Effects of Hemorrhagic Shock on the Heart and Circulation of Intact Dogs

By Donald B. Hackel, M.D. and Walter T. Goodale, M.D.

The metabolic, hemodynamic and pathologic effects of hemorrhagic shock on the hearts of intact dogs have been studied, using the technique of venous catheterization of the coronary sinus. Metabolic studies demonstrated an alteration in the pattern of myocardial carbohydrate metabolism during shock and evidence for a relative myocardial oxygen deficiency. Subendocardial hemorrhage or necrosis was found in the left ventricles of some of the dogs.

Evidence that terminal circulatory failure in hemorrhagic shock in dogs may be due to myocardial depression comes from three general sources: 1. from physiologic analysis of central venous pressure, left auricular pressure, cardiac output, ventricular pressure curves and electrocardiograms by Sarnoff and associates, Wiggers and his colleagues and others; 2. from in vitro biochemical demonstrations of an altered myocardial carbohydrate metabolic pattern of animals in shock, such as those reported by Burdette; 3. from pathological studies showing foci of myocardial damage in dogs killed at intervals after induction of various types of shock.

The present experiments employ our previously reported coronary venous catheterization technique for studying coronary blood flow and myocardial metabolism in intact dogs. This approach permits the measurement of both cardiodynamic and biochemical events in vivo, and their correlation with pathological changes.

From the Department of Pathology, Western Reserve University School of Medicine at City Hospital, Cleveland, Ohio; the Department of Medicine, Peter Bent Brigham Hospital and Harvard Medical School, and the Cardiorespiratory Laboratory, Children's Medical Center, Boston, Massachusetts.

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Methods

Twelve normal mongrel dogs were anesthetized with a mixture of Nembutal and Dial-Urethane,* following morphine premedication (3 mg. per kilogram). Each animal was given streptomycin (200,000 U) and aqueous penicillin (200,000 U) intramuscularly and heparin (2.5 mg. per kilogram) by intravenous route. The coronary sinus and pulmonary artery were catheterized under fluoroscopic control, and a third catheter was placed in the aorta via the femoral artery. Left ventricular coronary blood flow was measured over a ten minute period by the nitrous oxide desaturation technique. Coronary arterial and venous samples were also drawn during this period, enabling the simultaneous measurement of myocardial oxygen, lactate, pyruvate and glucose utilization. Cardiac output was calculated by the Fick principle with oxygen; blood pressures were recorded with a Sanborn electromanometer. Left ventricular work and efficiency could thus be calculated. The description of these procedures and the calculations employed have been given in detail in previous reports. Serial electrocardiograms were obtained with a Sanborn Visocardiette.

The dogs were then bled from the femoral artery in stepwise fashion, 50 to 100 ml. at a time, until the blood pressure decreased from the control mean of 121.2 ± 4.5 to 54.3 ± 2.3 mm. Hg. This procedure took 45 to 60 minutes and required the withdrawal of blood equal to about 3.4 per cent of the body weight. A second set of determinations similar to those described above were then carried out. At this point hypotension was reversible, and reinfusion of blood resulted in an immediate proportional increase in arterial pressure levels. In nine of the dogs the blood pressure was maintained at 40 to 50 mm. Hg for the next three hours by repeated small withdrawals of blood, averaging 0.9 per cent of body weight. A third set of similar determinations were then performed. The blood that had been removed was returned and the dogs were...
permitted to recover. Those that died were autopsied immediately.

A series of 10 additional dogs were studied in a similar fashion to those described above, except that hemorrhagic hypotension was not produced. These animals served as triple controls to assess the effects of the manipulative procedures and the duration of anesthesia.

RESULTS

A. Metabolic

1. Oxygen (table 1). The systemic arterial oxygen content decreased progressively during shock. This was the result of hemodilution plus some arterial oxygen unsaturation. Along with the low cardiac output, the pulmonary artery oxygen content decreased to very low levels. In a few dogs it was even lower than the coronary sinus oxygen after three hours of hypotension. The coronary sinus oxygen content was significantly decreased, however, and the coefficient of extraction of oxygen was significantly increased from the control value of 64 per cent, to 85 per cent after three hours of hypotension. With this increase in the percent extraction of oxygen and the maintained rate of coronary flow, the total utilization of oxygen by the myocardium was maintained within normal limits.

