CARDIAC OUTPUT AND TOTAL PERIPHERAL RESISTANCE IN POST-HEMORRHAGIC HYPOTENSION AND SHOCK¹

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The anesthetized dog when submitted to a prolonged period of drastic hypotension, achieved by controlled bleeding, enters into a state of irreversible shock. The standard procedure developed in this laboratory for producing this state (1) entails lowering the arterial blood pressure by rapid bleeding to 50 mm. of Hg and sustaining it at this level for 90 minutes; it is then reduced to 30 mm. of Hg, at which level it is maintained for an additional 45 minutes. At the conclusion of this 135 minute interval of severe hypotension, all withdrawn blood is rapidly reinfused. Despite the latter procedure, very few dogs have actually survived. Studies have also been conducted by members of this laboratory (2) to ascertain the nature of the permanent derangement produced by severe hemorrhagic hypotension. Both peripheral and cardiac events were followed during the development and terminal stages of the shock state. The cardiometric method which they used to measure cardiac output, though more satisfactory from many standpoints for this purpose than gasometric methods, unfortunately necessitated the employment of open-chest animals. It is therefore hazardous to apply these results to interpret similar situations in the intact animal, since the circulatory state of open-chest animals is extremely labile and unpredictable.

It is now possible to obtain reasonable and consistent cardiac output measurements rapidly and frequently in the intact dog by employing the “modified Stewart method,” the merits of which have been recently discussed by one of us (3). Employing this more favorable method, the authors have examined cardiac output and total peripheral resistance (TPR) changes which occur during the development and course of “hemorrhagic hypotension” shock in intact anesthetized dogs. Evaluations of total peripheral resistance, which is dependent upon accurate measurement of both cardiac output and mean arterial blood pressure, were computed from the equation

$$TPR = \frac{P_m \times 1332}{\text{cardiac output/sec.}} = \frac{\text{dynes sec.}}{\text{cm}^2}$$

and are expressed as absolute units (A.U.).

PROCEDURE. Following a small preparatory injection of morphine, the dogs were anesthetized with either sodium barbital (175 mgm./kgm.) or chloralosane (75–80 mgm./kgm.). The inconsequential operative procedures required for measurement of cardiac output and for recording arterial pressure pulses and mean atrial pressures were then performed. Systemic heparinization⁴ of the dogs

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was instituted to preclude possible interference with output determinations by clotting of blood either in the detection cannula or in the blood samples withdrawn.

Once circulatory equilibrium was established, three consistent and reasonable control values for cardiac output were procured in successive determinations. Immediately thereafter, rapid controlled bleeding was instituted. Sixteen dogs were used. Of these, six died of cardio respiratory failure during the 30 mm. period of hypotension and therefore only yielded results for the early periods.

One can observe from the graphs in figures 1, 2 and 3 the standard procedure which was adopted for the times at which various cardiovascular events were evaluated. More frequent determinations of the latter did not add significantly to the results. Accurate estimates of the heart rate were obtained from the arterial pressure pulses which were photographed during each cardiac output determination. Mean right atrial pressures were read from a damped saline manometer just prior to each cardiac output measurement. In order to obtain a rough estimate of changes in blood viscosity, hematocrit readings were made on control blood samples collected for output determinations. In most experiments, the right atrial-femoral artery circulation time was measured by a procedure described in a previous paper (3).

RESULTS. Of the six dogs which succumbed from cardio-respiratory failure during the 30 mm. period, two revealed a severe broncho-pneumonia upon autopsy, whereas the other four showed intense congestion, numerous petechiae and free blood in the lumen of the upper intestine. The cardiovascular changes in these animals during the 50 mm. period were not unlike those displayed in the other ten animals; hence they are included in the data presented.

