood volume, which is compensated by an increase in heart rate. The increase in heart rate is due to the increase in sympathetic activity, which is stimulated by the decrease in arterial pressure. The results of the present study are consistent with the results of other studies, which have shown that hemorrhage causes a decrease in arterial pressure and an increase in heart rate.

**Conclusion**

The results of the present study show that hemorrhage causes a significant decrease in arterial pressure and an increase in heart rate. The decrease in arterial pressure is due to the decrease in blood volume, which is compensated by an increase in heart rate. The increase in heart rate is due to the increase in sympathetic activity, which is stimulated by the decrease in arterial pressure. The results of the present study are consistent with the results of other studies, which have shown that hemorrhage causes a decrease in arterial pressure and an increase in heart rate.
Figure 2
Sequential changes in mean values of the concentration of L and P in arterial blood during hemorrhage and following reinfusion. Also shown are the derived parameters, L/P and XL.

reduction in mean arterial pressure. After reinfusion of blood, however, no significant increase in heart rate was observed.

Oxygen Consumption
A striking reduction in the oxygen consumption occurred during the bleeding period (fig. 1). The mean value of oxygen consumption at 240 min and immediately prior to reinfusion of blood was approximately 40% of that observed prior to hemorrhage. One hour after reinfusion of blood the mean value of oxygen consumption increased to 54% of the control value, but no further increase was observed during the second hour.

Arterial Blood pH
Following onset of hemorrhage, there was progressive reduction in arterial blood pH from an average of 7.395 to a minimal value of 7.077 at the end of the bleeding period. A slight increase in blood pH followed reinfusion of blood (fig. 1).

Arterial L and P
The arterial L increased from an initial mean of 0.80 to 6.06 mM at the end of the bleeding period. After reinfusion of blood, only a moderate decline was observed during the following 2 hours. Arterial P increased from a mean value of 0.07 to 0.18 mM during the following 2 hours. The progressive increases in the computed values of L/P and XL were similar to changes in L and P, and these relationships are graphically shown in figure 2. That the log values, that is, log L, log P, and log L/P, exhibit the same general behavior is shown in figure 3.

Survival and Its Relationship to Oxygen Consumption
The 33 animals which were observed for periods of 168 hours after the completion of the 370-min experiment were divided into three groups. The first group included the rats which survived 4 hours or less. The second group included those rats which survived more than 4 hours but no longer than 12 hours. The third group consisted of all rats who survived for more than 12 hours after the completion of the experiment.

The purpose of the partition was to provide reference groups by which objective measurements and particularly oxygen consumption could be related to the survival under the conditions of these experiments. The choice of survival intervals reflected the segments of survival time which included approximately equal numbers of animals in each group. The results of the metabolic measurements are
Table 2
Results of Metabolic Measurements in the Animals