2. Carbohydrate (table 2 and figures 1 and 2).

The arterial level of pyruvate increased from the control value of 1.59 mg per 100 cc. to 2.83 mg per 100 cc. in the immediate post-hemorrhagic period and to 3.82 mg per 100 cc. three hours later, a value approximately two and one-half times the initial blood level. The pyruvate arteriovenous difference was not significantly increased in the early period of hypotension, so that the pyruvate extraction coefficient was significantly decreased. After three hours of hypotension the changes were much more striking, with a negative coronary arteriovenous difference. As seen in figure 1, the values were shifted somewhat to the right of the normal regression line immediately after hypotension was established, reflecting the decreased coefficient of extraction. Three hours later, however, the values for pyruvate arteriovenous differences were either negligible or actually negative, despite the high arterial pyruvate levels.

The changes in lactate extraction were similar to those for pyruvate in the immediate period of hypotension (figure 2). There was a slight increase in the arteriovenous difference, which was not proportionally as great as the increase in arterial level, so that the extrac-

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Table 1.—A. Effects of Shock on Oxygen Metabolism (Mean ±sem)

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<tbody>
<tr>
<td>Initial control period</td>
<td>17.8</td>
<td>±6.6</td>
<td>13.5</td>
<td>63.6</td>
<td>.86</td>
<td>111.9</td>
<td>91.7</td>
<td>44.0</td>
<td>7.21</td>
<td>3.5</td>
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<tr>
<td>Immed. after hemorrh.</td>
<td>14.5*</td>
<td>±2.7</td>
<td>5.6*</td>
<td>±3.8</td>
<td>±.03</td>
<td>±9.9</td>
<td>±1.6</td>
<td>±1.5</td>
<td>±0.2</td>
<td>±5.5</td>
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<tr>
<td>3 hours after hemorrh.</td>
<td>±1.7</td>
<td>±1.7</td>
<td>2.0*</td>
<td>±1.6</td>
<td>±.03</td>
<td>±9.1</td>
<td>±2.0</td>
<td>±1.9</td>
<td>±0.1</td>
<td>±1.2</td>
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B. Triple Control Observations

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<tbody>
<tr>
<td>Initial control</td>
<td>17.3</td>
<td>±7.7</td>
<td>13.9</td>
<td>62.4</td>
<td>.85</td>
<td>113.8</td>
<td>87.7</td>
<td>45.3</td>
<td>7.28</td>
<td>3.3</td>
<td></td>
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<tr>
<td>30 min. control</td>
<td>17.3</td>
<td>±7.7</td>
<td>±6.6</td>
<td>±3.5</td>
<td>±.03</td>
<td>±8.9</td>
<td>±2.4</td>
<td>±1.4</td>
<td>±0.3</td>
<td>±3</td>
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<tr>
<td>3 hour control</td>
<td>±7.7</td>
<td>±7.7</td>
<td>±7.7</td>
<td>±3.5</td>
<td>±.04</td>
<td>±13.1</td>
<td>±2.5</td>
<td>±1.2</td>
<td>±0.3</td>
<td>±3</td>
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</tbody>
</table>

* Significant change from initial control period, p < .01.
† Change from initial control period of borderline significance, p < .05 > .01.

Abbreviations: Ao = aortic; Art. = arterial; B.O.C. = total body oxygen consumption; C.Ext. = myocardial coefficient of extraction (A-V/A); C.S. = coronary sinus; L.V. = left ventricle; P.A. = pulmonary artery; Resp. Vol. = respiratory volume; R.Q. = myocardial respiratory quotient; Sat. = saturation; σm = deviation of the mean.
EFFECTS OF HEMORRHAGIC SHOCK ON HEART AND CIRCULATION

Table 2.—A. Effects of Shock on Carbohydrate Metabolism (Mean ±σm)

