Evidence that severe hypotension produces electrocardiographic abnormalities and focal left ventricular myocardial lesions has been provided by numerous studies. In some cases these abnormalities are said to be accompanied by pathognomonic levels of glutamic oxaloacetic transaminase.

Experiments have indicated also that, in the terminal phases of vascular collapse, the heart fails to function adequately in the sense that the cardiac output is subnormal even though the venous pressure may be high. Wiggers subjected animals to hemorrhagic hypotension for 120 minutes. During this time the left ventricular filling pressure was normal or slightly low and the cardiac output much reduced. The shed blood was then reinfused and the cardiac output increased above normal control level with an accompanying rise in left ventricular filling pressure. During the next hour both filling pressure and cardiac output fell to figures below normal. Subsequently the cardiac output continued to fall but the filling pressure rose. It was this terminal and preterminal discrepancy between the increasing filling pressure and the decreasing ejection and contractility that led Wiggers to the conclusion that myocardial weakening played a role in the circulatory collapse that follows hemorrhage. In support of this viewpoint Wiggers cited abnormal ventricular volume and pressure pulses, an intractably falling arterial pressure, and abnormal electrocardiographic tracings.

Experiments by Sarnoff et al. pointed in the same direction. They showed that the rise in left ventricular filling pressure which appeared after an episode of hypotension could be reversed by increasing the left main coronary flow with a pump. This occurred in spite of continued hypotension but did not prevent death of the animal. Sarnoff regarded this finding as indication that insufficient coronary flow and myocardial failure play a complicating role in late hemorrhagic shock.

Crowell and Guyton studied the effects of bleeding animals into a reservoir that held arterial pressure at 30 mm Hg while changes in right and left atrial pressure were monitored and while circulatory function deteriorated and irreversible shock supervened. As this deterioration occurred, the right and left atrial pressures rose whether the cardiac output was held at a low (shock) level or was maintained at a normal level by extensive transfusions. The relation between atrial pressure and cardiac output was determined serially by transfusions and bleedings during irreversible shock and showed a progressive increase in both right and left atrial pressure with a progressive decrease in cardiac output. This was interpreted as a clear indication of myocardial failure. These experiments of Wiggers, Sarnoff, and Crowell indicate that the heart is damaged during the development of irreversible shock but they leave unanswered questions as follows:

1. Will a brief exposure to severe hypotension, which usually results in immediate abnormal electrocardiographic signs, produce an immediate functional deficit or will the appearance of functional impairment be delayed as is the appearance of the structural lesion?
2. If, after such exposure to hypotension, early tests show that the heart has not developed functional incapacity, will the return of arterial pressure, and hence the coronary perfusion pressure to normal, prevent the development of cardiac incapacity? An answer to this question will perhaps furnish a guide for the management of "shock," for if a relatively short episode of hypotension causes irreversible cardiac damage an urgency in the prompt treatment of the hypotension will be emphasized.

3. Is the reduction of coronary flow due to hypotension a necessary cause of the cardiac damage or is the cardiac weakness displayed also by hearts whose coronary perfusion has always been at normal pressures while other body areas have been perfused at hypotensive levels?

4. If the normally perfused heart can be damaged by influences from ischemic areas in other parts of the body, are these influences (presumably due to endotoxins) more important than coronary ischemia? Do they exert their effects at the same time as coronary ischemia does, or before? Are both sets of factors synergistic in the sense that if both are operating the damage occurs more promptly than if only the remote factor is operating?

5. Can evidence be adduced that there is damage to the peripheral vessels as well as to the heart?

Methods

EXPERIMENTAL DESIGN

Dogs under surgical pentobarbital anesthesia were subjected to blood loss and controlled hypotension. In order to demonstrate the earliest development of cardiac deficiency, the left ventricle was presented with a severe load involving a sudden increase in the volume of blood which the heart was forced to pump as well as an increase in the aortic pressure against which it worked. After some experimentation, it was found that infusion of blood into the appendage of the left atrium at a rapid rate (10 ml per second for 30 seconds) resulted in a large increase in cardiac output by an undamaged heart which was accompanied by only a small increase in left atrial pressure. On the other hand, if hypotension had produced cardiac damage, the infusions resulted in a smaller increase of cardiac output and a greater rise of left atrial pressure.

