Contributions of Coronary Perfusion Pressure, Metabolic Acidosis and Adrenergic Factors to the Reduction of Myocardial Contractility during Hemorrhagic Shock in the Cat

By Howard W. Siegel, M.D., and S. Evans Downing, M.D.

ABSTRACT
The contributions of metabolic acidosis, coronary perfusion pressure (CPP) and adrenergic support to left ventricular performance during hemorrhagic shock at aortic pressure (AP) of 30 ± 5 mm Hg were evaluated in cats in which AP, cardiac output (CO), and heart rate (HR) were controlled, and arterial pH, Po2 and Pco2 were continuously monitored. After 2 hours of shock, the stroke volume (SV), ejected at end-diastolic pressure of 10 cm H2O (SV10), was irreversibly reduced to 46 ± 4% (P < .001) of initial values (arterial pH 6.93 ± .05). In control animals SV10 after 2 hours was 86 ± 6% (pH 7.32 ± .07). Eight animals were subject to shock, but their CPP was held at 100 mm Hg. These showed no difference in SV10 from controls after 2 hours, although the pH had fallen to 6.90 ± .05. Reduction of CPP in these animals without correction of pH resulted in a rapid fall of SV10. In 10 animals subjected to shock for 2 hours, the arterial pH was maintained near 7.40 by infusion of Tris buffer. Five showed no greater reduction of SV10 than the controls, and five became severely depressed. In 5 cats subjected to beta-receptor blockade, hemorrhagic shock (pH 7.40) produced a rapid fall of SV10 which initially could be reversed by reelevation of AP. In less than 15 minutes, the SV10 depression became irreversible. Thus, shock (2 hours) and associated metabolic acidosis is detrimental to ventricular contractility only if CPP is also reduced. The contribution of acidosis may be related to the amount of sympathetic support during shock. With beta-receptor blockade, shock results in a marked reduction in SV10 even in the absence of metabolic acidosis.

ADDITIONAL KEY WORDS
beta-receptor blockade  hemorrhagic shock  cardiac function

Failure in hemorrhagic shock to inadequate coronary blood flow. In addition, it has been shown that contractile function of isolated papillary muscle strips obtained from hearts of animals during the oligemic and postoligemic phases of shock is impaired (4). The relative contribution of myocardial failure to the severity and irreversibility of hemorrhagic shock, however, has been questioned (5). The pathogenesis of cardiac depression in hemorrhagic shock is the subject of much discussion. Crowell and Smith (6) have reported a close correlation between an oxygen debt in excess of 120 ml/kg and irreversibility of shock in the dog. At this level of shock, the reduction of SV10 is even in the absence of metabolic acidosis.
of oxygen debt, cardiac depression was a consistent finding in experiments with this species reported by Crowell and Guyton (7, 8). The validity of the use of total body oxygen deficit as a measure of irreversibility of hemorrhagic shock has recently been challenged, however (9).

Lefer et al. (10, 11) have characterized and stressed the importance of a circulating polypeptide, which has been termed myocardial depressant factor (MDF). This substance appears in the plasma of animals subjected to oligemic hypotension and is capable of depressing the contractile activity of normal papillary muscle strips. The importance of the sympathetic nervous system has also been emphasized (5) and considered responsible for preservation of ventricular function during hemorrhagic shock after it had presumably reached the irreversible phase as defined by the 120 ml/kg oxygen debt criterion (8). Other evidence has suggested that there is progressive failure of sympathetic function during the course of oligemic shock (12).

Our earlier work suggested that a major contribution to the reduction of contractility in shock might be attributable to reduced coronary flow, presumably leading to cardiac hypoxia, and potentiated by progressive metabolic acidosis (13). It is also known that with loss of beta-receptor support, metabolic acidemia (14) and hypoxemia (15) can contribute to reduced ventricular contractility. These considerations suggested the possibility that the contractile depression observed in hemorrhagic shock could be related to several factors, including gradual loss of sympathetic support in the presence of myocardial hypoxia and increasing metabolic acidosis.

The purpose of this study was to further explore these mechanisms, and to examine the relative contribution which these factors may make to the reduction of myocardial contractility observed during hemorrhagic shock. A preliminary report on these findings has appeared (16).