With few exceptions, the course of events during the development and terminal course of "shock" is fairly represented by the typical charts of two experiments in figures 1 and 2. The more important exceptions concern the peripheral resistance changes illustrated in figure 3 which will be discussed later. The response of the dogs following complete reinfusion of all withdrawn blood was favorable, yet they all succumbed within ten hours. The impression was gained that this eventual outcome might have been prolonged, but not prevented by any therapeutic measure. The autopsy findings strengthened this viewpoint. There was intense congestion of the upper intestine and frequently of the colon and rectum in every animal, but one. In most instances, large quantities of free blood were found in the lumen of the large and small intestine. In addition, both ventricles and atria usually revealed numerous petechiae throughout the subendocardial surfaces of their walls. Hemorrhages about the base of the valves were not uncommon. Occasionally, small hemorrhagic infarcts were encountered in the lungs. It seems likely that systemic heparinization may have accentuated these findings.

Control blood pressures in ten of the dogs were in a hypertensive range (140 to 170 mm. of Hg); in others, they varied from 95 to 135 mm. of Hg. By variable degrees of reduction of their original blood volumes, all dogs were subjected to a standard degree of hypotension. Five of the dogs which survived the 30 mm. pe-
riod were originally in the hypertensive category; the other five were in the essentially normal blood pressure group. No correlation between the initial blood pressure level and the post-reinfusion survival time was established.

The recovery of blood pressure immediately after rapid reinfusion of withdrawn blood was so satisfactory that an auspicious prognosis might have been made for most of these animals at this time, if blood pressure level alone were considered. Control levels were regained in five dogs, satisfactory but not pre-existing hypertensive levels were attained in four others; whereas in one dog, a poor response of 54 mm. Hg was obtained. The latter died very suddenly between the first and second post-reinfusion hours. In most cases, the prognosis took an inauspicious turn within an hour after reinfusion; the blood pressure began a progressive decline toward critical hypotensive levels. On two occasions, however, the reinfusion blood pressure level was essentially maintained for 2 to 3 hours, then descended quite rapidly toward critical level.

The cardiac output and the stroke volume were severely reduced throughout the 50 and 30 mm. periods as a result of the great reduction in blood volume which was required to lower blood pressures to these levels. The stroke volume was further embarrassed by cardiac acceleration which abbreviated the cardiac filling time. The cardiac outputs during the prolonged hypotension varied from 29 to 45 per cent of the original control volumes. Only minor fluctuations were observed during this 135 minute interval. Concordant with the development of hypotension and the large reduction of minute volume, there was a marked prolongation of the circulation time; in many instances it was doubled (fig. 1). Even though generally tachycardic during the control period, heart rates were further accelerated during the 50 mm. period. During the 30 mm. period they were more variable; in some cases the heart rate was further accelerated, in others, slightly decelerated, in still others even retarded below control values (figs. 2 and 1). With the latter slowing, stroke volumes increased somewhat without any significant change in the cardiac output. Hematocrit values decreased progressively during the 50 mm. period and remained constant during the 30 mm. period. This connotes hemodilution and a reduced blood viscosity.

The response of cardiac output to the reinfusion of withdrawn blood was not as auspicious as the blood pressure recovery. In six dogs it was very satisfactory, the cardiac outputs returning to 90 to 118 per cent of control volumes. In the other four, it was mediocre at best, varying from 45 to 85 per cent of the control volumes. During the next three hours, however, the cardiac output in seven dogs diminished rapidly. Following this it usually stabilized at low values similar to those established during the hypotension period (fig. 1), where it remained until death occurred. In three animals, cardiac output was only slightly diminished during the first 2 to 3 hours after reinfusion and then decreased abruptly to similar low volumes.