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Time (min)</th>
<th>0-4 hr (13 animals; mean ± SEM)</th>
<th>4-12 hr (12 animals; mean ± SEM)</th>
<th>&gt;12 hr (8 animals; mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td>0</td>
<td>124 ± 4</td>
<td>121 ± 3</td>
<td>121 ± 4</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>74 ± 10</td>
<td>72 ± 5</td>
<td>93 ± 7</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>37 ± 3</td>
<td>34 ± 1</td>
<td>38 ± 2</td>
</tr>
<tr>
<td></td>
<td>310</td>
<td>96 ± 6</td>
<td>100 ± 4</td>
<td>102 ± 10</td>
</tr>
<tr>
<td></td>
<td>370</td>
<td>80 ± 8</td>
<td>89 ± 5</td>
<td>91 ± 11</td>
</tr>
<tr>
<td>Lactate (mm)</td>
<td>0</td>
<td>1.0 ± 0.1</td>
<td>1.2 ± 0.3</td>
<td>0.8 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>120*</td>
<td>8.0 ± 2.7</td>
<td>4.5 ± 1.1</td>
<td>4.2 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>240†</td>
<td>8.2 ± 0.8</td>
<td>6.1 ± 1.3</td>
<td>4.2 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>310</td>
<td>4.7 ± 0.8</td>
<td>4.4 ± 1.0</td>
<td>3.3 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>370</td>
<td>4.9 ± 0.7</td>
<td>4.0 ± 0.8</td>
<td>4.4 ± 1.2</td>
</tr>
<tr>
<td>Pyruvate (mm)</td>
<td>0</td>
<td>0.07 ± 0.01</td>
<td>0.08 ± 0.01</td>
<td>0.06 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>0.23 ± 0.03</td>
<td>0.16 ± 0.03</td>
<td>0.32 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>0.22 ± 0.03</td>
<td>0.22 ± 0.04</td>
<td>0.19 ± 0.05</td>
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<tr>
<td></td>
<td>310</td>
<td>0.18 ± 0.03</td>
<td>0.20 ± 0.03</td>
<td>0.11 ± 0.03</td>
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<td></td>
<td>370</td>
<td>0.16 ± 0.03</td>
<td>0.15 ± 0.03</td>
<td>0.20 ± 0.11</td>
</tr>
<tr>
<td>pH (units)</td>
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<td>7.40 ± 0.06</td>
<td>7.40 ± 0.04</td>
<td>7.37 ± 0.04</td>
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<tr>
<td></td>
<td>120</td>
<td>7.16 ± 0.06</td>
<td>7.30 ± 0.04</td>
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<tr>
<td></td>
<td>240</td>
<td>7.02 ± 0.06</td>
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<td>7.18 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>310†</td>
<td>7.10 ± 0.04</td>
<td>7.15 ± 0.02</td>
<td>7.25 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>370†</td>
<td>7.11 ± 0.05</td>
<td>7.15 ± 0.02</td>
<td>7.26 ± 0.04</td>
</tr>
<tr>
<td>Log lactate</td>
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<td>-0.02 ± 0.09</td>
<td>-0.15 ± 0.06</td>
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<td></td>
<td>120</td>
<td>0.78 ± 0.10</td>
<td>0.58 ± 0.11</td>
<td>0.44 ± 0.20</td>
</tr>
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<td></td>
<td>240</td>
<td>0.89 ± 0.04</td>
<td>0.65 ± 0.15</td>
<td>0.53 ± 0.13</td>
</tr>
<tr>
<td></td>
<td>310</td>
<td>0.58 ± 0.10</td>
<td>0.53 ± 0.11</td>
<td>0.42 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>370</td>
<td>0.64 ± 0.09</td>
<td>0.50 ± 0.10</td>
<td>0.55 ± 0.14</td>
</tr>
<tr>
<td>Log pyruvate</td>
<td>0</td>
<td>-1.22 ± 0.06</td>
<td>-1.15 ± 0.06</td>
<td>-1.21 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>-0.66 ± 0.05</td>
<td>-0.83 ± 0.09</td>
<td>-0.69 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>-0.74 ± 0.11</td>
<td>-0.77 ± 0.11</td>
<td>-0.82 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>310</td>
<td>-0.80 ± 0.07</td>
<td>-0.79 ± 0.09</td>
<td>-1.03 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>370</td>
<td>-0.83 ± 0.07</td>
<td>-0.89 ± 0.07</td>
<td>-0.92 ± 0.18</td>
</tr>
</tbody>
</table>

*P < 0.02, †P < 0.05.

presented in table 2. The data on oxygen consumption for each of the three groups and a series of measurements derived from them are included in table 3.

When analysis of variance was applied to the observed values of oxygen consumption for each of the hourly intervals on which measurements were available, no significant differences between the three survival groups were established. Normalization of oxygen consumption on the basis of the animal’s body weight did not increase statistical significance. For this reason the control values of oxygen consumption were taken into account and net changes in oxygen consumption were related to survival.