Methods
Ventricular function was studied in 23 adult mongrel cats of both sexes, anesthetized with sodium pentobarbital (30 mg/kg, ip). Eleven cats from previous work (1) are included for purposes of clarity and comparison (groups I and II). These had essentially similar experimental procedures. The trachea was exposed and intubated. A midline thoractomy was performed, with careful attention to hemostasis. Ventilation was maintained with a Harvard constant-volume, positive-pressure pump. The internal mammary vessels were ligated and transected. The remainder of the preparation was similar to that described previously (1). The descending thoracic aorta was cannulated as shown in Figure 1. The extracorporeal tubing, heat exchanger, and reservoir were primed with freshly drawn heparinized (5 mg/kg) blood from donor cats.

The pump-operated (Sarns) bypass system was used to vary cardiac output temporarily for accumulation of data used to construct ventricular function curves. This could be done at constant aortic pressure by use of the air pressure regulated blood reservoir. Cardiac output was measured with a cannulating-type electromagnetic flow probe in the extracorporeal circuit, and a Medicon microflowmeter (k-2000). Calibration curves were found to be linear for the entire flow range used. Occasionally, there was a small discrepancy between mechanical (occlusive) zero flow and the baseline zero of the flowmeter. When this was present, appropriate corrections were made in data calculation.

Proximal aortic blood pressure was measured with a Sanborn transducer previously calibrated with a mercury manometer. Distal aortic pressure was measured by catheterizing a femoral artery. Blood flow to the descending aorta could be controlled by means of a variable screw clamp on the extracorporeal tubing (Fig. 1). By adjusting this clamp, it was possible to maintain proximal aortic pressure (and therefore coronary perfusion pressure) at a mean of 100 mm Hg, while reducing distal aortic pressure to 30 mm Hg in selected experiments. Hemorrhagic shock was produced by rapid bleeding into the reservoir from the aorta.

The brachiocephalic and left subclavian arteries were ligated to abolish cephalic blood flow. Heparin, 10 mg/kg, was given immediately before aortic cannulation. Blood temperature was controlled within a range of 37 ± 1°C with a Sarns heat exchanger and a Haake constant-temperature bath. A variable intensity heating pad was also used. Aortic blood and rectal temperatures were continuously monitored with a Yellow Springs telethermometer.

The apex of the left ventricle was cannulated with a no. 15 needle and external cuff guide, connected to a Sanborn transducer. The full left ventricular pressure contour as well as an
In situ, autosupported heart preparation. TR = Sanborn transducers. Left ventricular output measured with Medicon cannulating-type electromagnetic flow probe. Screw clamp on descending aortic loop to permit partitioning of proximal and distal aortic pressures as desired. Aortic pressure regulated by a variable air pressure supply above blood reservoir. Heart rate held constant in each animal by electrical pacing of the right atrium. Cardiac output modified by changing venous return to superior vena cava using a Sarns roller pump. Blood temperature was maintained within a range of 37 ± 1°C with a Sarns heat exchanger. Arterial pH, PO₂ and PCO₂ were continuously monitored with a Jevett electrode assembly using a small constant-flow pump. The brachiocephalic and subclavian arteries were ligated in all preparations to eliminate centrally mediated autonomic reflexes.

amplified left ventricular pressure trace were recorded. The first derivative of left ventricular pressure (dP/dt max) was obtained in some experiments using an RC-differentiating circuit with a time delay of 0.286 msec.

The heart was paced by stimulation of the right atrium in most experiments with a Grass SD-5 stimulator. Pace rates were usually in the range of 180 to 240. All pressures, flows, and derivative functions were continuously recorded on a Sanborn 358 direct-writing oscillograph. Measurements were obtained from intermittent high-speed traces (100 mm/sec). Ventricular function curves relating stroke volume to left ventricular end-diastolic pressure (LVEDP) at constant heart rate and aortic pressure were obtained as described previously (17).