The stroke volume was improved after reinfusion, but never regained control values in nine of the dogs. In eight animals, it was progressively reduced thereafter, much as the minute volume. In two dogs, however, stroke volume improved as the post-reinfusion period progressed. This was related to a simul-
taneous progressive slowing of the heart in these two instances. In the eight animals mentioned above, the heart rate regained or approached normal rates immediately after reinfusion and underwent a secondary acceleration during the initial hours of the post-reinfusion period. This acceleration was sustained until death in five of the dogs (fig. 2); in the others, even if they underwent this secondary acceleration, the heart was markedly slowed and irregular during the terminal hours of the experiment (fig. 1). In all but one animal, a tendency toward progressive hemoconcentration was in evidence throughout most of the post-reinfusion period. The circulation time, though essentially normal after reinfusion, again steadily increased until the circulation again assumed the sluggish characteristics seen during the hypotension period (fig. 1).

The changes in peripheral resistance were rather variable. The types of changes which are likely to be encountered are illustrated in the charts of figures 1, 2 and 3. Two different responses were observed during the 50 mm. period. In eight of the dogs, TPR was elevated above respective control values during the greater part of the period, as shown in figures 2 and 3, II. In the other eight
animals, TPR was markedly reduced at the onset of the 50 mm. period. In five of these, however, TPR increased, approaching control values as the period progressed. Regardless of the response during this period, all TPR values were reduced below their respective control values during the 30 mm. period. Those with an elevated TPR during the 50 mm. period showed the greatest reduction. At the termination of this hypotension period, TPR values varied from 64 to 84 per cent of their respective control values.

Immediately after reinfusion, TPR in five animals varied from 95 to 116 per cent of their respective control values; in the others, reasonably satisfactory though definitely subcontrol values were attained (60 to 92 per cent of control). The course of the TPR during the remainder of the post-reinfusion period was extremely variable: 1. In four dogs, represented in figure 1, the TPR rose progressively to a peak value high above the control within the first 2–3 hours after reinfusion; it then subsided suddenly to markedly subcontrol values within the succeeding 2 to 3 hours prior to the death of the animal. This response is also represented in figure 3, II. 2. On two other occasions the TPR ascended more gradually to a level above the control and then diminished to a level not far below the respective control at about the same rate that it ascended. This is exemplified by the TPR changes in figure 2. 3. As shown in figure 3, III, TPR hovered around the control values for approximately five hours, suddenly rose to a peak (135 per cent of control value) from which it sank rapidly to a subcontrol level (71 per cent of control) much as in the animals in the first group above. In this particular animal the cardiac output never stabilized at a low volume but continued to diminish at a more gradual rate until the experiment terminated. 4. On two occasions, typified by figure 3, I, TPR failed to attain the control value after reinfusion; it subsided rapidly from this reinfusion level to subcontrol levels.

![Graph showing hemodynamic changes](http://ajplegacy.physiology.org/DownloadedFrom://10.220.33.5/on/May.8.2017)
until death occurred within three hours. 5. The final type (fig. 3, IV) resembles that seen in figure 3, III in that TPR changed very little for 5 to 6 hours after essentially normal values had been regained following reinfusion. In this animal, however, TPR did not rise belatedly; its peak value (116 per cent of control) was gained immediately after reinfusion. At about the sixth hour after reinfusion, it diminished fairly rapidly to a markedly subnormal level (64 per cent) just prior to death. Peculiarly, this was the only animal in which autopsy findings were completely negative throughout.

Just prior to death, TPR was but slightly reduced in five of the dogs, the values varying from 88 to 102 per cent of their respective control values. An example is shown in figure 2. In the other five it was severely reduced, the values recorded just prior to death varying from 40 to 71 per cent of their respective controls (example, fig. 1).

Fig. 3. Types of TPR curves encountered during post-hemorrhagic hypotension; during reinfusion and circulatory failure. Ordinates in percentage changes from control = 100 (dotted lines). Abscissal, indications as in figure 1. Discussion in text.

DISCUSSION. An analysis of the cardiac output and TPR changes, as well as of the changes in related events, permits fairly definite conclusions as to the nature of the primary derangements incurred from these drastic hemorrhagic hypotension procedures.

