Studies in Clinical Shock and Hypotension

IV. Variations in Reflex Vasoconstriction and Cardiac Stimulation

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With the technical assistance of Ann Eustace

The intensity of vasoconstriction in shock or hypotension depends upon the summation of neurogenic, humoral, and local metabolic factors at the time of observation. Thus, reflex release of catecholamines may induce vasoconstriction in some vascular beds, but the effect could be modified by the action of other circulating vasoactive substances or by the local accumulation of products of anaerobic metabolism resulting from tissue hypoxia.

In animals subjected to experimental shock, wide variations in the degree of vasoconstriction appear to be related to the individual, the species, the stage of shock, and the particular vascular bed studied. Calculation of total peripheral vascular resistance as an index of vasoconstriction in clinical shock of specific causes has given variable results. The peripheral resistance in hemorrhagic and traumatic shock in man has been reported as normal and increased. Septic shock has been associated with low and high vascular resistance. Shock accompanying myocardial infarction has been reported with increased and normal calculated resistance.

Since therapy of shock and hypotension should be based, at least in part, on the state of constriction of the peripheral vascular bed, assessment of the degree of vasoconstriction and its mechanism of development might have important clinical implications. The purpose of the present investigation was to examine in a group of patients with nonhemorrhagic shock or hypotension of varying causes the hemodynamic evidences of arteriolar and venous constriction and cardiac stimulation. The intensity of vasoconstriction and cardiac stimulation was related to the blood volume, body temperature, stage of the shock state, and the presence of underlying disease.

Selection of Patients

Studies were performed at the bedside of 44 patients on the medical wards of the Veterans Administration Hospital. Patients were included in the study if they became acutely hypotensive in the course of a serious medical illness or if the attending physician made a diagnosis of clinical shock because of low auscultatory blood pressure, cool, moist skin, and signs of insufficient peripheral blood flow. Some of these latter patients had normal intraarterial pressure despite reduced or absent auscultatory pressure. Patients with evidence of significant loss of blood were excluded from study. Studies reported herein were performed prior to institution of specific therapy for hypotension, or else during a period when blood pressure had stabilized after discontinuing the use of a pressor drug. The interval between onset of shock or hypotension and performance of hemodynamic studies varied widely from less than 1 hour to approximately 72 hours.

Methods

The femoral artery was cannulated with a Courand needle. A long polyvinyl catheter was threaded through a needle in the femoral vein and advanced into the right atrium, the position being verified by the contour of the recorded pressure wave. Usually the catheter was advanced into the right ventricle and was withdrawn into the atrium. Arterial and right atrial pressures were recorded

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Table 1

Hemodynamic Data in Forty-four Patients with Shock or Hypotension

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnoses</th>
<th>FAP (mm Hg)</th>
<th>CO (ml/min)</th>
<th>RAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>PVR (dynes sec cm⁻²)</th>
<th>Hct (%)</th>
<th>TBV (ml)</th>
<th>TBV (ml/kg)</th>
<th>CBV (ml)</th>
<th>CBV/TBV (%)</th>
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with a Statham P23Db strain-gauge transducer and Sanborn recorder. Mean pressures were obtained by electronic integration. Cardiac output was determined by the indicator-dilution method, utilizing a right atrial injection of indocyanine-green dye while femoral arterial blood was drawn at a constant rate through a Gilford cuvette densitometer. Cardiac output (CO) was calculated from the dye curve by the standard Stewart-Hamilton method.12

Total peripheral vascular resistance (PVR) was calculated from the formula:

\[
PVR \text{ (dyne sec cm}^{-5}\text{)} = \frac{(\text{MAP} - \text{RAP}) \times 1332 \times 60}{\text{CO} \text{ (ml/min)}}
\]

where MAP and RAP are, respectively, the mean arterial and mean right atrial pressures in millimeters Hg.

Central blood volume (CBV) was calculated as the product of the CO (ml/sec) and the mean transit time, which was corrected for catheter and cuvette delay.

