Hemodynamic Consequences of Induced Changes in Blood Volume

By James Conway, M.D., Ph.D.

With the technical assistance of Miklos Gellai

The acute effects of changes in blood volume on cardiac performance have been investigated intensively in the past in order to determine the relationship between filling pressure and cardiac output. The influence of sustained changes in blood volume on the entire circulation is, however, less well known. Yet an exploration of a possible interaction between the blood volume on the one hand and cardiac output and peripheral resistance on the other, is important since it might reveal that the control of the circulation and possibly blood pressure itself could be affected by changes in blood volume.

In the present investigation, therefore, blood volume has been increased by transfusion or reduced by hemorrhage, while the subsequent hemodynamic changes have been measured over periods from two to ten hours. Since it is known that cardiac output and peripheral resistance vary with hematocrit, infusions of dextran or packed red cells have been used after transfusion or bleeding in order to minimize the anticipated changes in that variable.

Methods

Trained, unaesthetized dogs weighing approximately 20 kg have been used throughout this study. They were prepared for the experimental procedures at least one week in advance by implantation of polyvinyl catheters, (2 mm, I.D.). These were introduced under pentobarbital sodium (Nembutal) anesthesia (30 mg/kg) through an incision in the side of the neck. One catheter was then passed into the right atrium or ventricle via the external jugular vein, and another into the aorta via the carotid artery. By means of a sharp probe the free ends of the catheters were run under the skin to the back of the neck and exteriorized through individual puncture holes. The catheters were filled with saline and plugged with steel pins.

The animals were repeatedly brought down to the testing laboratory and trained to lie unrestrained in the prone position on a padded surface for a period of approximately one hour. During these training exercises blood pressure, and occasionally also the cardiac output and plasma volume were measured. On the day of the experimental procedures the dogs were fasted but were otherwise given no premedication. For blood pressure measurements connections were made via polyvinyl tubing (2 mm I.D.) 10 cm in length for each catheter to a Statham strain gauge (P23B or P23G). The zero level was taken to be 8 cm above the table top. The arterial catheter was then connected to a Gilford densitometer for cardiac output measurements by the indicator dilution method. The dye, indigocarmine (8 mg in 1 ml water), was injected into the prefilled cardiac catheter. For inscription of the dilution curves arterial blood was drawn at 30 ml/min.

Cardiac output measurements were always made in duplicate and after the inscription of each curve a wedge of standard optical density was inserted into the light beam of the densitometer to check the gain of the apparatus. The output curves were calibrated at the end of the experimental procedures by the addition of known quantities of dye to 10 ml samples of blood. These were drawn through the densitometer at the same rate as used above. Records were made by means of a Gilson polygraph and for the cardiac output curves a servo-channel of the machine gave dye curves approximately 80 mm in height. The Stewart-Hamilton formulae were used for the calculation of cardiac output. From this and the mean circulation time, corrected for catheter delay, the central blood volume was calculated. Total peripheral resistance was expressed in units, as the ratio of mean arterial blood pressure in mm Hg divided by cardiac output in liters/min.
CARDIOVASCULAR FUNCTION AND BLOOD VOLUME

After drawing a control blood sample the plasma volume was measured\(^*\) with radioactive iodinated human serum albumin.\(^*\) A dose of approximately 5 \(\mu\)C was used for each measurement of plasma volume and samples of blood were drawn 10, 15, and 20 minutes after injection for extrapolation to the time of injection to determine the initial mixing volume. The hematocrit of arterial blood was measured in duplicate at the same time. An effort was made to reduce the volume of blood withdrawn for both the blood volume and cardiac output determinations, and also to limit the saline used to clear the catheters after drawing blood. For the cardiac output measurements the loss of blood was minimal since the sample was reinjected immediately after the determination was completed, and only 5 ml of saline were injected to clear the catheters of blood. For an hematocrit determination 2 ml of blood were withdrawn, for a plasma volume and hematocrit determination, a total of 20 ml of blood was withdrawn and 25 ml of saline given in flushing the catheters.