EXPERIMENTAL AND SURGICAL PROCEDURES

Under pentobarbital anesthesia a left lateral incision was made between the third and fourth ribs and artificial respiration was instituted. A probe connected with a Denison-Spencer square wave electromagnetic flowmeter was applied to the aorta to record the cardiac output (minus the coronary flow). Cannulae were placed in the right atrium, by way of the jugular vein, and in the aorta by way of the carotid. A fourth cannula was tied into the left atrial appendage. These four cannulae were connected with Statham strain gauge manometers of appropriate sensitivity and signals from the strain gauges and the flowmeter were recorded on an Electronics for Medicine DR-8 recorder. The apparatus was set to record mean pressures and all of the pressure flow and work data were presented as mean figures over at least one cardiac cycle. A bleeding tube was connected to a femoral artery and to a reservoir which was set 41 cm above the heart to fix the arterial pressure at 30 mm Hg during the hypotensive episodes. An infusion tube was tied into the left atrial appendage and connected with a reservoir. This reservoir was at such a height, and the tube was of such a caliber as to accommodate the standard infusion used. Pressure in the reservoir was monitored during the infusion by means of a sensitive strain gauge manometer to give assurance that the infusion was not interrupted accidentally.

It should be emphasized that these surgical procedures were traumatic and that if they had not been present the animals would, no doubt, have been able to withstand greater exposure to hypotension. The control and experimental animals were exposed to the same surgical procedures.

The animals were heparinized (4 mg/kg) and the cannulae left in place for 30 minutes before the first test of cardiac function was made. The contents of the thorax were kept moist with saline and warm by the judicious use of radiant heat. Infusions were made at body temperature.

The test procedure is illustrated in figure 1, which shows two identical infusions. The records on the left were obtained from a control animal 240 minutes after placing the cannulae and probe (control series below). The records on the right were also made 240 minutes after the operative preparation. This animal, however, had been subjected to 90 minutes of hypotension shortly following surgical preparation (hypotensive group below).

In studying figure 1, one must keep in mind that changes in base line and differing amplification in two entirely separate experiments prevent direct dimensional comparisons between the two parts of the figure. The difference, however, in the response of the two animals is qualitatively
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Corotid Pressure

5Sec 5 Sec

FIGURE 1

I

Flow
[ml/sec]

J-5

LAP cm H$_2$O

Flow

RAP

Infusion
10ml/sec

LAP cm H$_2$O

LAP

RAP

5 Sec

5 Sec

Left: control animal. Changes in left atrial pressure (LAP), right atrial pressure (RAP), carotid pressure, and aortic blood flow during infusion of 300 ml of fresh donor blood into the left atrium at a constant rate of 10 ml per second for a period of 30 seconds. Cardiac work rose from 3.7 to 39 gram meters per second. Right: animal that had been hypotensive. Test was the same as that shown at left. The infusion was done at the same rate but was recorded with a more sensitive manometer. Cardiac work rose from 3 to 27 gram meters per second.

clear from the reaction to infusion. Details will be considered under Results.

In order to make all tests as uniform as possible the arterial pressure was adjusted to 50 mm Hg by hemorrhage or infusion for a minute or two prior to the massive infusion into the left atrium. All experiments were terminated by an overdose of pentobarbital after four and one-half hours of observation in cases where the test showed no deterioration of cardiac function or, more usually, as soon as progressive deterioration of cardiac function was established.