Arterial pH, PO₂ and PCO₂ changes were continuously monitored by a Jevett electrode assembly (Fig. 1) and three Beckman 160 Physiological Gas Analyzers. During systemic shock when arterial pressure was low, blood was driven at a constant slow rate (15 to 20 ml/min) through the electrode bank by a small roller pump. Following each curve, a spot sample was taken (approx. 1 to 2 ml) and analyzed.
The experiments were designed to measure left ventricular function before and, periodically, during a 2-hour period of hemorrhagic hypotension at arterial pressures in the range of 30 ± 5 mm Hg. Myocardial function was evaluated by means of ventricular function curves which related stroke volume to LVEDP. The level of myocardial performance at each defined time was expressed as a percent of the initial stroke volume at LVEDP of 10 cm H2O (SV10). The choice of SV10 as a measure of ventricular performance has been previously discussed (17). From 8 to 12 ventricular function curves were performed in each experiment.

The effect of beta-receptor blockade (practolol) was studied in three animals (group IIIa) which were handled identically to group III. These animals were also given Tris buffer to prevent the development of metabolic acidosis. Groups III and IIIa were studied at the same intervals as groups I and II. One animal was treated as those in group IIIa, but was allowed to become spontaneously acidotic (no buffer was given).

Following 120 minutes during which femoral pressure was 30 mm Hg, the coronary perfusion pressure in groups III and IIIa was reduced from 100 ± 5 mm Hg to 30 ± 5 mm Hg by adjusting the reservoir air pressure. The screw clamp was also opened to maintain femoral pressure in a range of 30 to 30 mm Hg. In group III, ventricular function curves were performed from 0 to 5 minutes following reduction of coronary perfusion pressure. In group IIIa, curves were run at 5 minutes and between 20 to 30 minutes following CPP reduction.

Ten animals were placed in coronary and systemic hypotension, as in group II, and studied at similar times. However, these animals (group IV) were buffered with Tris throughout to maintain pH as close as possible to 7.40 (range, 7.30 to 7.43).

The effect of beta-receptor blockade (practolol) was accompanied by administration of practolol (AY, 21,001, Ayerst). This drug is believed to have less intrinsic myocardial depressant activity than propranolol.
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Myocardial contractility was studied in five animals with both coronary and systemic hypotension (group V). They were also studied similarly to group II. No buffer was used.

All data were processed and analyzed statistically with the Student's t-test on a Programma 101 computer.

Results

EFFECTS OF HIGH CORONARY PERFUSION PRESSURE (HCPP) WITH CONCOMITANT SYSTEMIC HEMORRHAGIC SHOCK

Hemorrhagic shock was produced by lowering the air pressure and rapidly bleeding the animal into the reservoir. Alternatively, distal aortic pressure could be reduced to shock levels while maintaining normotensive proximal aortic pressure by regulating the flow to the descending aorta with the screw clamp on the extracorporeal line (Fig. 1).

Left ventricular function curves relating stroke volume to end-diastolic pressure at 0, 60, and 120 minutes are shown in Figure 2. In the left panel, curves are shown from an animal in which the aortic pressure and coronary perfusion pressure were maintained at 100 mm Hg. There was minimal reduction of ventricular contractility during the 120-minute period. In contrast, the middle panel illustrates curves from an animal in which both aortic pressure and coronary perfusion pressure were held constant at 30 mm Hg. The curve at 60 minutes indicated a significantly reduced stroke volume throughout the same range of left ventricular end-diastolic pressures. The 120-minute curve showed a still greater reduction.

In the right panel of Figure 2, ventricular function curves are shown from a representative animal in which lower aortic pressure was maintained at 30 mm Hg, while the proximal aortic pressure, and hence the coronary perfusion pressure was maintained at normotensive levels (100 mm Hg). The curves at 0, 60, and 120 minutes are essentially unchanged.

Comparison of ventricular performance judged by changes in left ventricular function curves with increasing time. Left: control normotensive animal. Middle: hypotensive animal. Right: low systemic pressure, but high coronary perfusion pressure (HCPP). AP = aortic pressure in distal descending aorta; CPP = coronary perfusion pressure (proximal aortic pressure). Arrows indicate points on curves where SV$_{10}$ was estimated. In the right panel a ventricular function curve was run approximately 6 minutes after reduction of CPP to 30 mm Hg (open circles). This followed 2 hours of normovascular coronary perfusion pressure (100 mm Hg) with systemic hypotension (solid triangles).

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and are comparable to the control (left panel). When the coronary perfusion pressure was reduced to 30 mm Hg shortly after the 120-minute curve, however, there was an immediate and marked downward shift indicating rapid deterioration of left ventricular contractility.