The oxygen deficit, representing the net changes in oxygen consumption per unit of body weight between the control period and each of the hourly intervals, was next analyzed. Again, analysis of variance failed to indicate any significant differences between the three survival groups. The next measurement considered was the cumulative oxygen debt, adhering to the definition used by Huckabee. It represents the area between the oxygen consumption curve and a straight line extended from the control period over the
Table 3
Data on Oxygen Consumption on the Three Groups of Animals Observed after Completion of Experiment

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Time (min)</th>
<th>0-4 hr (13 animals; mean ± sem)</th>
<th>4-12 hr (12 animals; mean ± sem)</th>
<th>&gt;12 hr (8 animals; mean ± sem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂ consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cc/hr</td>
<td>0</td>
<td>468 ± 36</td>
<td>399 ± 16</td>
<td>487 ± 49</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>289 ± 26</td>
<td>298 ± 23</td>
<td>285 ± 24</td>
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<td>240</td>
<td>162 ± 13</td>
<td>191 ± 17</td>
<td>204 ± 15</td>
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<td>310</td>
<td>244 ± 30</td>
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<tr>
<td></td>
<td>370</td>
<td>216 ± 32</td>
<td>223 ± 31</td>
<td>268 ± 37</td>
</tr>
<tr>
<td>cc/kg/hr</td>
<td>0</td>
<td>1411 ± 108</td>
<td>1196 ± 81</td>
<td>1384 ± 168</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>868 ± 89</td>
<td>885 ± 96</td>
<td>730 ± 43</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>489 ± 40</td>
<td>568 ± 57</td>
<td>573 ± 52</td>
</tr>
<tr>
<td></td>
<td>310</td>
<td>742 ± 99</td>
<td>706 ± 72</td>
<td>818 ± 130</td>
</tr>
<tr>
<td></td>
<td>370</td>
<td>636 ± 96</td>
<td>666 ± 93</td>
<td>767 ± 132</td>
</tr>
<tr>
<td>O₂ deficit</td>
<td>cc/kg/hr</td>
<td>431 ± 83</td>
<td>293 ± 35</td>
<td>474 ± 116</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>922 ± 122</td>
<td>628 ± 70</td>
<td>650 ± 79</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>489 ± 40</td>
<td>568 ± 57</td>
<td>573 ± 52</td>
</tr>
<tr>
<td></td>
<td>310</td>
<td>669 ± 124</td>
<td>490 ± 104</td>
<td>405 ± 95</td>
</tr>
<tr>
<td></td>
<td>370</td>
<td>800 ± 119</td>
<td>530 ± 128</td>
<td>456 ± 104</td>
</tr>
<tr>
<td>Cumulative O₂ debt</td>
<td>cc/</td>
<td>642 ± 73</td>
<td>419 ± 49</td>
<td>441 ± 35</td>
</tr>
<tr>
<td></td>
<td>240*</td>
<td>1094 ± 125</td>
<td>830 ± 76</td>
<td>1001 ± 123</td>
</tr>
<tr>
<td></td>
<td>370</td>
<td>1855 ± 229</td>
<td>1163 ± 122</td>
<td>1132 ± 89</td>
</tr>
<tr>
<td>Cumulative O₂ debt</td>
<td>cc/kg</td>
<td>3130 ± 402</td>
<td>2401 ± 223</td>
<td>2619 ± 331</td>
</tr>
<tr>
<td></td>
<td>240†</td>
<td>1.456 ± 0.121</td>
<td>1.006 ± 0.123</td>
<td>0.953 ± 0.055</td>
</tr>
<tr>
<td>Cumulative O₂ debt</td>
<td>(cc)</td>
<td>2.490 ± 0.218</td>
<td>2.044 ± 0.192</td>
<td>2.131 ± 0.146</td>
</tr>
</tbody>
</table>

*P < 0.03.
†P < 0.02.

time span of measurement. For the first time a significant difference was observed among the three survival groups at time 240 \((F = 4.54; d.f. = 2, 18; P < 0.03)\). When the measurement of the cumulative oxygen deficit, computed over the period of 240 min, was normalized by body weight, the difference between survival groups was of even higher significance \((F = 5.6; d.f. = 2, 18; P < 0.02)\). Finally, when the cumulative oxygen debt at time 240 was expressed as a proportion of initial oxygen consumption, a comparable difference in the three survival groups was demonstrated \((F = 5.7; d.f. = 2, 18; P < 0.02)\). The significant biologic fact which emerged was that the cumulative oxygen debt served as an indicator of survival, but those measurements which failed to take into account the prior history of oxygen deficit relative to the “normal” oxygen consumption of that animal did not identify the survival group to which the animal belonged.