Because cardiac output is governed in some degree by the aortic pressure and because aortic pressure is the resultant of peripheral resistance as well as of cardiac function, it was thought that the rate of cardiac work, or power, would be a better index of the functional capacity of the heart than would the output. The left ventricular work in gram meters per second was calculated using the formula:

$$ W = F \times \frac{AP - LAP}{100} $$

where $F$ = the flow in ml per second, $AP$ = arterial pressure, and $LAP$ = left atrial pressure, both measured in cm H$_2$O.\(^*$

\(^*$This calculation does not include the work done in maintaining coronary flow or in accelerating the aortic column of blood. The energy required for this latter function is revealed by the finding that mean aortic (or ventricular) pressure during systole is 10% to 40% above mean arterial pressure and is the actual force against which the heart works. This excess energy never appears a part of mean pressure, probably because it is damped out by viscous forces during diastole. From this it follows that the conventional formulations for calculating cardiac work, including the kinetic term as it is usually seen, correctly indicate the work done by the heart against peripheral frictional forces but underestimate the work of the heart against aortic pressure by 10 to 40%. A detailed discussion of this interesting point is to be found elsewhere.\(^{12}\)

The quantitative presentation of the results of these massive infusion tests is in the form of plots of left atrial pressure against cardiac work per second, and is given in figures 2, 3, and 4. These plots are analogous to the ventricular function curves of Sarnoff.\(^{11}\) They differ superficially in the fact that each point on the Sarnoff curve was determined when the heart was working in a steady state, whereas on the curves plotted here the points are instantaneous ones showing the simultaneous relation of left atrial pressure and rate of cardiac work during a rapid change experimentally induced. Both types of curve evaluate ventricular function in essentially the same way.

In order to explore the relation between hypotension and functional handicap the animals were divided into four series which were treated as follows.
1. A control series was set up in which the animals were tested immediately after surgery and again after the lapse of 90, 190, and 240 minutes.

2. A hypotensive group of five dogs was studied in which the animals were tested immediately after surgery. Right after this test the arterial pressure was maintained at 30 mm Hg for 90 minutes. The animals were tested again and the arterial pressure raised to 100 mm Hg, where it was maintained until the end of the experiment by infusing the dog's own blood, supplemented when needed by fresh donor blood. The test was repeated after the time intervals mentioned in describing the control experiments.

3. The term "partially hypotensive" is applied to a series of five dogs prepared by placing a clamp on the descending aorta just below the subclavian branches. Two equilibrating reservoirs were set up so that the cephalad arteries, including the coronaries, had normal perfusion pressure (100 mm Hg) while the rest of the animal was hypotensive at 30 mm Hg. The amount of blood in the low pressure reservoir connected to the femoral artery was held constant by repeated adjustment of the aortic clamp. A reserve of blood in the high pressure reservoir (connected to the carotid artery) was maintained by the addition of fresh donor blood when needed. Tests were made immediately after surgery and 90, 210, and 270 minutes later. In this series only the lower part of the animal suffered hypotension and this for a period of 90 minutes.

4. Another partially hypotensive group of four dogs was set up exactly like series 3 except that hypotension was maintained in the caudal part of the animal for 150 instead of 90 minutes. Tests were made when the operation was finished and again after the lapse of 150, 210, and if possible, 240 minutes.

Approximate account was kept of the blood needed for infusion to maintain arterial pressure at normotensive levels during the control period and during experimental testing.

Results

The data used in calculating the results described below were obtained from records similar to figure 1 which shows the effects of the infusion test on pressure and flow. The record on the left is from the control animal. The infusion was made 240 minutes after completing the operation to insert the probe and cannulae. The right atrial pressure rose minimally and the left atrial pressure remained within physiological limits. The aortic flow increased continuously to a figure about three times the rate of infusion.

The record on the right shows the effect of the same left atrial infusion (300 ml in 30 seconds) on an experimental dog. These animals had been treated in exactly the same way as the control animal except that they had been made hypotensive for 90 minutes immediately after the operation and had then been held at normal arterial pressure levels for the next 150 minutes. Before and during early infusion the levels of left atrial pressure and of aortic pressure and flow were essentially the same as in the controls but by the time the flow had increased by roughly the amount of the infusion, it remained constant or even declined while the left atrial pressure rose rapidly. In the case illustrated it rose to an unusually high peak during a temporary asystole and the few succeeding beats.