To facilitate comparisons of various curves, the stroke volume ejected at a left ventricular end-diastolic pressure of 10 cm H$_2$O was obtained by extrapolation, as indicated by the arrows in Figure 2. A comparison of these values, which will be referred to as the $SV_{10}$, serves as a convenient means for evaluating and comparing contractile changes.

Left ventricular contractility measured by $SV_{10}$ showed little change in the group I animals throughout the 120-minute period, when studied at aortic and coronary perfusion pressures of 100 ± 5 mm Hg (Fig. 3). At time 0, the mean control $SV_{10}$ was 2.19 ( ± .21 SE) ml. This did not differ significantly from the two previous initial control curves at −20 and −5 minutes. After 120 minutes, the mean $SV_{10}$ was 1.85 ( ± .08 SE) ml, or 86 ( ± 6 SE)% of its initial values at 0 minute. The mean arterial pH fell slightly from 7.42 ( ± .09 SE) at time 0 to 7.32 ( ± .07 SE).

The animals subjected to hemorrhagic shock with systemic and coronary perfusion pressure...
of 30 ± 5 mm Hg (group II) demonstrated a gradually progressive decrease in left ventricular contractility (Fig. 3). The initial control curves at -20 and -5 minutes were the same in both the control and shock groups. The mean SV\text{10} values of both groups at 0 minutes did not differ significantly, indicating no mechanical effect of aortic pressure reduction on the SV\text{10} measurement. After 120 minutes of shock, the mean SV\text{10} had fallen from 2.25 (±.16 SE) ml at 0 minute to 1.04 (±.14 SE) ml, or 46 (±4 SE)% (P<.001). A significant reduction of contractility was apparent after 30 minutes of hypotension. The mean pH of this group fell from 7.44 (±.03 SE) to 6.93 (±.05 SE).

As indicated in Figure 3, the initial control SV\text{10} values of the group III animals at -20 and -5 minutes were comparable to the first two groups as were those at time 0 (initiation of hypotension). These animals with systemic shock but normal coronary perfusion pressures showed no difference from controls throughout the shock period. The mean SV\text{10} fell from 2.52 (±.13 SE) ml at 0 minute, to 2.00 (±.20 SE) ml or 80 (±8 SE)% of initial contractility (0 minute) to 26 (±3 SE) due to a sharp reduction of left ventricular contractility. These findings are summarized in Figure 4, and compared with group I controls, and group II shock preparations. The mean SV\text{10} of group III fell from 80 (±8 SE)% of initial contractility (0 minute) to 26 (±3 SE) after 30 minutes of hypotension.

**TABLE 1**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Group III (Shock + HCPP)</th>
<th>Group IIIb (Shock + HCPP + Beta-Receptor Block)</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>2.52 (±.13 SE)</td>
<td>2.52 (±.13 SE)</td>
</tr>
<tr>
<td>60</td>
<td>2.00 (±.20 SE)</td>
<td>2.00 (±.20 SE)</td>
</tr>
<tr>
<td>90</td>
<td>1.96 (±.24 SE)</td>
<td>1.96 (±.24 SE)</td>
</tr>
<tr>
<td>120</td>
<td>2.00 (±.20 SE)</td>
<td>2.00 (±.20 SE)</td>
</tr>
</tbody>
</table>

HCPP = high coronary perfusion pressure (100 mm Hg); LCPP = low coronary perfusion pressure (30 mm Hg).
sr) (P < .001) after 11 minutes (mean) of combined coronary and systemic shock. The mean pH of these animals (Table 1) dropped only slightly further during this period, from 6.90 to 6.86 (±.02 sr).

To assess the contribution made by sympathetic support, three animals were studied following beta-receptor blockade with practolol (group IIIa). It is known that acidosis in the presence of beta-receptor blockade will cause a reduction of left ventricular contractility (14). Hence, the appearance of metabolic acidemia was prevented by continuous Tris infusion. The mean SV10 at −20 minutes was 2.75 (±.06 sr) ml, and following the administration of practolol (Table 1), it was 2.69 (±.02 sr) ml (P > .4). With the onset of systemic shock, the mean SV10 was 2.76 (±11 sr) ml and after 120 minutes it was 2.53 (±.02 sr). This was not significantly different (P < .2).