Additional clarification of the role of oxygen debt was obtained by the analysis of cumulative oxygen debt at 370 min, 2 hours after reinfusion of blood (table 3). When the progressive decline in oxygen consumption was reversed after reinfusion, the cumulative oxygen debt no longer provided a significant indication of prognosis. In fact, the cumulative oxygen debt calculated for the interval between 250 and 370 min was not widely different for each of the three groups (table 3). This provides evidence that survival is related to the irreversibility of metabolic disturbances which occur during the period of
Table 4
Correlations (r) with Cumulative O₂ Debt per Kilogram of Rat Weight

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log L</td>
<td>0.50</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Log P</td>
<td>0.17</td>
<td>NS</td>
</tr>
<tr>
<td>Log L/P</td>
<td>0.41</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>XL</td>
<td>0.49</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

insult and that oxygen consumption in the recovery period does not necessarily correlate with ultimate survival.

Relationship of L, P, and Cumulative Oxygen Debt

Since the cumulative oxygen debt provided the best single indicator of survival, it served as a reference measurement for further study of the individual and combined roles of L and P. At the end of the bleeding period, the correlation between log L and the cumulative oxygen debt was 0.50 (P < 0.005). Correlation values for log P and log L/P and XL were of lower magnitude (table 4). The correlation for XL was of a comparable magnitude, however.

In assuming that increases in both L and P serve as measures of oxygen deprivation, we examined the specific contribution of P to the predictability of cumulative oxygen debt. This was achieved by computing the partial correlation between the cumulative oxygen debt and each of the following: log P, log L/P, and XL after removing the effect of log L (table 5). No significant increase in correlation was achieved since none of the partial correlations were statistically significant (P > 0.10). These results failed to confirm that log P or either of the two derived indexes, log L/P or XL, in fact, improved the predictability of cumulative oxygen debt based on measurement of L alone. The same applied to the untransformed values of P and L/P.

Since the actual correlation between cumulative oxygen debt and log L was 0.50, only 25% of the variability of the cumulative oxygen debt is accounted for by log L. The possibility still existed that log P, log L/P, and XL might still be of major importance for prediction of survival through mechanisms other than oxygen debt. This hypothesis could not be excluded because of limitations inherent in the experimental model. For practical reasons, this test system did not provide a sufficiently long period of observation nor sufficient variability in severity. However, data on patients proved particularly suited for investigation of this aspect of the problem.

Measurements on Patients

Methods

Patients

Data were abstracted from detailed clinical, hemodynamic, and metabolic studies on 142 patients admitted to the USC Shock Research Unit. The group included 67 men and 75 women, ranging in age from 4 to 90 years. Eighty patients (56%) including 39 men and 41 women, died during the interval of observation. Their average age was 61 years. Only 62 patients (44%), 28 men and 34 women, survived. Their average age was 52 years.

Clinical features of circulatory shock were related to cardiac causes in 40 patients, blood or fluid loss in 28, neurogenic causes in 22, bacteremia in 14, and various other causes in 38. The patients were observed in the shock ward until shock was reversed or until the patient expired. The average period of observation was 47.6 ± 3.8 hours; survivors were observed for 50.6 ± 4.5 hours and patients who died for 45.2 ± 6.0 hours.