During each experiment the dogs were given 200 units of heparin/kg at hourly intervals; no anticoagulant was used on days between experimental procedures.

With the exception of procedure no. 1, which required multiple transfusions, the animals were always infused with their own (autologous) blood, which had been collected by aseptic techniques five or six days before each experiment and preserved in commercial ACD solution. The volume of fluid selected for infusion or bleeding was limited to approximately 10% of the estimated normal blood volume in order to avoid acute embarrassment to the circulation and to stay within the range of possible physiological change. The volume of the ACD solution infused has not been included in the volume of blood transfused. Bleeding or infusion of liquid was always done slowly, over a period of approximately 20 minutes, to minimize the activation of neurogenic reflexes. No adverse systemic reactions or evidence of discomfort were observed after any of the infusions or during the measurements of cardiac output or blood pressure.

After control measurements of blood volume and hematocrit, the cardiac output and intravascular pressures were determined. Blood was then infused or withdrawn and the physiological measurements repeated at specific intervals for several hours, timed from the beginning of the transfusion or bleeding. In the intervals between measurements the dog was returned to his run and allowed free movement. In order to limit the change in hematocrit, blood transfusions were accompanied by infusions of dextran, 6% solution in saline (mean mol wt 75,000),\(^*\) and in the bleeding experiments by infusion of autologous packed red cells. Optimal amounts of these for each type of procedure were determined in preliminary experiments. In each experiment the hematocrit was kept within 5% of the control value.

Six procedures were used:

1. Sustained Expansion in Blood Volume. In ten experiments on eight dogs, after the control measurements, three infusions of 90 ml of blood and 70 ml of dextran were made at intervals of two and one-half hours. Seven experiments were performed with homologous blood but in the others autologous blood was used. Cardiac output and blood pressure were measured at intervals of two and one-half hours for a period of ten hours. Blood volume and hematocrit were determined before each cardiac output measurement. The entire group of control measurements were repeated on the following morning, 24 hours after the first infusion.

2. Short-Term Expansion. In seven experiments on five dogs, the effect of the infusion of 100 ml of blood plus 50 ml of dextran on cardiac output and blood pressure was measured at half-hourly intervals over a period of two and one-half hours. Blood volume and hematocrit were measured at the beginning and at the end of the procedure.

3. Short-Term Expansion During Ganglionic Blockade. In seven experiments on five dogs, the preceding experiment was performed after the administration of pentolinium, 7.5 mg iv + 7.5 mg sc. This amount blocked the pupillary light reflex. Subcutaneous doses of the drug were then repeated to maintain this condition throughout the period of observation. In these experiments the first measurement of cardiac output after the infusion of blood and dextran was omitted because by this time the dogs tended to become restless since they had been on the experimental table for a period exceeding one hour while ganglionic blockade was being established and the transfusion performed. In all other respects the experiment was the same as the preceding one.

4. Hemorrhage With the Replacement of Red Cells. In eleven experiments on six dogs, after control measurements, 150 ml of blood was withdrawn. Cardiac output, blood pressure, and hematocrit were measured at half-hourly intervals for four hours. Since preliminary experiments had shown that the hematocrit reached its minimum value at the third hour, 50 ml of packed red cells

\(^*\)Iso-Serve Inc., Cambridge, Massachusetts.

*Circulation Research, Vol. XVIII, February 1966

Supplies of dextran were generously provided by the Pharmachem Corporation, New York.
were rein infused after completion of the measurements of blood pressure and cardiac output at the two and one-half hour period. In seven experiments the period of observation was extended from four and one-half to five and one-half hours.

5. Sustained Reduction in Blood Volume. In seven experiments on six dogs, 150 ml of blood were withdrawn as in the previous experiment and packed red cells were replaced after two hours. Another 150 ml of blood were then withdrawn and 50 ml of packed cells replaced after an additional hour. Cardiac output and pressure measurements were made at two, four, six, and seven hours after the first withdrawal of blood. Blood volume and hematocrit were measured at the beginning and the end of the experiment.