Plasma volume was measured using T-1824.13 Four or more arterial blood samples were collected from 10 to 40 minutes after injection and the disappearance slope for T-1824 was extrapolated logarithmically back to the time of injection for calculation of plasma volume. Total blood volume (TBV) was computed from the plasma volume using the arterial hematocrit, which was corrected for plasma trapping14 and multiplied by 0.91 to correct for the discrepancy between large vessel and total body hematocrit.15 Average TBV by this method in 22 hospitalized subjects with diseases not known to affect blood volume was 69.4 ± 8 (SD) ml/kg.

**Results**

Hemodynamic data obtained during study of these 44 patients are shown in table 1.

**Total Peripheral Vascular Resistance**

PVR varied widely at the time of study, ranging from 240 to 3,686 dynes sec cm\(^{-5}\). Nineteen subjects had PVR greater than 1,500 dynes sec cm\(^{-5}\) (high PVR group), while the other 25 patients had PVR of less than 1,500 dynes sec cm\(^{-5}\) (low PVR group).

The nature of the disease associated with the shock had some relationship to the height of the observed PVR, but the findings varied in individual patients. For example, five of six patients with acute myocardial infarctions and eight of 11 with septicemia had high PVR, whereas severe liver disease and pulmonary emphysema were usually associated
of these had a history of hypertension, in which PVR is usually elevated, and two had congestive heart failure with high right atrial pressure and reduced cardiac output. Increased vascular resistance and expanded blood volume are common manifestations of congestive heart failure.16 Fourteen of the patients with low PVR had blood volumes within the normal range; however, significant reduction in volume without an elevated PVR was noted in 11 others (left lower quadrant, fig. 1). Six of these 11 patients (R.C., W.H., F.R., B.W., W.C., and J.L.) may have been in a preterminal state of vascular dilatation, since they expired soon after study. Two of the others had pulmonary emphysema, one had carcinoma of the lung, and the other two had Laennec's cirrhosis related to heavy alcoholic intake.

No relationship was noted between body temperature and PVR. Of 20 patients with rectal temperatures over 101 F, 11 exhibited TBV (ml/kg) low PVR, and nine others had high PVR (see fig. 5).

Relationship between total blood volume (TBV) and peripheral vascular resistance (PVR) in 44 patients with shock or hypotension. Patients with hemodynamic evidence of heart failure are depicted by (+); patients without heart failure shown by (●). Values above the horizontal broken line reflect increased PVR. Values to the left of the vertical broken line indicate hypovolemia. Correlation coefficient, $r = -0.508$.

with low PVR. Eight of nine patients with far-advanced cirrhosis and all four with pulmonary emphysema were hypotensive with low PVR, regardless of the immediate precipitating event.

A significant inverse relationship was noted between blood volume and PVR ($r = -0.508$, $P < 0.01$) (fig. 1). Blood volume was lower in the high PVR group than in the low PVR group ($P < 0.02$) (fig. 2).

Blood volume was reduced in 15 of the 19 patients with high PVR, the measured volume being more than 1 standard deviation below the predicted value in 12 of the subjects (fig. 1). Only 5 patients with blood volume over 62 ml/kg exhibited an increase in PVR. Two

Figure 1

Figure 2

Measured blood volume (TBV) (hatched bar) related to predicted normal volume (open bar). Vertical line is standard error of the mean. TBV significantly reduced in patients with high PVR.
**CBV/TBV Ratio**

The CBV calculated from dye curves as recorded in this study measures the volume of blood contained in the heart, the lungs, and the arterial bed as far as the femoral artery and temporally equidistant points. The fraction of total blood volume contained in this "central" area (CBV/TBV ratio) would be influenced not only by changes in CBV but also by alterations in systemic vascular capacity, which is primarily determined by the cross-sectional area of the large veins. Constriction of the venous capacitance vessels unaccompanied by comparable reductions in vascular capacity of the heart and lungs should result in an increase in CBV/TBV ratio.