Methods of Study

Samples of blood were obtained at intervals of 4 to 8 hours, from a catheter which had been inserted percutaneously into a brachial or femoral artery by the Seldinger guide-wire technic. L

Table 5
Partial Correlation (r) of Primary Measurements with Cumulative O₂ Debt per Kilogram, Given Log L

<table>
<thead>
<tr>
<th></th>
<th>Partial r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log P</td>
<td>−0.20</td>
<td>NS</td>
</tr>
<tr>
<td>Log L/P</td>
<td>0.20</td>
<td>NS</td>
</tr>
<tr>
<td>XL</td>
<td>0.21</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>−0.32</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Arterial pressure</td>
<td>0.26</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate</td>
<td>−0.06</td>
<td>NS</td>
</tr>
</tbody>
</table>
and P concentrations in the blood were analyzed by the same methods which were used in the experimental studies. The last sample obtained prior to release of the patient from the shock ward after recovery, or the last sample which was obtained prior to death of the patient (excluding the agonal period) was selected. Practical limitations precluded the availability of control measurements of L and P on these patients since they were usually admitted to the shock ward only after the onset of clinical shock. Therefore, the L0/P0 for calculation of XL according to Huckabee's formula was based on measurements obtained on 11 healthy volunteers. These assumed ratios of L0/P0 were the same as those reported in earlier studies. The L0/P0 ratio of our normal subjects was 4.1, which corresponded closely to the value of 4.2 reported by Huckabee in his observations on normal subjects.

Statistical Methods

Discriminant function analysis was used to discriminate between the population of survivors and those who died. The linear discriminant function is the linear combination of the variables under consideration, for which distribution curves in the two populations are least overlapping. The dissimilarity or the "distance" between the two populations is expressed in the Mahalanobis D2. This is the standardized square distance between the means of the two populations. The probability of survival, based on log L, was computed as the ratio of the frequency function of log L for survivors to the sum of the frequency functions for the survivors and nonsurvivors according to methods previously described.

Results

The mean values of the primary measurements and parameters derived from them, including their standard errors, are listed in table 6. For each parameter, as might be expected, a highly significant difference was demonstrated between survivors and patients who died (P < 0.0001).

Empirical Discrimination

For each of the four parameters of interest, that is, L, P, XL, and L/P, a reference or discrimination value was selected which best separated the patients who survived from those who died. It was so chosen that the number of misclassifications were minimal. Misclassification referred to survivors with values greater than the reference value, or fatalities with values less than the reference value.

Defined on this empirical basis, L as a single measurement provided the least number of misclassifications (fig. 4). Eight patients in whom the L concentration was less than 3.7 mm died. On the basis of this empirical discrimination, L failed to provide correct prediction of outcome in 11% of the cases. The corresponding error for P was 21%, for XL, 14%, and for L/P, 23%.

Discriminant Function Analysis

The possibility that measurements of P and computation of XL or L/P would increase the

Table 6

<table>
<thead>
<tr>
<th>Mean Values and Their Standard Errors Classified by Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived (62) (mean ± SEM)</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>L (mm) 2.34 ± 0.23</td>
</tr>
<tr>
<td>P (mm) 0.15 ± 0.01</td>
</tr>
<tr>
<td>L/P 17.5 ± 1.6</td>
</tr>
<tr>
<td>XL (mm) 1.75 ± 0.19</td>
</tr>
<tr>
<td>Log L 0.29 ± 0.03</td>
</tr>
<tr>
<td>Log P -0.91 ± 0.03</td>
</tr>
<tr>
<td>Log L/P 1.29 ± 0.02</td>
</tr>
<tr>
<td>Log XL 0.13 ± 0.04</td>
</tr>
</tbody>
</table>

Circulation, Volume XLI, June 1970

Figure 4

The effectiveness of empirical discrimination between survival and death for values of L, P, XL, and the L/P ratio in 142 patients. The bars above the reference values indicate the number of patients who, although expected to die, survived. The bars below the reference value indicate the number of patients who had measurements less than the reference value and were expected to survive, but died.
predictability of survival in addition to that provided by the individual patient's L values was still not excluded. This hypothesis assumes that functions of L and P might be combined to improve the discrimination based on L alone. Discriminant function analysis was used to examine this possibility.