6. Controls. Three types of control procedures were studied. In seven experiments cardiac output and arterial and venous pressures were measured at hourly intervals over a period of five hours to determine whether trends would be evident during the day in the absence of transfusions. To detect possible hemodynamic effects of administered blood, five experiments were done in the same manner with administration of two transfusions of 100 ml of blood; one after the control measurements and one two and one-half hours later. Immediately after each transfusion was completed, however, the same volume of blood was withdrawn.

Finally, in five experiments a single infusion of 50 ml of dextran was given and cardiac output and blood pressure were followed for two and one-half hours as in procedures two and three. Blood volume and hematocrit were also determined at the beginning and end of all these procedures.

**Figure 1**

Hemodynamic effects over a ten-hour period of three transfusions of blood and dextran (mean ± SEM, 10 experiments). Mean initial value is given with mean changes (± 1 SEM). By means of the significance ratio the significance of differences from the initial value are given. * indicates P < 0.01 and ** indicate P < 0.001. For the blood volume curves, the measured values are indicated by dots but the line includes calculated changes immediately resulting from transfusions or hemorrhage.
Results

1. Sustained Expansion in Plasma Volume. In this group of experiments, blood and dextran were administered on three successive occasions, two and one-half hours apart. After each infusion the blood volume tended to return toward normal but the reduction did not equal the quantity of fluid infused (fig. 1) and the measured total blood volume before each transfusion increased. Dilution of the infused blood with dextran prevented a rise in the hematocrit, but with successive infusions there was a slight overcorrection of the tendency to hemoconcentration and the mean hematocrit declined from 38 to 35% at seven and one-half hours.

The changes in central blood volume followed the increases in total blood volume and of end diastolic pressure. This association, which has been emphasized by Gauer and Henry,1 was characteristic of most of these experiments. The mean blood pressure rose with the first infusion from 92.2 to 112 mm Hg and remained at this level throughout the ten-hour period of observation. In spite of a mean elevation in end diastolic pressure of approximately 6 cm water, the heart rate and the cardiac output changed little throughout the experiment. The mean total peripheral resistance rose from a control value of 33.2 to 40.0 units at two and one-half hours and remained elevated. The significance ratio showed that the changes in blood pressure and peripheral resistance were significant (P<0.001). On the following day, 24 hours after the first infusion, all measurements had returned to control levels.

Since the peripheral resistance and cardiac output levels appeared to be stable by the time the first observations were completed, the sequence of events during the first two and one-half hours after the transfusion was examined more closely in the next two procedures.

2. Short-Term Expansion. The blood volume was expanded by an infusion of 100 ml of blood plus 50 ml of dextran and measurements were made more frequently, at one-half hour intervals, for two and one-half hours (fig. 2A).

Hemodynamic effects over a two and one-half hour period of a single infusion of blood and dextran (mean ± SEM, seven experiments). For symbols see legend to figure 1.

End diastolic pressure was elevated at one-half hour and along with this cardiac output, heart rate, and blood pressure rose. The change in output was, however, small, 0.4 liter/min, and two hours after the infusion it had returned to the control level. The calculated peripheral resistance then rose significantly above the control value of 38.7 to 46.9 units (P<0.001).

In order to determine whether the sequence of changes in the cardiovascular response to transfusion resulted primarily from reflex adjustments, this experiment was repeated after pharmacologic blockade of the dogs' autonomic nervous system.
3. Short-Term Expansion During Autonomic Blockade. The pattern of response seen in the previous group of experiments was again observed in dogs with ganglionic blockade (fig. 2B). The initial heart rate, 135 beats/min, was high because of the autonomic blockade, and changed little throughout the procedure. The mean initial cardiac output of 3.2 liters/min after increasing at the first hour returned to the control level at the next half-hour. The mean level of blood pressure increased from an initial value of 99.6 to 132.6 mm Hg in two and one-half hours with a similar rise in mean total peripheral resistance, from 32.8 to 41.5 units (P < 0.01).