<table>
<thead>
<tr>
<th></th>
<th>Pyruvate</th>
<th></th>
<th></th>
<th>Lactate</th>
<th></th>
<th></th>
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<th>Glucose</th>
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<tr>
<td></td>
<td>Ao. mg. %</td>
<td>A-V mg. %</td>
<td>Util. mg/100 Gm./min.</td>
<td>C. Ext.</td>
<td>Ao. mg. %</td>
<td>A-V mg. %</td>
<td>Util. mg/100 Gm./min.</td>
<td>C. Ext.</td>
<td>Ao. mg. %</td>
<td>A-V mg. %</td>
<td>Util. mg/100 Gm./min.</td>
<td>C. Ext.</td>
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<tr>
<td>Initial control period</td>
<td>1.59 ±.15</td>
<td>1.20 ±.34</td>
<td>1.70 ±.39</td>
<td>11.2 ±.14</td>
<td>5.9 ±.11</td>
<td>7.2 ±.12</td>
<td>53.5 ±.12</td>
<td>90.2 ±.12</td>
<td>4.7 ±.11</td>
<td>6.3 ±.12</td>
<td>5.0 ±.12</td>
<td></td>
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<tr>
<td>Immediate after hemorrh.</td>
<td>2.83* ±.23</td>
<td>0.56 ±.43</td>
<td>38.0* ±.50</td>
<td>9.9* ±.50</td>
<td>12.1* ±.50</td>
<td>31.1* ±.50</td>
<td>180.0* ±.50</td>
<td>4.6 ±.13</td>
<td>3.8 ±.13</td>
<td>3.8 ±.13</td>
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<tr>
<td>3 hours after hemorrh.</td>
<td>3.82* ±.42</td>
<td>-.37* ±.22</td>
<td>-9.6* ±.45</td>
<td>75.2* ±.87</td>
<td>10.4* ±.19</td>
<td>2.7* ±.25</td>
<td>15.0* ±.12</td>
<td>160.8 ±.42</td>
<td>1.8 ±.12</td>
<td>1.9 ±.12</td>
<td>.4† ±.12</td>
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B. Triple Control Observations

<table>
<thead>
<tr>
<th></th>
<th>Pyruvate</th>
<th></th>
<th></th>
<th>Lactate</th>
<th></th>
<th></th>
<th></th>
<th>Glucose</th>
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<tbody>
<tr>
<td>Initial control</td>
<td>1.55 ±.22</td>
<td>.81 ±.15</td>
<td>.84 ±.34</td>
<td>11.4 ±.19</td>
<td>5.9 ±.13</td>
<td>6.1 ±.14</td>
<td>49.0 ±.14</td>
<td>82.1 ±.14</td>
<td>3.2 ±.13</td>
<td>3.6 ±.14</td>
<td>4.1 ±.14</td>
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<tr>
<td>30 min. control</td>
<td>1.63 ±.23</td>
<td>.82 ±.14</td>
<td>.85 ±.26</td>
<td>13.1 ±.22</td>
<td>6.6 ±.12</td>
<td>7.0 ±.14</td>
<td>50.6 ±.14</td>
<td>82.0 ±.14</td>
<td>4.7 ±.13</td>
<td>5.0 ±.14</td>
<td>6.4 ±.14</td>
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<tr>
<td>3 hour control</td>
<td>1.58 ±.12</td>
<td>.66 ±.29</td>
<td>.82 ±.33</td>
<td>13.7 ±.20</td>
<td>6.0 ±.10</td>
<td>9.4 ±.15</td>
<td>46.9 ±.15</td>
<td>87.1 ±.15</td>
<td>8.1 ±.14</td>
<td>14.6 ±.15</td>
<td>9.1 ±.15</td>
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* See table 1.
† See table 1.

Abbreviations: See table 1; A-V = coronary arterio-venous difference.

tion coefficient was significantly reduced. After the dogs were hypotensive for three hours, however, the lactate findings were in marked contrast to those for pyruvate. The arterial lactate level at this time was almost seven times the control value. The arterio-venous difference and total utilization were still significantly positive, although the extraction coefficient decreased.

The arterial glucose level increased significantly during the immediate posthemorrhagic period, but after three hours there was a great deal of variation. In some animals the elevated levels were maintained or increased, whereas they dropped in other animals. The ability to maintain the elevated level of glucose could not be correlated with the eventual survival or death of the dog. There was also much variation in the findings for glucose extraction with no significant change from the control period, except for the consistently decreased glucose extraction coefficient after three hours.

B. Hemodynamic (table 3)

Since both arterial blood pressure and cardiac output were decreased during shock, left ventricular work was correspondingly lowered. There was much variation in the values for coronary flow, but despite the very low systemic arterial pressures and low cardiac outputs during shock, the coronary flow was not decreased. Myocardial oxygen utilization was thus maintained (see table 1) with consequent marked reduction in the mechanical efficiency of the heart during the hypotensive

Fig. 1. Relation of coronary arteriovenous difference to arterial level of pyruvate. Open circles represent normal control values, x = values during immediate posthemorrhagic period, and T = values after three hours of sustained hypotension.
period. After three hours of hypotension the coronary vascular resistance was significantly decreased to less than half that of the initial control value, indicating coronary vasodilatation. At the same time there was marked variation in both systemic and pulmonary vascular resistance, so that no significant changes could be demonstrated during the experimental period. The heart rate increased strikingly from the control mean value of 76 to 174 after three hours of hypotension.