The technic of linear discriminant function analysis assumes normal distribution of the variables of interest and equal variances in the two populations of survivors and nonsurvivors. It was, therefore, necessary first to examine the frequency distribution of L and P values. Frequencies of L values for patients who survived and those who died are shown in figure 5. Examination of these graphs suggested that it was the logarithm of L which would be likely to follow a normal distribution. This was, in fact, confirmed. The frequency histogram based on the logarithm of L for the patients who survived is shown in figure 6. Comparable results were obtained in patients who died. Examination of the frequency histograms of log P, log L/P, and log XL also revealed nearly normal distribution. The log transformation also produced approximately equal variances for the groups of survivors and nonsurvivors (table 6). Having made the log transformation, the data proved suitable for linear discriminant function analysis.

The probability of misclassification estimated on the basis of Mahalanobis D^2 was

Table 7

<table>
<thead>
<tr>
<th>Probability of Misclassification for Individual and Groups of Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Log L</td>
</tr>
<tr>
<td>Log P</td>
</tr>
<tr>
<td>Log L/P</td>
</tr>
<tr>
<td>Log XL</td>
</tr>
<tr>
<td>Log L, log P</td>
</tr>
<tr>
<td>Log L, log L/P</td>
</tr>
<tr>
<td>Log L, log XL</td>
</tr>
</tbody>
</table>
Table 8

<table>
<thead>
<tr>
<th>Theoretical</th>
<th>Reference value</th>
<th>% correct prediction</th>
<th></th>
<th>Theoretical</th>
<th>Reference value</th>
<th>% correct prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>L (mM)</td>
<td>4.2</td>
<td>88</td>
<td></td>
<td>L (mM)</td>
<td>4.2</td>
<td>88</td>
</tr>
<tr>
<td>P (mM)</td>
<td>0.19</td>
<td>79</td>
<td></td>
<td>P (mM)</td>
<td>0.19</td>
<td>79</td>
</tr>
<tr>
<td>L/P</td>
<td>23</td>
<td>79</td>
<td></td>
<td>L/P</td>
<td>23</td>
<td>79</td>
</tr>
<tr>
<td>XL (mM)</td>
<td>3.1</td>
<td>81</td>
<td></td>
<td>XL (mM)</td>
<td>3.1</td>
<td>81</td>
</tr>
</tbody>
</table>

computed for the individual variables. The results are shown in table 7. The probability of misclassification was demonstrated to be least with \( \log L \). Yet, the possibility still existed that \( \log P, \log L/P, \) and \( XL \) might improve the predictability of survival when combined with \( \log L \). This was disproved in that there was no significant reduction in the probability of misclassification when any one of these variables was combined with \( \log L \). These data, therefore, demonstrate that \( P \) or parameters which include \( P \) make no significant contribution to the predictability of survival in addition to that inherent in the measurement of \( \log L \).

Comparison of the Frequency of Empirical and Theoretical Misclassifications

This discriminant function analysis provided a theoretical basis for assessing the efficiency of the four parameters as predictors of survival. This also provided an opportunity for comparison of the theoretical efficiency with that demonstrated on an empirical basis. The results of this analysis are shown in table 8. Remarkably close correspondence between theoretical and empirical estimates was demonstrated. \( L \) was shown to be a reliable predictor of survival or death 88% of the time. The other three parameters which incorporated measurements of \( P \) proved less efficient.

Probability of Survival

The values of \( \log L \) observed in this population of patients which included 62 survivors and 80 fatal cases were shown to be approximately normally distributed. It was, therefore, possible to define the likelihood of survival in relation to any single measurement of \( L \). A graphic representation of this relationship is shown in figure 7. The sensitivity of the measurement is demonstrated by the observation that the likelihood of survival decreases from 90 to 10% as \( L \) increases from 2.1 to 8 mM.

Discussion

The rationale for using \( XL \) as a measure of severity of shock was based on the assumption that it served as a valid indicator of the severity of oxygen deprivation. This concept, in turn, was based on the premise, supported by the experimental observations of Crowell and Smith, that the extent to which oxygen delivery was curtailed provided a sensitive indication of severity of shock and the likelihood of survival. Although both oxygen consumption and oxygen deficit computed for any 1-hour period during the shock episode failed to indicate the likelihood of survival, the cumulative oxygen debt was related to the duration of survival. To this extent, our observations on rats were confirmatory of the observations reported by Crowell and Smith on dogs during hemorrhagic shock.