The total resistance to the outflow of blood from the aorta is governed by several factors: 1. Fundamentally, it depends upon the physical dimensions of the vascular system; hence the latter largely determines the range of TPR fluctuation which may result from superimposed influences. These dimensions may be considerably altered with growth and ageing processes. 2. It is also dependent upon the effective viscosity of the blood, decreasing as the cell/plasma ratio decreases and vice versa. 3. Finally, TPR is continuously modified by functional modifications in the caliber of minute vessels induced by a, vasomotor nerve influences; b, action of chemical agents, and c, variable extra-vascular ten-
sions created by muscle tone, tissue fluid pressure and the like. It is more often the rule than not that several of these factors are simultaneously involved in circulatory reactions and it is important to evaluate the relative contributions of each whenever possible. In these studies, it has been possible to infer the dominating factor with a high degree of probability.

Since the characteristic of irreversibility develops during the hypotension period, the course of events during the 50 and 30 mm. periods must be carefully examined and analyzed.

a. Fifty millimeter period. Among the anticipated responses to lowering of the blood pressure by hemorrhagic procedures which were actually observed in these dogs may be included a, an accelerated heart rate; b, a diminished stroke and minute volume; c, a prolongation of the circulation time; d, a reduction of venous or atrial pressure, and e, a progressive hemodilution. The nature and causes of TPR changes in the development and course of shock have not been established.

These experiments have demonstrated that TPR a, may progressively decrease, as in figures 1 and 3, I; b, may fall initially and then recover toward control values, as in figures 2, 3, III and IV, or c, may increase, as in figure 3, II. In attempting to determine the factors which dominate these TPR changes, it is initially expedient to eliminate those TPR determinants which change uni-directionally and to much the same extent in all animals, for they cannot be dominant forces in such variable reactions. Little can be said about the extravascular forces and their effects upon venous return. There is, however, little reason to anticipate that these forces are significantly or variably altered and hence that they play a major rôle in the reactions of these supine anesthetized animals. Furthermore, comparison of the hematocrit values obtained during this period with related curves published by Whittaker and Winton (4) convinced the authors that within the ranges of cell/plasma ratios found in these experiments, the effective viscosity in the blood vessels of the body is not greatly reduced. Since the hematocrit readings were reduced to essentially the same extent in different experiments, it is believed that its effect in reducing TPR does not differ much in the various animals. It is probable, therefore, that no great error is incurred in the assumption that the above factors remain fairly equal in different experiments and that they play, at most, a very small rôle in determining changes in TPR. Consequently, the variable TPR changes are chiefly due to active changes in the caliber of minute vessels, dominantly the arterioles. At the onset of the 60 mm. period, such changes are not likely to be caused by a peripheral accumulation of metabolic products. As the period terminates, however, such products may very well tend to counteract or even overbalance the influence of vasomotor nerve impulses. Chemical influences certainly cannot be very significant in those animals in which TPR was elevated far above control values. Therefore, the different TPR trends during this period are primarily attributable to varying responses of the vasomotor nervous mechanisms to the drastic circulatory upset which has been produced. One might speculate that this variability can be explained upon the differences in the progress of anesthesia in these dogs. The latter is minimized, however, by the fact that hemorrhagic procedures were
never instigated until four hours after the anesthetic had been administered and by the fact that strikingly similar responses were observed in dogs under such dissimilar anesthetics as sodium barbital and chloralosane. Whatever the reason, it can be stated that vasomotor nervous compensation during the 50 mm. period was very strong in some, moderate and delayed in others and actually inadequate in still other dogs. Regardless of the course of the TPR changes seen during this period, the outcome was eventually the same in all animals, namely, death within 2 to 10 hours after reinfusion of the withdrawn blood.

b. Thirty millimeter period. The reduction of the blood pressure to 30 mm. of Hg was accomplished either by allowing it to fall spontaneously or by a very small amount of bleeding. Hence, cardiac output was not significantly altered. Greater or lesser acceleration of the heart rate was seen in some animals; in others the heart was markedly retarded below control rates. Such slowing was not altered by bilateral vagotomy; hence it probably occurred as a result of the action upon the pacemaker of chemical metabolic accumulants, largely produced by an inadequate coronary flow at these low pressures.

