Myocardial Performance in Hemorrhagic Shock in the Dog and Primate

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ABSTRACT

Myocardial performance was investigated in nine dogs and six monkeys during experimental hemorrhagic shock under conditions of constant afterload. Left ventricular function curves were obtained by opening an aorta to left atrial bypass, and simultaneous recordings of stroke volume, peak stroke power, maximal dP/dt, maximal dF/dt, heart rate, atrial pressure and end-diastolic pressure were made. Total plasma catecholamine content was also measured in the monkeys during the control period and at death. The dogs showed a marked increase in performance, in contrast to the control group, 0-2 hours after reinfusion. Performance then deteriorated significantly by 2-4 hours, although it was still comparable to control levels. However, higher atrial and end-diastolic pressures were obtained, and in most cases cardiac failure developed soon thereafter. Two additional dogs were subjected to all stresses except the hypotension for 10 hours without evidence of deterioration. The monkeys did not withstand the surgical procedure as well as the dogs did and survived a maximum of 136 minutes after reinfusion. Catecholamine levels decreased in five of the six monkeys but not below normal levels, which indicates that failure was not due to depletion of myocardial stores. The data are interpreted as direct evidence for a factor(s) seriously depressing myocardial performance during the postinfusion period of experimental hemorrhagic shock in the dog and the monkey despite the high levels of performance in the early postinfusion period and the maintenance of coronary driving pressure and arterial oxygen content.

KEY WORDS catecholamines heart failure cardiodynamics stroke work cardiac work cardiac output peak stroke power atrial pressure ventricular function

Crowell and Guyton (1, 2) measured right and left atrial pressures and cardiac output and reported a depression of myocardial performance during experimental hemorrhagic shock in the dog. They based their conclusion on the increase in right and left atrial pressures needed to maintain cardiac output at the control level during hemorrhagic shock. Lefer and co-workers (3) demonstrated the release of a myocardial depressant factor from the pancreas during experimental hemorrhagic shock in the cat. This factor, which also exists in the dog (4), might significantly depress myocardial contractility and result in myocardial failure; it might be the primary mechanism responsible for the gradual decline in systemic arterial blood pressure observed in the postinfusion period of hemorrhagic shock.

Longnecker and Abel (5), using a cardiopulmonary bypass preparation, found no significant decline in arterial blood pressure or venous compliance in the 4 hours following simulated hemorrhagic shock. They concluded that the decline normally seen must be the result of a failure of the heart-lung system or a loss of circulating blood volume. Considerable evidence (6, 7) demonstrates that the loss of circulating blood volume is significant, but the precise role of the loss of myocardial vigor remains undetermined.

However, Weidner et al. (8) failed to find a decrease in myocardial force or a rise in atrial pressure during the phase of declining arterial blood pressure. Chimoskey and Bohr (9) did not demonstrate a decrease in the ability of rat left ventricular papillary muscle to develop tension. Rothe and Selkurt (10) and Rothe (11) found cardiac “weakening” but no evidence for frank cardiac failure. Hinshaw et al. (12) found no evidence for cardiac depression during the early stages of endotoxin shock, but they did find significant depression 6-9 hours after the administration of endotoxin.
A major difficulty in many of these experiments was the failure to control afterload while measuring ventricular performance. Arterial blood pressure, if untreated, will gradually decrease in the postinfusion period; this decrease influences ventricular performance (13). Decreased coronary flow might also lead to further myocardial damage. This study was designed to overcome this problem by maintaining a constant arterial blood pressure. Ventricular performance was measured by several traditional methods in an effort to demonstrate early alterations, recognizing, however, that such methods might be insensitive to small changes.