Since these changes in resistance after transfusion were not expected, and the mechanism for them not evident, it was decided next to investigate whether reduction in blood volume would produce the contrary result.

4. Hemorrhage With Replacement of Red Cells. Withdrawal of 150 ml of blood from the circulation reduced end diastolic pressure and central blood volume. There was an immediate increase in heart rate, a small decrease in cardiac output, and a proportionate increase in peripheral resistance (fig. 3). The heart rate returned to the control level at two and one-half hours and cardiac output at three and one-half hours. The combination of a minor fall in blood pressure and a rise in cardiac output evident at four and one-half hours resulted in a reduction in mean total peripheral resistance from the control value of 30.1 to 26.9 units which, though unimpressive, was significant (P < 0.01). The reduction in resistance persisted to five and one-half hours in the seven experiments which were extended to this period.

5. Sustained Reduction in Blood Volume. Results obtained in this experiment were similar to those of the preceding one (fig. 4), but with the more prolonged reduction in blood volume, there was a gradual decline of mean blood pressure throughout the experiment from 105 to 93 mm Hg. Cardiac output rose from an initial value of 2.9 to 3.2 liters/min at the seventh hour, and the overall reduction in peripheral resistance over the seven-hour period was greater than in the preceding experiment, falling from 39.9 initially to 30.9 units. All these changes were significant (P < 0.01). It may be noted incidentally that the heart rate in this group increased after the first hemorrhage and remained elevated to the end of the experiment.

6. Controls. Repeated measurements of blood pressure, cardiac output, and hematocrit at hourly intervals over a period of five hours showed small variation during the period of observation. The mean control values were 105 (± 4.3) mm Hg for blood pressure, 3.7 (± 0.4) liters/min for the cardiac output, and 0.46 (± 0.05) for the hematocrit.

Figure 2B

Hemodynamic effects over a two and one-half hour period of a single infusion of blood and dextran during autonomic blockade with pentolinium (mean ± SEM, seven experiments). For symbols see legend to figure 1.
0.74) liters/min for cardiac output and at five hours these values were 114 (SE 3.1) mm Hg and 4.0 (SE 0.73) liters/min, respectively. With the administration and withdrawal of blood there was likewise very little change in blood pressure or cardiac output, the mean initial values being 106 (SE 2.9) mm Hg and 3.7 (SE 0.31) liters/min. After five hours during which 100 ml of blood had been administered and then withdrawn on two occasions, the mean arterial pressure was 107 (SE 3.9) mm Hg and cardiac output 4.1 (SE 0.65) liters/min. In none of these experiments therefore, were there significant changes in peripheral resistance, nor were directional trends in cardiovascular performances apparent in the course of the day.

The infusion of 50 ml dextran caused no systemic reactions and produced little change in cardiac output in any animals at any of the half-hourly measurements. The mean control value was 3.7 (SE 0.38) liters/min and after two and one-half hours 3.3 (SE 0.31) liters/min. The blood pressure varied little in this period and the mean peripheral resistance which was 29.3 (SE 2.9) units initially was 33.1 (SE 4.0) at two and one-half hours.

Discussion

Blood volume expansion over a period of ten hours left the cardiac output practically unchanged despite an increase in filling pressure and central blood volume. Peripheral resistance however, increased by approximately 25% over the control value. The absence of a demonstrable cardiac response can not be ascribed to the development of congestive heart failure since no tachycardia
occurred and the rise in end diastolic pressure was small (6 cm water). The restoration of blood volume, hematocrit, and cardiovascular parameters to normal levels by the next morning is probably the result of the removal of protein and cells from the circulation, which is known to occur in the dog. 

Although it has been shown that cardiac output does not necessarily increase in proportion to the rise in filling pressure, the absence of change in output was unexpected. A closer study of the initial phase of the response revealed a small increase in cardiac output and heart rate immediately after the transfusion; this disappeared after one and one-half hours while blood pressure remained elevated and peripheral resistance rose to approximately 20% above the control value in two hours.