C. Pathologic

Out of nine dogs subjected to the full three-hour period of hemorrhagic shock, five died without regaining a normal stabilized blood pressure level despite reinfusion of all removed blood. When the hearts were excised there was marked subendocardial hemorrhage in the left ventricle of two of these dogs (fig. 3), and three showed marked hyperemia and submucosal hemorrhage in the small intestine (particularly in the duodenum). In one of the five dogs no pathological changes were found. Of the four dogs that survived the immediate postexperimental period, two survived until they were sacrificed seven months later. Two died within two weeks and in both foci of myocardial necrosis were present, especially in the subendocardial region of the left ventricle (fig. 4). No significant correlations could be made between the metabolic findings, and the survival or death of the animal, or the nature of the pathological findings.

D. Triple Controls

There were no significant changes in any of the observations throughout the duration of the triple control period. There was much

<table>
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<th>Table 3.—A. Hemodynamic Effects of Shock (Mean ±SEM)</th>
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<td>MAPH mm. Hg</td>
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<td>Ao.</td>
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<td>Initial control period</td>
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<td>Immed. after hemorrh.</td>
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<td>3 hours after hemorrh.</td>
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<td>3 hours after hemorrh.</td>
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B. Triple Control Observations

| Initial control | 123.2 | 11.4 | 3.6 | 114.4 | 4.2 | 5.3 | 20.1 | 81.9 | 2.10 | .156 | 73.5 |
| Initial control | ±4.0 | ±9 | ±4 | ±11.4 | ±4 | ±.7 | ±1.6 | ±10.8 | ±.25 | ±.029 | ±10.6 |
| 30 min. control | 118.2 | 10.3 | 3.6 | 116.0 | 4.3 | 5.1 | 17.8 | 84.0 | 1.96 | .117 | 65.7 |
| 30 min. control | ±3.8 | ±6 | ±3 | ±9.6 | ±4 | ±.5 | ±.8 | ±8.7 | ±.17 | ±.015 | ±6.7 |
| 3 hour control | 130.0 | 11.6 | 2.7 | 123.6 | 6.1 | 4.1 | 15.6 | 78.0 | 2.78 | .304 | 85.9 |
| 3 hour control | ±4.4 | ±3 | ±2 | ±44.7 | ±2.0 | ±.5 | ±3.7 | ±9.0 | ±.22 | ±.022 | ±17.9 |

* See table 1.
† See table 1.

Abbreviations: See table 1; CF/CO = coronary flow + cardiac output; C.I. = cardiac index; Cor. = coronary; Eff. = efficiency; MABP = mean arterial blood pressure; Pulm. = pulmonary; Syst. = systemic; Vasc. Res. = vascular resistance.
random variation after three hours, however, particularly in the values for coronary flow, cardiac output and vascular resistance.

Discussion

A negligible or negative myocardial pyruvate extraction was the most consistent and striking abnormality found during hemorrhagic shock of three hours duration. A possible mass action effect of the disproportionately elevated lactate level might be suspected in suppressing pyruvate extraction and utilization but for the following evidence to the contrary: In previous experiments we have shown that glucose, lactate and pyruvate extractions appear to depend primarily on the arterial level of each metabolite independent of other substrate concentrations. In addition, lithium lactate infusions, to produce elevated lactate levels comparable to those in shock, were found recently to have no effect upon pyruvate extraction.

Both glucose and lactate extractions were maintained by the myocardium during shock, although at greatly increased arterial levels, with correspondingly reduced myocardial extraction coefficients. The somewhat similarly altered pattern of myocardial carbohydrate extraction observed in thiamin deficiency may be due to a deficiency in co-carboxylase, and in diabetic heart muscle, to insulin lack. In starvation, as well as in the presently described state of hemorrhagic shock, comparable reductions in myocardial carbohydrate extraction coefficients occur without known cause. In congestive heart failure due to valvular heart disease, however, the pattern of myocardial carbohydrate metabolism is quite different with normal or greatly elevated glucose extraction coefficients, and a well maintained extraction of lactate and pyruvate.