Methods
The studies were performed in 11 male mongrel dogs (11–21.5 kg) and 6 monkeys (young baboons) (5.6–8.2 kg). Two of the dogs served as controls and were not subjected to the hemorrhagic shock procedure. The animals were anesthetized with sodium pentobarbital (30 mg/kg, iv), and endotracheal tubes were inserted. A respirator delivering approximately 10 ml/kg stroke−1 at a rate of 16/min with a 40/60 inspiratory-expiratory duty cycle was attached to each endotracheal tube. Supplemental oxygen, at a rate of 1–2 liters/min, was also given via the respirator intake port to maintain PO2 at 150–200 mm Hg. The chest was opened by a left thoracotomy, and an electromagnetic flow probe was placed around the root of the ascending aorta. Left ventricular pressure and right atrial pressure were measured through appropriately placed catheters attached to Statham transducers. The ventricular pressure transducer was a P23De gauge attached to PE 190–240 tubing inserted via pulmonary vein branch or directly through the apical dimple with a small purse-string retaining suture. The natural frequency response was about 50 Hz using a step input (14); the overall recording system response was 3 db down at 30 Hz. A glass cannula was inserted into the left subclavian artery and connected through a servo-controlled bidirectional pump to a blood reservoir containing cross-matched dog blood or, for the monkeys, Dextran 75 (Abbott). A T-connection in the arterial blood pressure line was made to the left atrial appendage, and a separate catheter was inserted into the left atrium. Atrial pressure could then be varied by controlling the amount of bypass from the aorta to the left atrium. The arterial blood pressure-sensing gauge from a separate aortic catheter was connected to the summing junction of an operational amplifier, and the reading was compared with the desired reference pressure level. The output of the summing amplifier, with approximately a 1-second time constant, was further amplified by a zener-limited amplifier to operate the reversible pump motor. Figure 1 illustrates the resultant preparation; mean arterial blood pressure could be maintained constant with a variation of less than ±5 mm Hg.

Simultaneous recordings of ascending aortic flow, left ventricular pressure, left and right atrial pressure, and systemic arterial blood pressure were thus obtained. These variables were passed to an on-line analog computer, and simultaneous recordings were also obtained of stroke volume, maximal dP/dt, maximal dF/dt, stroke work, peak stroke power, and left ventricular end-diastolic pressure. The resulting data were grouped by the level of end-diastolic pressure obtained during each period of the experiment.

Control ventricular function curves were obtained by altering the opening of the screw-clamp arrangement to the left atrium, which allowed the atrial pressure to stabilize; a reading was obtained about 1 minute after the new atrial pressure level was set. Initially, 5 minutes were allowed for stabilization, but this procedure required too much time to record a complete curve and did not appear to be necessary; transient adjustments were seen for only the first few beats at the new level. By this method three ventricular function curves at 10–20-minute intervals were obtained at arterial blood pressures of 80 or 100 mm Hg during the control period. During the bleeding period, curves were obtained 30 minutes after the pressure was lowered to 40 mm Hg (early oligemic shock) and 30 minutes before reinfusion (late oligemic shock) in the dogs only. Similarly, curves were obtained 30 minutes after reinfusion and at 30–60-minute intervals thereafter. No attempt was made to control heart rate, since it remained relatively constant due to the constant arterial blood pressure. In the dog experiments, the reduced pressure was maintained for 4 hours; in the monkey experiments, it was maintained for 2 hours. At the end of this period, the pressure was returned to 80 mm Hg, and the atrial pressure was observed for signs of impending failure. In some cases the animals could not tolerate a rapid (1–2 minutes) return to 80 mm Hg, because of the rapid rise in left atrial pressure when the higher afterload was imposed. These animals were returned to 60 mm Hg for 10–20 minutes and then to 80 mm Hg.

Blood gases and pH were monitored at approximately 1-hour intervals; adjustments were made with sodium bicarbonate to maintain the pH within approximately
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normal limits. Blood samples (25 ml in the dogs and 12.5 ml in the monkeys) for determinations of circulating catecholamine content were obtained at the beginning and the end of the experiment. These samples were analyzed for total plasma catecholamine level using the ethylenediamine fluorescent method of Wel-Malherbe (15). Care was taken to avoid use of catecholamines during the experiment.