Thus, myocardial performance was preserved during systemic shock, even in the absence of sympathetic support, provided coronary perfusion was adequate. Five minutes following reduction in coronary perfusion pressure in these animals, there was no significant change of mean SV10 (Table 1) and it remained at 88 ± 1 (sr)% Within 20 to 30 minutes, however, it had fallen to 49 ± 1 (sr)% of the initial value. The mean pH at this time was 7.37 (±.03). This was less than the reduction in contractility seen after 11 minutes in the group III animals which had a mean pH of 6.86 (±.02). Po2 values showed little change throughout the experiments, and never fell below 75 mm Hg.

One additional animal was studied similarly to those in group IIIa. That is, coronary perfusion pressure was held at 100 mm Hg and practolol was given, but no buffer was used and spontaneous metabolic acidosis developed. The initial control curves at −20 and −5 were comparable to all other groups, as was the SV10 (2.14 ml at 0 minute). At this time the pH was 7.41. After 90 minutes of systemic shock, the pH dropped to 6.91 and the SV10 fell to 71% of its initial value. At 2 hours, the pH was 6.86 and the SV10 had fallen to 62% of its initial value. Thus, as would be expected, cardiac performance deteriorated much more in this animal with beta-receptor blockade and acidemia than any of those in which acidemia was prevented by Tris infusion (14).

**Myocardial Function During Hemorrhagic Shock With Continuous Correction of Acidemia**

During the initial control period, the mean SV10 for the 10 animals in group IV was comparable to the other groups, indicating similar levels of contractility. After 60 minutes of hypotension at 30 ± 5 mm Hg, five animals showed depression of the SV10, but five did not. Figure 3 illustrates ventricular function curves obtained at 120 minutes in two representative animals. As shown in the left panel, one manifested minimal depression of the ventricular function curve after 120 minutes, with little change of arterial pH from 7.36 to 7.34. However, a large shift of the
buffered shock cat | buffered shock cat

• 0 MINUTES
120 MINUTES

LVEDP in cm H2O

**Figure 5**

Left ventricular function curves in two animals exposed to 2 hours of hemorrhagic shock (AP, 30 ± 5 mm Hg), but with continuous correction of arterial pH with Tris buffer. Left panel is representative of five animals that manifested minimal reduction of cardiac performance. Right panel illustrates one of five animals that manifested severe reduction of contractility indicated by the depressed ventricular function curve (solid triangles) in the presence of a near normal arterial pH. LVEDP = left ventricular end-diastolic pressure.

Coronary and systemic hypotension at 30 ± 5 mm Hg in animals with beta-receptor blockade (group V) was followed almost immediately by a severe reduction of left ventricular contractility. Figure 7 illustrates ventricular function curves from two representative animals. The effects of hemorrhagic shock after beta-receptor blockade are shown in the left panel. The curve following beta-receptor blockade (C + B) was only minimally shifted from the control (C) position. With the onset of shock (S + B), however, there is a marked shift down and to the right, indicating reduced left ventricular contractility. The curve after 15 minutes of hypotension (open circles) shows a still greater shift downward.

Those animals that showed a reduction of ventricular performance were separated from those that did not, and were analyzed separately (Fig. 6). At 90 minutes the latter group (IVA) had a mean SV10 of 2.33 (±0.19 se) ml or 98 (±8 se)% of initial values. This may be compared with 1.46 (±0.10 se) ml or 57 (±3 se)% for group IVB (P < .01).

The mean pH of groups IVA and IVB, as well as the mean for the entire group, were comparable (Fig. 6 and Table 2). No further reduction of mean SV10 occurred at 120 minutes, although the difference between groups IVA and IVB remained highly significant. Mean arterial Po2 values were statistically equivalent for each group at comparable time intervals in shock (Table 2).