The CBV/TBV ratio in these patients varied from 14 to 51% (table 1). Excluding the subjects with hemodynamic evidence of congestive heart failure (CHF), a significant correlation was observed between PVR and CBV/TBV ratio ($r = 0.393$) (fig. 3). The CBV/TBV ratio was significantly higher in the 16 patients with high PVR and no heart failure than in the 16 subjects with low PVR and no heart failure ($P < 0.01$) (fig. 4). The diagnosis of heart failure was made in 12 patients with elevated right atrial pressure in the control period or a normal atrial pressure which rose abruptly to abnormal levels during blood volume expansion. Data shown were obtained prior to volume expansion. As expected, these patients all had increased CBV and high CBV/TBV ratios (figs. 3 and 4).

**Heart Rate**

Heart rate did not correlate significantly with PVR in the group as a whole, averaging $107 \pm 4$ (SEM) beats per minute in patients with elevated PVR and $102 \pm 5$ beats per minute in those with low PVR.

However, certain patterns emerged when the data were examined more carefully (fig. 5). Slow heart rates usually indicated absence of vasoconstriction, since seven of eight patients with rates less than 80 beats per minute had low PVR. Heart rates of 120 or more beats per minute were observed in seven patients with high PVR and six with low PVR. That the low PVR in this situation might indicate an advanced shock state is suggested by the observation that all six of those with low PVR expired shortly after study while four of the seven with tachycardia and high PVR survived.
Fever was at least in part responsible for tachycardia in these patients. Heart rate averaged 119 ± 6 beats per minute in the 20 patients with rectal temperatures of 101 F or greater, and only 94 ± 4 in those with temperatures less than 101 F (P < 0.01) (fig. 5).

**Total Blood Volume**

Although none of the patients had sustained significant external losses of blood or plasma, 23 of the 44 subjects had reductions in total blood volume more than 1 standard deviation below the predicted value. Seventeen of these hypovolemic patients had rectal temperatures over 101 F at the time of study or had been febrile within the preceding 24 hours. Fever causes vasoconstriction, and plasma volume loss may result from increased capillary hydrostatic pressure.\(^{17, 18}\) Vasopressor drugs, which also deplete intravascular plasma,\(^{19}\) had been administered to 11 of these patients at some time during the 12 hours preceding the study.

**Clinical Signs**

Ten of the 19 patients with high PVR had cold, moist skin at the time of study (fig. 6). In four others, the skin was cool and blanched, but dry. These patients all had thready peripheral pulses. In five subjects the high PVR could not have been predicted from examination of the skin. One patient with low PVR (W.C.) had cool, moist skin at the time of study, while two others (A.A. and B.W.) appeared to have cutaneous vasoconstriction, but the skin was dry. The other patients with low PVR did not have obvious cutaneous vasoconstriction and usually had full peripheral pulses. All patients with cool, moist skin had blood volumes reduced more than 1 standard deviation below the expected normal except patient H.M., who had congestive heart failure.

Twenty-one of the patients died within 48 hours following hemodynamic studies, while in the other 23 shock or hypotension was reversed and the patients survived beyond this period without requiring further blood pressure support. The mortality rate was 42% in patients with high PVR, and 52% in those with low PVR.

**Discussion**

The PVR is determined largely by the caliber of arterial resistance vessels and by blood viscosity. In hypotensive states, arteriolar narrowing could result from active vasoconstriction or from the passive effect of a reduced...
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transmural pressure. Furthermore, reduced flow velocity in shock and resultant red cell sludging may increase apparent blood viscosity.