Blood in the reservoir system normally exchanged slowly with the animal except when the function curve was actually being determined; during such a determination, 100-300 ml was rapidly (5-10 minutes) infused or withdrawn. In an effort to maintain this blood in a physiologically acceptable state, oxygen was bubbled through the reservoir and a heat lamp was used to warm it. The animals were also heparinized with 3 mg/kg of sodium heparin, and approximately half this dose was repeated every 4 hours. Body temperature was monitored via a rectal thermistor and was maintained constant by a heat lamp and a heating pad. All experiments were done using sterile techniques during the operative procedure; in particular, all tubing and the reservoir system were either new or cleaned by boiling for 2 hours in 2% sodium bicarbonate followed by acid neutralization, thorough rinsing, and sterilization.

Results

Dog Experiments

Figures 2 and 3 show the results obtained in nine dogs subjected to the hemorrhagic shock procedure for 4 hours. The dogs were maintained at afterloads of 80 or 100 mm Hg, and, because the results obtained at these two afterloads were sufficiently similar, the data were combined. The data were grouped by end-diastolic pressures and by time. As previously reported (16), stroke work and peak stroke power tended to give the more classic type of ventricular function curve. In the period 0-2 hours after reinfusion, there was a significant increase in most of the variables at end-diastolic pressures comparable to the control values; all variables increased at some level of left ventricular end-diastolic pressure but not at all levels. The function

Ventricular performance during hemorrhagic shock in nine dogs. Values are means ± se. Early shock is 30 minutes after bleeding; late shock is late oligemia 30 minutes before reinfusion. Asterisks represent significant (P < 0.05) decreases at 2-4 hours relative to the levels at 0-2 hours postinfusion. Stroke volume is in ml/kg, stroke work in ml mm Hg/kg, peak stroke power in ml mm Hg/kg sec⁻¹ × 10⁻⁴, maximal dP/dt in mm Hg/sec, and maximal dF/dt in ml/sec kg⁻¹. Boxes represent standard errors.

Right atrial pressure is in mm Hg, peripheral resistance in mm Hg kg/ml min⁻¹ × 10⁴, cardiac work in ml mm Hg/kg min⁻¹ × 10⁻⁴, cardiac output in ml/kg min⁻¹, and heart rate in beats/min. See Figure 2 for details.

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curves, however, declined 2-4 hours after reinfusion. Using a two-tailed Student's t-test (17), significant declines ($P < 0.05$) in the curves 2-4 hours after reinfusion relative to those 0-2 hours after reinfusion are shown by the asterisks. There was a significant decrease in the 2-4 hours postinfusion period in maximal $dF/dt$, maximal $dP/dt$, peak stroke power, stroke work, and stroke volume at many of the end-diastolic pressure levels compared with the curves obtained 0-2 hours after reinfusion (Fig. 2). Most of the values were not significantly depressed relative to the control values, however. Stroke volume, maximal $dP/dt$, and maximal $dF/dt$ were decreased in the 10-15-mm Hg left ventricular end-diastolic pressure group only.

Figure 3 shows similar data for heart rate, cardiac output, cardiac work, peripheral resistance, and right atrial pressure. Since aortic pressure was held constant, peripheral resistance was simply the inverse of the cardiac output curve. For cardiac output and cardiac work, there was a significant decrease 2-4 hours after reinfusion relative to the levels 0-2 hours after reinfusion at similar end-diastolic pressure levels. The 0-2-hour values were increased over control values for cardiac output in the 0-5-mm Hg and the 5-10-mm Hg left ventricular end-diastolic pressure groups and for cardiac work in the 10-15-mm Hg left ventricular end-diastolic pressure group. Peripheral resistance decreased and right atrial pressure increased in the 0-2-hour group vs. the control group. Right atrial pressure, heart rate, and peripheral resistance increased in the 2-4-hour group vs. the 0-2-hour group. It should be noted that the maximal end-diastolic pressures were considerably larger, particularly 2-4 hours after reinfusion, than they were in the control dogs. That is, with the same shunt flows, end-diastolic pressures and right atrial pressures were higher after the shock procedure than they were during the control period, even though the base diastolic pressure with the shunt closed was not altered. Left atrial pressure was also monitored, and the changes were similar to those given for left ventricular end-diastolic pressure.