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TABLE 2

Hemorrhagic Shock with Raffing

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVo (ml)</td>
<td>1.96</td>
<td>2.15</td>
<td>2.46</td>
<td>2.08</td>
<td>2.31</td>
</tr>
<tr>
<td>SVo (%)</td>
<td>(±16)</td>
<td>(±30)</td>
<td>(±13)</td>
<td>(±18)</td>
<td>(±21)</td>
</tr>
<tr>
<td>pH</td>
<td>7.24</td>
<td>7.34</td>
<td>7.49</td>
<td>7.34</td>
<td>7.34</td>
</tr>
<tr>
<td>Po2 (mm Hg)</td>
<td>(±93)</td>
<td>(±93)</td>
<td>(±93)</td>
<td>(±93)</td>
<td>(±93)</td>
</tr>
<tr>
<td>Po2 (mm Hg)</td>
<td>106</td>
<td>103</td>
<td>123</td>
<td>98</td>
<td>84</td>
</tr>
</tbody>
</table>

Values are mean ± SE.

comparable to the values of 59 (±5% SE)% seen in animals with beta-receptor blockade at the beginning of shock with normal pH. If the hypotension was allowed to continue for 15 minutes, the reduction of contractility in the animals with blockade became more severe (P < .02), and reached 32 (±5% SE)% in the absence of acidemia.

Discussion

The present investigations were undertaken to assess changes of myocardial contractility during the course of oligemic hypotension, and to explore the contribution of a number of associated factors to these changes. It is clear that under the conditions of the experiments reported herein, hemorrhagic shock leads to a progressive decline of myocardial contractility, which is significant within 30 minutes and which continues to decline throughout the 2-hour period of measurements. After 2 hours of sustained hypotension at arterial pressures of 30 mm Hg, left ventricular contractility, assessed by the stroke volume ejected at an end-diastolic pressure of 10 cm H2O (SVo), was 46% of values at the initiation of hypotension. Normotensive control animals studied at comparable intervals were 86% of initial control values after the 2-hour period. These findings are consistent with previous work from this laboratory (1, 2), and also appear to agree with a number of other investigators (3, 4, 7, 8).

While these observations appear to differ somewhat from those of Goodyer (5), it is likely that they represent quantitative rather than qualitative differences. In the present investigation, for example, cephalic blood flow was interrupted to eliminate centrally medi-
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Figure 6

Ventricular performance at specified time intervals in 10 animals subjected to hemorrhagic shock, but with continuous correction of arterial pH. Vertical bars = standard error of mean. Symbols same as in Figure 2. See text for additional description.

LVEDP = left ventricular end-diastolic pressure.

The observations from animals subjected to hemorrhagic shock while maintaining proximal aortic pressure (and hence coronary perfusion pressure) at normotensive levels were of particular interest. The same degree of metabolic acidosis appeared at comparable time intervals as other animals in shock, but the level of contractility was indistinguishable from normotensive controls (Fig. 4). Hence, with adequate coronary perfusion, severe metabolic acidosis had little detrimental effect on cardiac performance. This concept is consistent with earlier observations (18).

Shortly after reducing coronary perfusion pressure in these animals, myocardial performance began to deteriorate (Fig. 2). Within approximately 10 minutes, it fell to 26% of initial control values, even though there was minimal progression of metabolic acidosis. Although direct evidence is lacking, the late reduction of proximal aortic pressure in these animals presumably led to a substantial reduction in coronary blood flow and oxygen delivery to the myocardium. This occurred in the presence of severe metabolic acidemia. Reduced oxygen tension sufficient to produce...
minimal depression of myocardial contractility with a normal hydrogen ion concentration has been shown to produce substantially greater depression with concomitant acidemia (13). This potentiation effect of acidemia, therefore, suggests an explanation for the observations in the present experiments.

Another possibility which was considered is that maintenance of ventricular performance in animals with systemic shock, but normal coronary perfusion pressure, was related to better preservation of myocardial adrenergic mechanisms. This consideration was rendered unlikely by the finding that contractility was equally well preserved in animals subjected to beta-receptor blockade (Table 1). The appearance of metabolic acidemia was avoided by continuous buffering in these latter studies, because earlier observations have shown that acidemia depresses myocardial contractility in normotensive animals with beta-receptor blockade (14). These findings were confirmed in the present study by permitting the development of metabolic acidosis in an animal which was otherwise studied in the same manner as those in group IIIa. As would be expected, cardiac performance deteriorated with the progression of metabolic acidosis.