Figure 2 is a composite plot of the collective results of the infusion experiments on the controls (series 1) and the hypotensive group (series 2). The experimental animals served in some degree as additional controls because the first test in the five experimental animals could not be distinguished from either the first or last test of the three controls. In all cases the rate of work increased throughout the infusion in direct proportion to the increase in left atrial pressure. These quantities rose steadily as the infusion continued for its allotted 30 seconds. The highest level attained by the figure for work rate varied from experiment to experiment between 53 and 28 gram meters per second. Two uncontrolled variables affected this variation. Although the infusion was monitored in each experiment and was kept constant in amount and rate, the actual aortic blood flow reached rates three to five times the 10 ml per second of the infusion. The peak output depends upon the effectiveness with which the infusion augments the venous return via the venae cavae, and upon the ability of the left ventricle to pump the augmented stream into the aorta. If the heart cannot do this task, some of the infused blood remains in the left atrium and the left atrial pressure increases.
The control animals were given the infusion test at intervals after surgery. In all cases cardiac performance changed very little. During the final test the hearts could work at rates of 50, 46, and 39 gram meters per second at peak left atrial pressures of 13, 22, and 16 cm H$_2$O. In the eight initial tests, immediately after surgery, including the experimental as well as the control dogs, the left atrial pressure rose to peak values between 9 and 15 cm H$_2$O. Since there was no tendency for the work rate to become constant or to decrease during the infusion either in the tests immediately after surgery, or in the tests after the control animals had lain on the table for 240 minutes, it was concluded that the cardiac performance of these dogs did not deteriorate significantly during the experimental period. This is in marked contrast to the performance of the hearts of the experimental animals.

The dotted lines show the response of the hearts of experimental animals to the same infusion after exposure to 90 minutes of hypotension followed by 150 minutes of normal blood pressure. Before infusion and during early infusion, the load was low and the responses of the hearts of the hypotensive animals were very nearly normal both as to filling pressure and as to work accomplished. As the infusion continued and as the infused blood resulted in an augmented stream which began to return by way of the venae cavae the functional capacity of the heart was exceeded and its output remained constant or decreased.
as indicated in figure 1 (right). Since there is a significant rise of arterial pressure, it is the failure of the heart to pump out the augmented volume of the caval stream that accounts for the curtailment of the response of the heart in terms of work, as well as for the accumulation of blood in the left atrium and the rise in left atrial pressure. In only one of the experiments did the final seconds of infusion bring about an increased rate of work (fig. 2). This was at an extraordinarily high left atrial pressure. The usual response was a downward trend. In all cases the left atrial pressure rose much more in these last seconds than it did in the control tests.

This diminution in the functional capacity of the left ventricle occurred as the result of exposure to 90 minutes of hypotension followed by 150 minutes during which the arterial and coronary pressures were at normal levels. It is in contrast to the behavior of the hearts of the control animals which had been subject to the same surgical and anesthetic procedures and had lain in the lateral recumbent position for the same length of time. These control animals had never been hypotensive and therefore did not develop the incapacity found in the hypotensive animals.

When the test was administered immediately after the hypotensive episode the response was nearly normal. In spite of the fact that blood pressure was maintained at 100 mm Hg, tests an hour and two hours later showed a steady functional decline. In a few cases another test was given again 240 minutes after the hypotensive episode with the arterial pressure maintained at 100 mm Hg for the whole time. It showed evidence of further decline in cardiac function. It is concluded, therefore, that the heart had suffered damage during the hypotensive period which showed no evidence of reversibility when arterial blood pressure was returned to normal for a prolonged period even though the return to normal pressure occurred before the damage was manifest.