Figure 4 shows the final time course for the six dogs that still survived 3 hours after reinfusion. (One dog died 35 minutes after reinfusion with a large fluid uptake of over 1 liter and possible air embolism; one died 54 minutes after reinfusion and one died 164 minutes after reinfusion, both of frank cardiac failure.) The figure shows peak stroke power measured at an end-diastolic pressure of 15 mm Hg as a percent of the reading at about 2 hours after reinfusion. All dogs showed a decrease in power; all but dogs 5 and 6 were definitely near death. Dog 4 might have had an air embolism during rapid fluid uptake; the other five dogs were terminated due to continued fluid requirements. Therefore, of the nine dogs, at least six had serious decreases in function associated with high atrial pressures, i.e., frank myocardial failure. Of the remaining three dogs, one died of an air embolism and two were terminated at moderately depressed levels.

To show that the decrease in myocardial performance was not simply a result of the surgical procedure, which did add considerable stress to the dogs, two dogs were subjected to the same procedure, but their pressure was never reduced to 40 mm Hg. Ventricular function curves were obtained over a period of 10 hours in these two
dogs. The results for cardiac work, cardiac output, maximal \( \frac{dP}{dt} \), and peak stroke power are shown in Figure 5. Dog 7 had large changes and good ventricular function curves and showed no deterioration at all over a 10-hour period; actually, some tendency for function to increase was observed. Dog 8, unfortunately, showed little change in function on opening the shunt, probably because the shunt flow was relatively small. Again, no deterioration in function could be demonstrated. The data are shown only for lumped afterloads of 80 and 100 mm Hg, although these two dogs were also tested at afterloads up to 140 mm Hg without apparent undue effects.

**PRIMATE EXPERIMENTS**

The results from four monkeys are shown in Figure 6. Cardiac work, cardiac output, peak stroke power, maximal \( \frac{dP}{dt} \), and maximal \( \frac{dF}{dt} \) are plotted vs. absolute values for the end-diastolic pressure in the control period and vs. percent values for the end-diastolic pressures in the postinfusion period. The reasons for this procedure were the small group of monkeys and the large changes in end-diastolic pressure, i.e., comparable data in the same end-diastolic pressure groupings shown in the control period could not be obtained after reinfusion. Also because of the small number of monkeys, statistical tests could not be applied. These monkeys were subjected to the 40-mm Hg hypotensive episode for only 2 hours instead of the 4 hours used in the dogs.

All monkeys showed essentially the same results during the control period; there was very little change in their functioning parameters relative to end-diastolic pressure, i.e., the flat ventricular function curves were similar to those seen in control dog 7, probably because of the difficulty of obtaining adequately large shunt flows in these small monkeys. Monkey 1 demonstrated a large increase in function 0-1 hour after reinfusion and some increase 1-2 hours after reinfusion, although this monkey died before the end of the 2-hour period (at 108 minutes postinfusion). Monkey 2 likewise showed increased performance 0-1 hour after reinfusion but a marked decrease 1-2 hours after reinfusion; this monkey fibrillated at 129 minutes. Monkey 3 showed little if any change 0-1 hour after reinfusion and little decrease in function initially in the 1-2-hour period following reinfusion except that he shifted to higher end-diastolic pressure levels. Monkey 3 died 100 minutes after reinfusion. Monkey 4 showed large increases 0-1 hour after reinfusion at high end-diastolic pressure levels. This monkey survived 136 minutes but had a slow heart rate with large T waves in the electrocardiogram tracing during the last hour; a satisfactory ventricular function curve could not be obtained during this period. Another monkey was subjected to 4 hours of hypotension, survived for 45 minutes after reinfusion, and died of cardiac failure. Therefore, of the six monkeys, four died in cardiac failure, one fibrillated, and one died accidentally due to a possible air embolism 19 minutes after reinfusion.