The PVR also could be influenced by body size, which was not used to correct the measurements of cardiac output. Since many of these patients had chronic illnesses associated with edema, dehydration, and large changes in body weight, it was not felt that correction for body surface area from a standard table would give a meaningful cardiac index. If body size had been an important factor in the level of the PVR, then the PVR should have been generally higher in the smaller individuals. However, body weight at the time of study averaged 64 kg in the patients with PVR greater than 1,500 dynes sec cm\(^{-5}\) and only 60 kg in those with PVR less than 1,500 dynes sec cm\(^{-5}\). The significant negative correlation between total blood volume, which was corrected for body weight, and PVR further attests to the hemodynamic significance of the calculated PVR. Division of these patients into high and low PVR groups was largely arbitrary, since PVR was distributed over a normal frequency curve (fig. 6). However, separation on the basis of PVR above or below 1,500 dynes sec cm\(^{-5}\) placed most of the patients with signs of cutaneous vasoconstriction into the high PVR group and most of those with warm skin and full peripheral pulses into the low PVR group.

The wide variations in PVR in these patients with similar levels of hypotension suggest that passive constriction was not the primary determinant of resistance to flow. Since a fall in aortic blood pressure might be expected to induce reflex sympatho-adrenal discharge and increased blood catecholamine levels have been demonstrated in a variety of experimental shock states, it is natural to postulate that the increased PVR in these patients was due to heightened adrenergic activity. This hypothesis is supported by the observation of high CBV/TBV ratios in the patients with high PVR. Since adrenergic hormones constrict the systemic veins and shift blood into the central circulation, the proportion of the total blood volume contained in the systemic circulation should decrease and the CBV/TBV ratio should rise. If sympathetic discharge produces precapillary and postcapillary constriction, a further rise in PVR would result from the increased blood viscosity and red cell sludging related to slowing of microcirculatory flow.

In the hypotensive patient undergoing adrenergic stimulation to support blood pressure, tachycardia should accompany the high PVR and increased CBV/TBV ratio. While slow heart rates usually were associated with low PVR, tachycardia was nearly as common in the low as in the high PVR group. In some subjects, the rapid heart rate could be explained on the basis of fever, which was associated with a significant tachycardia in this series. However, adrenergic stimulation to the heart in the absence of peripheral vasoconstriction could result if humoral or local factors counteracted reflex sympathetic vasoconstriction. The rapid demise of most of the patients with tachycardia and low PVR indicates that, by the time they were studied, anaerobic metabolites may have already accumulated and produced terminal vasodilation. This syndrome of tachycardia and low PVR often accompanied by hypovolemia might then be classified as a form of "irreversible shock."

The observation that blood volume was reduced at the time of study in nearly all the patients with high PVR, but not in those with low PVR, suggests that generalized vasoconstriction may be more closely related to reduced blood volume than to reduced arterial pressure. It is not clear, however, whether hypovolemia precedes or follows the vasoconstriction. Von Baumgarten and his associates provide data to support the concept that small losses of blood volume may induce vasoconstriction due to reflexes which originate in the low pressure system. On the other hand, fever, infusion of catecholamines, and prolonged sympathetic discharge may lead to sizable losses of plasma volume. Other studies from this laboratory have demonstrated that
acute expansion of plasma volume with dextran in these hypovolemic patients usually reduces PVR to normal. Thus, hypovolemia may not necessarily initiate the vasoconstriction, but it apparently plays an important role in perpetuating it.

The 25 patients without evidence of generalized vasoconstriction despite severe hypertension represent a heterogenous group. In some, the expected adrenergic vasoconstriction was probably counteracted by the accumulation of acid metabolites. Eight of these patients apparently had this syndrome, since they expired shortly after study. All had low PVR, despite marked tachycardia in six and hypovolemia in six. A low blood volume would be expected in prolonged tissue hypoxia, because precapillary dilatation may precede postcapillary dilatation leading to a rise in capillary hydrostatic pressure.30