To determine how much damage was done by lessened coronary perfusion, the experiment was modified to maintain pressure in the coronary arteries at normal levels. In order to have a large enough "Windkessel" to insure coronary diastolic flow the blood in the aortic arch and in the arteries to the head and forelimbs was held at normal pressure by means of a clamp. Two Lamson reservoirs were used to maintain pressure above and below the clamp at normal and hypotensive levels. (See Methods.) The duration of the partial hypotension was 90 minutes.

The results of these experiments were contradictory. They are plotted in figure 3. In three of the five animals the hearts could perform about as well as before the hypotension. In a fourth animal performance had deteriorated only slightly. In these four cases the rate of work continued to increase throughout the infusion as it did in the initial test and

![Figure 3](http://circres.ahajournals.org/)

Same as figure 2 except that 90 minutes of hypotension were confined to the aortic branches below the subclavian. Only one curve shows definite evidence of cardiac damage.
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The infusion tests for cardiac functional reserve in these dogs with 150 minutes of partial hypotension were three in number. Results are summarized in figure 4. The initial tests, which were made immediately after surgery, produced a normally continued increase in rate of work throughout the infusion. The second tests, performed immediately after the period of hypotension, showed little or no functional cardiac deterioration. The third tests (last test, fig. 4), performed after the animals had been held normotensive for one hour, all demonstrated functional deterioration. In each case the last part of the infusion showed a decrease in rate of work coupled with an increase in left atrial pressure. In one case the heart worked as well as the best normal heart, but only when the left atrial pressure was higher than normal. Further increase in left atrial pressure was associated with a decrease, rather than the normal increase, in rate of work.

The implication of this last series of experiments is that some fault had developed in the circulating blood as a result of the hypotension. Consideration must be given to the possibility that the blood had been depleted of nutrients and other supportive substances by some effect of the hypotension even though this possibility is diminished in part by using large amounts of fresh donor blood to maintain normal arterial pressure.

Another possibility is that some part, perhaps the visceral part, of the hypotensive vascular bed absorbs a cardiotoxic substance which is transported to the heart. It is possible that the functional cardiac impairment shown in the tests of figure 4 is due to this substance. The design of the test is such that the damage occurs even though the myocardium has never been directly subjected to the effects of hypotension. Whether this toxic substance is the shock producing endotoxin which has been given exhaustive analysis by Fine and co-workers in numerous publications and what role systemic hypotension may play in interfering with various detoxifying mechanisms must await further work.

During the course of these experiments with
prolonged partial hypotension, a decided difference appeared in the amount of blood needed to return the animal's arterial pressure to an overall value of 100 mm Hg. After 90 minutes of hypotension, either in the whole animal or in its hind parts only, reinfusion of the shed blood sufficed in many experiments. In other experiments the amount of fresh donor blood needed rarely exceeded 250 ml. Additional volumes of fresh donor blood were usually needed to maintain the level of arterial pressure at 100 mm Hg for the experimental period. These volumes, ranging from 500 ml to 1000 ml, were of the same order as those required in the control animals and may be regarded as a substitution of blood lost in heparinized dogs.

When partial hypotension was maintained for 150 minutes and then the blood pressure was raised to an overall figure of 100 mm Hg, an immediate infusion of about 1 liter was required. This is a larger volume than was needed after 90 minutes of hypotension. It implies a greater enlargement of the capacity vessels in the longer experiments owing, presumably, to intravascular pooling. This enlargement of vascular capacity occurred while the right atrial pressure was low and cannot be regarded as an example of receptive or stress relaxation.

After the arterial pressure had been returned to normal, further massive infusions averaging 1.4 liters were needed to maintain normal arterial pressure for about an hour. No data are available to justify a decision as to what fraction of infused volume went to enlarge the intravascular pool and how much was lost into the tissue spaces. In either case, the results of these experiments lead to the conclusion that the peripheral vascular bed suffers a functional abnormality because of the prolonged partial hypotension and that the nature of this abnormality favors the development of "shock."