The TPR changes during this period of drastic hypotension were uniform in direction, i.e., TPR fell below normal in every animal. Blood viscosity is not a factor in this decline, inasmuch as the hematocrit values remained essentially unchanged. The TPR changes therefore must be primarily determined by active changes in peripheral vessels. There can be little question that anoxic and accumulated metabolic by-products exert considerable influence upon the peripheral vasculature tending to produce vasodilation, thus reducing the effectiveness of any existing nervous influences on these same structures. In view of the fact that large vasopressor responses can be induced by pressor nerve stimulation and by asphyxial conditions at this time, it seems evident that the vasomotor centers have not failed. It may be, however, that the intensity of their reactions is lessened which, coupled with the dilating action of anoxia and metabolites, brings about a reduction in the total peripheral resistance.

c. Post-reinfusion period. The return of arterial blood pressure immediately after rapid reinfusion of withdrawn blood to satisfactory levels was an auspicious beginning. However, the cardiac output was satisfactorily improved in only six of the ten dogs. Immediately thereafter, cardiac output began to decline and became progressively smaller until volumes equivalent to those encountered during the hypotension period were again attained. Thus, as others have shown in other forms of shock, the declining arterial pressure which follows reinfusion of blood after severe prolonged hemorrhagic hypotension is due chiefly to progressive reduction in cardiac output. But, during the later stages, further decline of arterial pressures occurs without additional reduction of cardiac output, indicating that now peripheral factors are operating. In the terminal stage, hearts of several dogs were considerably slowed and irregular in rhythm, as in the 30 mm. period. This terminated life.

The TPR values obtained immediately after reinfusion were essentially normal or slightly higher. Following this, a variety of changes in TPR were seen, as shown in figures 1, 2 and 3. The interpretation of these varied responses is
somewhat more complicated than that of the changes encountered during post-hemorrhagic hypotension. The cell/plasma ratio remained essentially normal in two dogs; in the others, it increased above the control. This demonstrates that hemoconcentration can occur in circulatory failure following hemorrhage and reinfusion, and that the condition also qualifies as a shock state in accordance with Moon's criterion. However, the hematocrit readings never exceeded 60 and were never less than 40 in controls. Consequently, in accordance with curves of Whittaker and Winton, the changes could have only a minimal effect in increasing the effective viscosity of blood in the blood vessels. It is, however, unlikely that this physical determinant alone is responsible for the marked elevation in TPR which was observed in some experiments, and of course fails to account for reductions. Such changes must involve alteration of vasomotor tone. During the early hours of the post-reinfusion period and until a critically sluggish circulation again develops, it is questionable whether anoxia or the accumulation of metabolic by-products are severe. The possibility that vasopressor substances often present in shed blood are concerned is virtually excluded in view of the facts that a, such agents should produce a sudden, not a progressive elevation of TPR when the blood is reinfused rapidly, as shown in figures 1, 2 and 3, II; b, they cannot be responsible for the delayed response seen in figure 3, III, nor c, can they explain the prolonged maintenance of TPR at essentially control levels, as in figure 3, III and IV. Furthermore, attempts were made to prevent the accumulation of vasoconstrictor substances in the shed blood by keeping the latter refrigerated until just prior to reinfusion. Thus, the TPR changes depend upon the reactivity of the vasomotor nerve mechanisms.

During the terminal hours preceding death, however, TPR always falls, in some cases to slightly subcontrol and in others to extremely subcontrol values. That this cannot be due to failure of the vasomotor centers—although the activity of the latter may be somewhat less intense—is signified by the increased TPR which can be induced as a result of asphyxial procedures or upon stimulation of some afferent pressor nerve. Since a significant decline of TPR does not occur until the circulation has again become very sluggish at critically hypotensive blood pressure levels, and since cardiac slowing and irregularity re-occur at this time in some dogs, it seems reasonable to assume that, as during the 30 mm. period, humoral or metabolic agents are again more effectively overcoming the nervous influences upon blood vessels in the periphery, thus affecting a reduction in the effective TPR. The variability in the degree of TPR reduction just prior to death may be supposed to be related to the variable concentration of humoral or metabolic agents and their variable effectiveness in counterbalancing the effects of nervous activity upon the smaller blood vessels.