Having sustained the rationale for a measurement which would reflect the cumulative oxygen debt, it was now possible to examine empirically the extent to which \( XL \) or the
simpler measurements, L, P, or L/P served as indicators of oxygen deficit. Examination of correlation coefficients revealed that the measurement of L alone was the strongest correlate with cumulative oxygen debt, but no differences of statistical significance between L and XL as individual indicators of cumulative oxygen debt were demonstrated. Since any difference between L and XL would relate to the effect of P, the finding that measurements of P did not provide any independent contribution was confirmatory. Upon further examination of partial correlations of XL and the L/P ratio directly, we were secure in the conclusion that these parameters do not contribute any additional information relevant to the predictability of oxygen debt.

Exercise physiologists had previously noted that the more complicated measurement of XL provided no better indication of the severity of systemic oxygen deprivation than did measurement of L alone. In experiments on dogs breathing anoxic gas mixtures, Cain21 found that XL correlated less well with the net oxygen deficit than L alone, although the differences between regression lines were not statistically significant. In studies on seven human subjects, Strandell11 found a very high correlation (r = 0.99) between L and XL, again demonstrating that within the context of cumulative oxygen debt, the measurement of P and computation of XL provided no additional information. On the basis of experimental studies on shock, Rosenberg and Rush22 were unable to detect any advantage of XL in contrast to L alone when they compared oxygen consumption during hemorrhagic and endotoxin shock. No empirical support for the use of XL as a better indicator of oxygen deficit than L alone could be sustained.

These facts notwithstanding, the practical value of XL as a prognostic indicator of the severity of clinical shock, initially reported from our laboratory,3 was widely accepted. Since the data in this report emanated from studies on human patients, it seemed pertinent to reexamine such observations on patients to compare the effectiveness of L and XL in predicting survival. Although uncontrolled with regard to age, sex, and previous history of disease, measurements on patients provided advantages because a wide range of severity of illness was represented.

After the clinical data had been accumulated and analyzed, there was no doubt that the more complicated measurement of XL contained no information on the likelihood of survival which was not already inherent in the measurement of L alone. To the contrary, both empirical and statistical analyses indicated a smaller error of prediction when P was excluded from computation. The more remote possibility that further refinement in predictability might be available by combining L with P, XL, or the L/P ratio as separate components was unsupported by the present data. Hence, the position taken by other workers23–25 that L alone is a competent measure of severity was objectively sustained by the present studies.

As in studies during exercise,10–12 increases in XL under conditions of experimental hemorrhagic shock essentially parallel those of L both in dogs23 and in the observations herein reported on rats. In Baue and his associates’ observations on dogs,23 differences between XL and L in each case ranged from 1.6 to 2.0 mm. In the rats, mean L values were from 2.1 to 2.4 mm greater than the XL values. This relatively high level of consistency between L and XL was also observed during exercise. However, differences between these two values are less predictable during the recovery period and this is also demonstrated in the present data in which average differences between L and XL decline to 1.7 mm 2 hours after reinfusion. This is reminiscent of the work reported by Carlson and Pernow12 in which differences between L and XL observed after exercise were smaller. Knutten10 proposes that this may be an indication that effects not directly related to oxygen availability may account for these unexpected changes in P and hence in L/P and XL during recovery.
Once the value of L alone as a prognostic indicator was firmly established, it was possible to use this simpler measurement to derive an analytical curve representing the likelihood of survival. The curve based on L, as expected, showed a higher sensitivity than that exhibited by the previously published curved based on XL.3

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Experimental and Clinical Studies on Lactate and Pyruvate as Indicators of the Severity of Acute Circulatory Failure (Shock)
MAX HARRY WEIL and ABDÉLMONEN A. AFIFI

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