Discussion

In answering the questions which were posed at the end of the introduction, it seems that the functional defect produced by surgical procedures followed by 90 minutes of hypotension at 30 mm Hg is not evident until an hour or more after the termination of the hypotension. Even though the arterial pressure is promptly returned to, and maintained at, a normal level the heart deteriorates steadily over the next two or three hours. It is concluded that the effects of surgical operations together with those of hypotension have produced irreversible cardiac damage. The control experiments indicate that the surgical procedures alone produce no such damage. These findings make apparent the potential danger of an episode of hypotension or perhaps better, the danger resulting from the vasoconstriction and reduced blood flow which is the result of the hypotension.

The cardiotoxic material carried by the blood stream from hypotensive and ischemic regions elsewhere in the body caused, in these experiments, functional cardiac damage even when the heart was perfused at a normal coronary pressure. The source and nature of this substance can only be speculated upon at present. It is clear that this damage from remote sources acts more slowly when the heart is normally perfused. Cardiac ischemia and remote toxic influences from hypotension elsewhere in the body seem to act synergistically. Neither cardiac ischemia nor remote ischemia are shown to be prepotent.

The need for large transfusions to return arterial pressure to normal and to maintain it when the hypotensive episode lasts 150 minutes (after surgery) at 30 mm Hg indicates that the functions of the peripheral vascular bed have also been deranged.

The idea that functional failure of the heart plays an important role in the development of circulatory collapse has not had widespread acceptance. Because even in extremis the heart seems to be able to pump out the blood which naturally returns, it has been thought that the small cardiac output characteristic of shock is due to a small venous return rather than to a myocardial fault. Rarely is attention drawn to the circular reasoning involved in this sequence. It must be recognized that in order to return through the veins, blood must
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be pumped out through the arteries, and the question as to whether the heart is weakened is not answered by the assumption that the small venous return is the cause of the small output rather than vice versa.

The experiments described here show that the major surgical procedures employed, together with the added burden of 90 minutes of hypotension, set the stage for an inevitable deterioration of the pumping function of the heart. Immediately after these episodes the heart reacts normally to light and heavy loads. An hour later it reacts normally to resting loads and to small added experimental loads but cannot handle larger loads. After the lapse of more time, the heart has become weaker in spite of normal coronary perfusion pressure maintained during the entire period after the hypotensive episode. There is thus no evidence that the cardiac damage is reversible even though the blood pressure is returned to normal when the pumping function of the heart is also still normal. The experiments give no definite evidence of deteriorating function at resting volume loads. The heart of the hypotensive dog must be faced with a large load in order that it may be differentiated from a normal heart.

Summary

A massive infusion test has been devised to evaluate the functional capacity of the heart.

In five dogs extensive surgical procedures followed by episodes of arterial hypotension at 30 mm Hg and lasting 90 minutes caused severe cardiac incapacity, which was demonstrated by failure of rate of cardiac work to increase throughout the infusion together with a large rise in left atrial pressure. This incapacity was not evident in tests made immediately after the hypotensive episode. The damage became more and more severe in tests performed 90 and 150 minutes after the end of the hypotension even though mean arterial pressure was maintained at 100 mm Hg. Operated control dogs did not show cardiac deterioration in tests timed as above. The rate of cardiac work continued to increase throughout the infusion with a relatively small rise of left atrial pressure.

In a series of five dogs, flow to the coronary arteries and to those supplying the head and forelimbs was maintained by normal blood pressure while the rest of the animal was made hypotensive for 90 minutes. The arterial pressure in the whole animal was then returned to an average level of 100 mm Hg. Tests made at intervals after the hypotension showed equivocal evidence of cardiac deterioration.

In another series of four dogs, prepared as above, the partial hypotension lasted 150 minutes before the arterial pressure was returned to normal. Tests at intervals after hypotension showed cardiac damage in all the animals and severe damage in three. Evidence is presented indicating that the peripheral vascular bed had deteriorated functionally as a result of 150 minutes of partial hypotension.

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Functional Cardiac Deterioration During Development of Hemorrhagic Circulatory Deficiency
OSCAR A. GOMEZ and WILLIAM F. HAMILTON

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