The observation that reduced myocardial contractility is not a feature of hemorrhagic shock, if coronary perfusion pressure is maintained at normotensive values, is of interest in relation to the contribution of a "depressant factor" in the genesis of cardiac failure in hemorrhagic shock (10). It would seem reasonable to expect that this material would be liberated from tissues below the diaphragm when perfused for 2 hours at an...
arterial pressure of 30 mm Hg. Failure to detect decreased contractility which could be attributed to the appearance of a depressant factor invokes several possible explanations. For unknown reasons, this substance may have appeared in very small concentrations, insufficient to alter myocardial function. A second possibility is that its potency in producing myocardial depression in the intact ventricle is too little to be detected by the hemodynamic measurements employed in this study, or correspondingly the effects of this polypeptide may have been masked by quantitatively more important metabolic or autonomic factors. A third possibility is that this material may be detrimental to hearts in shock, but not those operating at normotensive pressures with adequate coronary perfusion. Which, if any, of these considerations is valid must be determined from more direct experimental evidence.

One point that emerges clearly from this study is that metabolic acidosis is a complementary factor of major importance in determining cardiac performance in hemorrhagic shock. It is called a complementary factor because severe metabolic acidosis in the presence of normal coronary perfusion pressure failed to detectably reduce cardiac performance, while minutes after reducing coronary perfusion pressure to shock levels, approximately the same degree of acidosis was
associated with a reduction of contractility to 25% of control values (Fig. 4). The complementary role of metabolic acidosis is emphasized further by the studies in which the development of acidemia was continuously corrected by infusion of Tris buffer. After 2 hours of hemorrhagic shock, half of these animals showed little or no cardiac depression with an average contractility of 93% of initial values (Table 2). It is important to note that none of the animals subjected to hemorrhagic shock without correction of acidosis maintained comparable levels of contractility.

While the appearance of cardiac depression in hemorrhagic shock was prevented by buffering in half of the animals, in the remainder, which were studied in the same manner, progressive cardiac depression appeared and contractility was reduced to 54% of initial values (Table 2). To explain these random differences, the possibility was considered that failure of myocardial adrenergic support developed in some of the animals, but not in others (12). This hypothesis was tested by studying the effects of beta-receptor blockade on normotensive animals and assessing ventricular performance following the induction of hemorrhagic shock (Fig. 7). Although blockade with practolol caused minimal reduction of contractility at normotensive pressures, immediately after the institution of hypotension, ventricular performance was found to be markedly diminished, and within 15 minutes fell to still lower values (Fig. 8). These changes occurred in the presence of a normal arterial pH. The increased sensitivity of these hearts to hemorrhagic shock following beta-receptor blockade cannot be explained by direct evidence, but may be related to the enhanced sensitivity of the myocardium to hypoxia following interruption of adrenergic support (15).

In view of the observation that hemorrhagic hypotension is associated with depletion of norepinephrine (19), and that myocardial responsiveness to stellate stimulation may diminish as the duration of hypotension increases (12), it is likely that failure of adrenergic support would have appeared in some of the animals in the present study, and that they would behave much as though subjected to beta-receptor blockade. This idea is also suggested by the quantitative similarity of those animals who developed myocardial depression after 2 hours of hypotension in the presence of a normal arterial pH, with those who showed cardiac depression at the beginning of hypotension with a normal arterial pH after prior administration of practolol. Thus, with the former group, the SV was 54% of initial values, and in the latter, 59%.

It may be concluded that prolonged hemorrhagic hypotension is associated with a progressive deterioration of cardiac performance. Although there may be quantitative differences related to experimental approaches or species differences (8), this finding appears to be firmly established (1, 3, 4, 7, 8). Whether reduced myocardial contractility represents a principal or contributory factor leading to irreversibility of shock in either the clinical or experimental setting remains to be determined. In the experimental conditions described in these studies, sustained hemorrhagic hypotension for a period of 2 hours leads to a major reduction of myocardial contractility which is not reversible (1). Under different experimental conditions, this takes substantially longer (5).

The genesis of the myocardial depression observed in the present studies appears to be primarily related to the interrelations of metabolic acidemia, coronary perfusion pressure (and presumably coronary blood flow), and the level of cardiac adrenergic support. The interactions of these three variables, based on principles derived from earlier studies (13-15, 18), would appear sufficient to account for the observed changes in cardiac performance. Contributions from a myocardial depressant factor (10, 11), or intestinal factor (20, 21), must have been quantitatively substantially less important. These findings are not inconsistent with the concept that reduced myocardial performance is related to impairment of high energy phosphate production (22). However, evidence that this is an
important additional contributory factor remains to be established (23).

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References
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