A failure of myocardial energy production
may be reasonably postulated in hemorrhagic shock, along with the other conditions mentioned above, as suggested by Olson and Schwartz. This again contrasts with congestive heart failure where one suspects a failure of conversion of chemical energy into effective mechanical work as the primary defect. In both types of situation the heart is mechanically inefficient. Whether the extreme tachycardia is the result or, in part, the cause, of an altered pattern of energy production and defective conversion is not yet clear. The presence of tachycardia is almost certainly significant as a sign of stress, and is accompanied by a release of adrenalin and adrenocortical hormones in increased quantity to account for the extreme rise in circulating glucose, lactate and pyruvate. Yet tachycardia alone, observed in comparable degree in normal nembutalized dogs, was accompanied by a normal myocardial metabolic pattern and mechanical efficiency. Tachycardia plus maximal coronary vasodilatation under the influence of local metabolic stimuli could account for the remarkable maintenance of coronary flow despite the presence of oligemic shock with greatly diminished systemic blood pressure and cardiac output. Again, the role of increased circulating epinephrine, a potent coronary vasodilator, is fairly certain. The pH remained normal and serum carbon dioxide was kept at a minimum through hyperventilation in these experiments, and thus probably contributed little, if any, to the coronary vasodilatation.

Myocardial oxygen consumption was remarkably unchanged throughout the prolonged period of hemorrhagic shock, although some reduction relative to the greatly diminished cardiac work might have been expected. The mean myocardial oxygen extraction coefficient was actually increased, from 64 per cent to 85 per cent, indicating relative myocardial hypoxia and coronary insufficiency. The local tissue hypoxia could well be the initiating factor favoring maximal coronary vasodilatation. Full compensation for myocardial hypoxia through optimal increases in coronary flow could have been thwarted by the low arterial coronary perfusion pressure and low cardiac output, thus forcing the myocardium to increase its oxygen extraction coefficient.

The maintenance of myocardial oxygen consumption despite acutely reduced cardiac work, with marked tachycardia and relative myocardial hypoxia in hemorrhagic shock, is in sharp contrast to the effects of the hypotension produced by spinal anesthesia. Here there is no tachycardia, a reduced myocardial oxygen extraction coefficient, and a diminished coronary flow paralleling the fall in blood pressure. The basic difference between the two states is between hyper- and hypoactivity of the sympathetic nervous system. It is tempting to postulate that extreme sympathetic hyperactivity, as in hemorrhage, anoxia and other conditions involving acute stress, causes an alteration in myocardial metabolism of the pattern presented, with inefficiency in the performance of mechanical work. This may predispose to the terminal circulatory and cardiac failure that eventually occurs.

**Summary**

The metabolic, hemodynamic and pathologic effects of hemorrhagic shock on the hearts of intact dogs have been reported.

Metabolic studies demonstrated alterations in the pattern of myocardial carbohydrate metabolism during shock, the most striking change being a reduction in the normally high myocardial extraction coefficient of pyruvate to negative values.

Oxygen was extracted by the heart in relatively large amounts in comparison with the small amount of mechanical work done, resulting in very low values for myocardial efficiency. Nevertheless, a relative oxygen deficiency was indicated by the increased myocardial oxygen extraction coefficient.

Subendocardial hemorrhage or necrosis was found in the left ventricles of some of the dogs. No correlation could be found, however, between the nature of the pathological findings, the immediate survival of the animal or the metabolic alterations.

The changes observed can best be ascribed to hyperactivity of the sympathetic nervous system and increased circulating adrenalin
with a myocardial metabolic pattern similar to other situations involving severe shock.

**Summario in Interlingua**

Es reportata le effectos metabolic, hemodynamic, e pathologic de choc hemorrhagic super le cordes de canes intacte.

Studios metabolic demonstrava le ocurrencia, durante le choc, de alterationes in le configuration del metabolismo myocardiac de hydratos de carbon. Le plus frappante de iste alterationes esseva le reduction, usque a valores negative, del normalmente alte coefficiente de extraction myocardiac de pyruvato.

Viste le parve quantitate de labor mechanic, le quantitate de oxygeno extrahite per le corde eseva relativamente grande. Le resultat eseva bassissime valores pro le efficacia myocardiac. Nonobstante, un deficientia relative de oxygeno eseva revealate per le augmentate coefficiente myocardiac de extraction oxygenic.

Hemorrhagia o necrosis subendocardiac esseva observate in le ventriculo sinistre de alunicus inter le canes. Sed nulle correlation esseva estabibibile inter le natura del constataiones pathologic, le supervivencia immediate del animales, o le alterationes metabolic.

Il pare melio ascriber le alterationes observate a un hyperactivitate del systema nervose sympathic e a un augmento de adrenalina circulante. Il eseva permissibile concluder que le configuration del metabolismo myocardiac resimilava illo trovate in altere situationes de chokes sever.

**Acknowledgments**

We would like to thank Dr. Thomas D. Kinney for his advice and encouragement. Acknowledgement is also given for the excellent technical assistance of Ernest Shiwanov, Eileen Mikat and Jacqueline Berg.

**REFERENCES**


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