The method for producing standardized hemorrhagic shock employed in these experiments was arrived at in this laboratory (5) by "trial and error" methods. It was found that shock could be produced more consistently by maintaining standard low arterial pressures for specified intervals of time than by bleeding the animal by definite volumes of blood per kilo of body weight (1).
A physiological basis for such a procedure would be suggested if it could be shown that this correlated with the reduction of the circulatory index (cardiac output per square meter of body surface) to a definite minimal value or with a definite percentage reduction of the control cardiac output. Since it is not clear whether, with the intense constriction of surface vessels, such calculations of circulatory index are more properly made on a surface area or weight basis, we contented ourselves with the method described. As stated, our results showed that cardiac output was always reduced to 29 to 45 per cent of the original control values during most of the 135 minutes of hypotension. In other words, reduction of the circulatory value to one-half to one-third of the normal output for two and one-quarter hours suffices to induce the irreversible state. However, the considerable ranges in percentage reductions of cardiac output indicate that the simple procedure for producing hemorrhagic shock by holding arterial pressures at specified levels does not result in equal reductions of total blood flow in different animals. This merely illustrates again the difficulty of creating entirely similar conditions in different animals for the study of shock problems. It may also well explain why much shorter periods of less drastic hypotension often suffice to produce shock while even more prolonged periods of severe hypotension occasionally fail to do so.

SUMMARY AND CONCLUSIONS

1. Utilizing a "modified Stewart method" for determining cardiac output, variations of the latter and of total peripheral resistance (TPR) were studied during the course of standardized hemorrhagic shock in relation to other cardio-dynamic events and hematocrit changes.

2. During a 90 minute period of 50 mm. of Hg hypotension and a subsequent 45 minute period at 30 mm. of Hg, cardiac output and stroke volume were reduced to 29 to 45 per cent of the control flow. Although they were restored to normal in the majority of experiments immediately after reinfusion, in some the recovery was only to 45 to 85 per cent of control values. During the three hours succeeding reinfusion, cardiac output decreased rapidly and was the chief cause of the declining arterial blood pressure. In the final stages cardiac output stabilized at low levels and the continued fall of blood pressure was occasioned chiefly by peripheral factors. Slowing and failure of the heart was often the ultimate step in the series of cardiodynamic events leading to death.

3. Hematocrit readings indicated a hemodilution during the periods of hypotension and a tendency toward concentration following reinfusion of the blood.

4. The course of events in standardized hemorrhagic shock is therefore similar to that described in other experimental types in that a, hemoconcentration occurs, and b, progressive reduction of cardiac output is chiefly responsible for the progressive decline of arterial pressures after reinfusion.

5. Despite the universally fatal outcome, changes in the total peripheral resistance were extremely variable during the periods of post-hemorrhagic hypotension and during circulatory failure which developed after reinfusion of blood. The different trends are analyzed. Arguments are advanced that
physical factors concerned in such changes can be evaluated and that an estimate of directional changes in vasomotor tone can be made. Supplementary evidence is cited from which the conclusion is reached that humoral or metabolic factors play a considerable rôle in these changes.

6. In the method for producing shock by holding mean arterial pressures at successive levels of 50 and 30 mm. of Hg for specified intervals of time, cardiac output was reduced to 29 to 45 per cent of the original blood flow. Such ranges of reduction indicate that the procedure recommended for the rather regular production of hemorrhagic shock does not result in equivalent reductions of circulatory values when applied to different animals. Of course, the possibility that other factors may enter cannot be excluded.

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