The immediate response to the transfusion was therefore a small and transient increase in cardiac output and after hemorrhage cardiac output decreased. The change in output was, as reported by others, not proportional to the change in end diastolic pressure. Fowler et al., have also noted that the initial increase in output to transfusion was transient and in their experiments was no longer evident after 20 minutes. Similarly, in studies on man, those who have observed a correlation between filling pressure and cardiac output have made their observations during the actual expansion or contraction of blood volume, whereas those who were unable to

**FIGURE 4**

Hemodynamic effects over a seven-hour period of two hemorrhages with replacement of red cells to minimize changes in hematocrit (mean ± SEM, 7 experiments). For symbols see legend for figure 1.
demonstrate this relationship made their observations after changes in blood volume had been produced. Experiments in the anesthetized dog in which serum transfusions were followed for four hours, have shown a pattern of response similar to that observed in the present experiments, with an initial increase in cardiac output which returned to control level in one hour. In only two of five dogs, however, was an increase in resistance found at this time. Other observations consistent with the present series of experiments have been the incidental reports of an increase in resistance two hours after large blood transfusions and reduced resistance some hours after hemorrhage.

It has been suggested that the inability to demonstrate a consistent relationship between filling pressure and cardiac output in the intact animal is due to the interference of regulatory reflexes. The immediate response to both transfusions and hemorrhage in this study was modified almost certainly by neurogenic reflexes since they evoked prompt changes in heart rate. Although it has been shown that reflexes initiated by distension of the central venous system elevate arterial pressure, the delayed rise in resistance and the observation that the pattern of response to the expansion in blood volume was unaffected by autonomic blockade, make it unlikely that the changes of resistance seen in the present study are the result of neurogenic regulation.

Changes in resistance which occur after bleeding are consistent with those occurring after transfusion and suggest that both are the result of changes in blood volume. The mechanism which restores cardiac output and increases resistance is unknown. Its occurrence under autonomic blockade suggests that it may be similar to the mechanism operating in anemia and polycythemia. It seems possible the changes in peripheral resistance with transfusion and hemorrhage may be the same as those concerned with autoregulation and with oxygen delivery to the tissues.

The primary effect of changing blood volume is almost certainly on cardiac output but secondary adjustments then emerge which affect peripheral resistance and restore cardiac output to normal. This raises the possibility that some part of the long-term control of the circulation might be an indirect one through the control of blood volume. If it can be demonstrated that this persists over periods of days, it would lend support to the idea that chronic hypertension can result from derangements of fluid volume control. Such a concept has, in fact, been postulated to occur after the application of a Goldblatt clamp to the renal artery.

**Summary**

The effects of transfusion or bleeding on cardiac output and blood pressure have been followed for periods of seven to ten hours in trained, conscious dogs.

When blood volume is increased by transfusion of blood, supplemented by dextran to minimize the expected change in hematocrit, cardiac output and blood pressure increase initially. After one and one-half hours the cardiac output returns to the initial level but blood pressure remains elevated and calculated peripheral resistance increases. This state has been maintained for a period of ten hours by repeated transfusion.

After bleeding, with replacement of packed cells, again to minimize the change in hematocrit, cardiac output decreases initially and peripheral resistance increases, but after three hours, output returns to its former level, and peripheral resistance falls below the control value. These changes become more prominent when a second hemorrhage is performed two hours after the first one. The reduction of resistance was then maintained for seven hours.

These findings demonstrate that the effects of changes in blood volume are not limited to the acute changes in cardiac output and filling pressure. After periods of one to three hours, changes in peripheral resistance also become evident.

**References**

Hemodynamic Consequences of Induced Changes in Blood Volume
James Conway and Miklos Gellai

Circ Res. 1966;18:190-198
doi: 10.1161/01.RES.18.2.190

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/18/2/190

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/