**TOTAL CATECHOLAMINE CONTENT**

Plasma samples were collected from the six monkeys at the end of the control period and just before death, and total catecholamine content (epinephrine and norepinephrine) was analyzed. Because of the required sample size (12.5 ml), it was not feasible to collect samples more frequently.
Catecholamine levels had decreased in all monkeys except one at death. The control value was $55.7 \pm 6.5$ ng/100 ml (mean ± se). The terminal value was $57.9 \pm 10.6$ ng/100 ml due to a 239% increase in one monkey. Eliminating this value, possibly associated with sample hemolysis, the terminal value was $51.3 \pm 7.7$ ng/100 ml. Normal range in our laboratory is 29 to 49 ng/100 ml. One of the control dogs (dog 8) also had samples taken; the control value was 38.0 ng/100 ml and the terminal value was 23.1 ng/100 ml. Three other dogs, not a part of this series, subjected to a similar surgical procedure yielded values in the normal range.

Discussion

The results indicate that in both the dog and the monkey there is a transient increase in ventricular performance following a hypotensive episode; this increase is then followed by a steady decrease ultimately leading to cardiac failure. Specifically, in the dog a progressive and marked decrease in function occurred from 0–2 hours to 2–4 hours after reinfusion and resulted in death within 5 hours. Right and left atrial pressures at equivalent shunt flows were increased in the postinfusion period relative to levels during control periods. Although the pump system stressed the animals, two dogs, which were not subject to a hypotensive episode, were maintained for 10 hours without deterioration in function. Similar data were not obtained for the monkeys, and, because of their small size and the lack of readily available cross-matched blood, it might be difficult to obtain any consistent information using this technique. Control periods lasting up to 2½ hours in the monkey showed no significant deterioration in function, but the slight additional stress produced by the hypotensive episode could have aided in producing cardiac failure, although monkeys 1 and 2 showed definite increases in performance after reinfusion. There can be little question that the rate of decline in function was markedly increased in the postinfusion period, i.e., the shock procedure apparently weakened the myocardium significantly. In the dogs, there was a marked

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increase in function on reinfusion after a full 4 hours of hypotension, but a rapid decrease in the function curves associated with frank failure or suggestive shifts in atrial pressures followed.

Elevation of the early postinfusion curves above normal undoubtedly represented increased sympathetic activity or adrenal catecholamine release. But eventually the ventricle lost its ability to respond, perhaps because of circulating toxins or a decrease in catecholamine levels below the higher level to which it had become adapted. Many other mechanisms, such as acid-base balance, also could have been important. Although plasma catecholamine levels did decrease in most instances, there was little evidence that depletion of tissue stores was a cause of the decrease in myocardial performance. An injected dose of catecholamine is rapidly (within 1 minute) taken up by the tissues in proportion to their sympathetic innervation and their fraction of the cardiac output distribution (18). When circulating levels are high, the only situations that would produce depletion are denervation or interference with the active binding process. At the present time we have no evidence that would support such an interference, although some loss of binding function apparently does occur in congestive heart failure (19). Claviano and Klouda (20) also failed to demonstrate a difference in myocardial content of catecholamines in shock despite a decrease in responsiveness to stellate stimulation. However, there is evidence that persistently high levels of catecholamines, which have been demonstrated during the hypotensive phase of hemorrhagic shock (21, 22), might actually cause a deterioration in myocardial performance (23, 24). Insufficient data were collected from the dogs, but five of the six monkeys showed some decrease in catecholamines terminally. This factor might have been operating for too short a period to cause failure by itself, although it might have contributed to other biochemical derangements associated with myocardial hypoxia during the bleeding phase. Acidosis alone does not appear to be responsible for impaired function at a pH above 6.8 without associated hypoxia (25).

Our results are similar to those of Gomez and Hamilton (26), who maintained arterial blood pressure at 100 mm Hg, except during the abrupt testing procedure when it was 50 mm Hg. However, their results might have been partially related to the very rapid infusions (10 ml/sec) used. In our experiments, step increments (about 2 mm Hg) of pressure were added to atrial pressure, thereby requiring only slow infusion rates representing graded amounts of stress. Our changes were less pronounced than those observed by Siegel and Downing (27), who found markedly depressed function in areflexic cats using an in situ autosupported heart preparation. In their experiments, ventricular function was evaluated from stroke volume and maximal dP/dt values; it decreased 30 minutes into the hypotensive phase. Reelevation of pressure after 2 hours of hypotension did not restore function to normal. Their cats were extremely acidotic (pH 6.93), but this condition did not appear to be primarily responsible for the depression. The severity of the stress in their preparation might have been responsible for the more rapid and severe failure as well as the severity of acidosis. Small doses of sodium bicarbonate were given to some of our animals to maintain the pH within a range of 7.2–7.5, but wider deviations were seldom seen, particularly in the dogs which were equilibrated with fresh, cross-matched blood rather than with dextran.