In the other 17 patients with low PVR, a cause for the failure of reflex vasoconstriction must be sought. Either hypotension itself without hypovolemia was not an adequate stimulus for adrenergic response, or there was some defect in the normal sympathetic nervous system reflex pathways. In eight of these patients alcoholism and Laennec's cirrhosis, which may be associated with low PVR31 and impaired adrenergic responses,32 were diagnosed. Inoperable carcinoma was diagnosed in three others, diabetes mellitus in one, and severe pulmonary emphysema in four. Adrenergic insufficiency has been demonstrated with malignancies33 and is commonly seen in diabetes.34 The reason for the low PVR in emphysema is not clear, although cardiac output may be increased in this disease and blood flow and peripheral resistance may be normal even in the presence of right heart failure.35

In patients without vasoconstrictor reflexes, small losses of blood volume can induce severe hypotension. Since venous capacitance vessels may be dilated in such individuals,32 blood volume may be larger than normal and functional hypovolemia may occur without a reduction in volume below the predicted value.

Calculation of total vascular resistance allows no conclusions regarding the behavior of individual vascular beds. The evidence of reduced cutaneous blood flow in most of the subjects with high PVR and its absence in those with low PVR suggest that the cutaneous circulation often reliably reflects total vascular responses. However, further knowledge regarding regional vascular resistance in clinical shock must await more detailed hemodynamic studies.

Summary

Hemodynamic studies were performed on 44 patients with nonhemorrhagic shock or hypotension in order to assess the degree of vasoconstriction and cardiac stimulation.

In 19 patients, reflex adrenergic discharge was characterized by elevated total peripheral vascular resistance, a high ratio of central blood volume to total blood volume, tachycardia, and clinical signs of skin vasoconstriction. Reduced total blood volume in most of these patients at the time of study could be explained as the result of fever, administration of vasopressor drugs, or prolonged reflex vasoconstriction.

Eight patients were hypotensive with low peripheral resistance usually associated with tachycardia and hypovolemia. The fact that all died within several hours suggests that this "irreversible" syndrome was related to local accumulation of acid metabolites with terminal failure of vasoconstriction.

In 17 patients, absence of reflex vasoconstriction despite hypotension was manifested by low or normal peripheral resistance, low ratios of central blood volume to total blood volume, warm skin, and normal total blood volume. While tachycardia often was absent in this group, heart rate was more closely related to body temperature than to vasoconstriction. Lack of intense adrenergic discharge in these hypotensive patients could be attributed either to the absence of a hypovolemic stimulus or to impairment of normal sympathetic nervous system pathways. The high incidence of alcoholism, cirrhosis, malignancy, pulmonary emphysema, and diabetes
in these patients suggests the possibility that adrenergic insufficiency was a factor in the failure of vasoconstriction in at least some of them.

The frequency of hypovolemia in the patients with vasoconstriction stresses the need for recognition and correction of occult depletion of blood volume in shock of diverse etiologies.

References
Early Investigation on Glomerular Filtration

When I got into the problem of trying to withdraw glomerular fluid, the work proved to be so delicate that we could not have interruptions or even heavy footsteps that shook the apparatus. Therefore, I began to work at night when the only visitors to my laboratory were a friendly mouse and an occasional cockroach.

Richards came in one evening and, seeing the light in my laboratory, looked in and from that time on throughout the time I worked with him, he came into the laboratory frequently for long hours of uninterrupted work in the evenings.

A preliminary report of our findings was made in Edinburgh at the International Physiological Congress in 1923. We took American frogs with us but they did not survive the crossing of the Atlantic, and when I prepared to set up a demonstration of a glomerular puncture, I had to use Scotch frogs. Richards arranged for a quiet room and I had a very difficult time getting the preparation ready as the Scotch frogs were very thrifty with their glomerular filtrate.—JOSEPH T. WEARN: Acceptance of the Kober Medal for 1965. Trans Ass Amer Physicians 78: 50, 1965.
Studies in Clinical Shock and Hypotension: IV. Variations in Reflex Vasoconstriction and Cardiac Stimulation
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