Initially, we examined ventricular function in animals in which afterload was not held constant. They showed an increase in performance after reinfusion followed by a steady deterioration with time, similar to the curves presented by Goodyer (25). However, arterial blood pressure steadily declined along with atrial pressure because of either loss of fluid from the vascular bed or intravascular pooling, and ventricular performance could not be adequately assessed except by returning aortic pressure to comparable levels. This procedure increased atrial filling pressure and resulted in a more vigorous beat.

If failure is occurring, higher than normal atrial pressures should be obtained for similar cardiac outputs, as pointed out by Crowell and Gutzon (1, 2). In their experiments right and left ventricular function curves (cardiac output vs. atrial pressure) steadily declined from the high levels present after reinfusion to very low levels, i.e., there was low cardiac output despite high atrial pressures, by about 5 hours after reinfusion. They ascribed this condition to vicious cycles associated with positive feedback systems resulting from the prolonged decrease in cardiac output. These changes occurred despite the provision of additional fluid to restore atrial pressure. Atrial pressure also increased when arterial blood pressure was held constant. Survival time was correlated with total oxygen debt and improved by digitalizing the animal. Although their
experiments appear to represent conclusive evidence for the deterioration of myocardial function in hemorrhagic shock, they have been criticized (10, 11) because of their lack of measurements of cardiac work and because the cardiac weakening itself was insufficient to produce the progressive course usually seen in the postinfusion period of hemorrhagic shock. This factor is, of course, virtually impossible to quantify because weakening might result in positive feedback mechanisms leading to rapidly progressive failure. Rothe and Selkurt (10) and Rothe (11) did not find cardiac failure to be a primary mechanism but did see significant cardiac weakening which might have been reversible. They suggested that infusion at too rapid a rate might be responsible for overloading the myocardium, a condition seen frequently in our animals when we attempted to restore arterial blood pressure to normal at the end of the hypotensive phase. Slow restoration and maintenance of atrial pressure at low levels, however, did not prevent later cardiac failure.

Since atrial pressure was maintained at levels sufficient to keep arterial blood pressure at 80–100 mm Hg, the open-chest condition appeared to influence our data only to the extent of the additional surgical stress involved and the danger of continued blood loss from the wound site in the heparinized animal. However, in the dogs, an adequate amount of cross-matched blood was provided to permit continuation of the experiment for 4 hours after reinfusion at adequate hematocrit and oxygen saturation levels. Moreover, the arterial blood pressure levels of 80–100 mm Hg can scarcely be regarded as being too high; the control dogs, which also had open chests, readily withstood the procedure for 10 hours without any evidence for deterioration in their cardiac functional status.

Relative to right vs. left ventricular failure, these studies were designed primarily to look at left ventricular function. Right atrial pressure, however, showed marked increases immediately after reinfusion when left ventricular function curves were showing an increase in performance. This finding appears to be evidence for earlier right heart failure, although this point was not investigated further. We were not able to demonstrate pulmonary hypertension, pooling, or edema (28), which might cause the right ventricle to show earlier failure due to increased work load.

These experiments provided no biochemical evidence regarding the exact nature of the myocardial depressant factor(s) involved. They suggested that the myocardium was more affected in the monkey than it was in the dog, although again the relative stress of the experimental preparation cannot be fully accounted for. Both groups of animals showed a delayed depression after the hypotensive episode, and it was not clear as to when the depressant factor was released or how long it took to act on the heart. Wangensteen et al. (29) showed that hemodialysis at the time of reinfusion resulted in improved cardiac output but did not return the animals to control levels. Hemodialysis also altered other factors, such as pH and the ratio of lactate to pyruvate.

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References


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