Vascular Capacitance and Fluid Shifts in Dogs during Prolonged Hemorrhagic Hypotension

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SUMMARY The mean circulatory pressure (Pmc) in dogs anesthetized with chloralose-urethane was estimated from 0.5 to 150 minutes after hemorrhages of 0, 17, or 34 ml/kg, or that volume giving an arterial pressure (Pa) of 40 mm Hg. The Pmc was determined by fibrillating the heart and then rapidly pumping blood from aorta to vena cava until Pa = venous pressure (Pv) = Pmc. Within about 10 seconds, the heart was defibrillated. Vascular compliance was estimated as the ratio of a test blood volume change (0, ±8.5, or 17 ml/kg) to the change in Pmc, determined 0.5 minute after the start of the test volume change. Erythrocyte and plasma volumes were measured by 125I-albumin dilution.

ALTHOUGH reflex venoconstriction is an effective homeostatic response to hemorrhage and apparently is more resistant to local ischemia than are the precapillary resistance vessels, the time-varying, quantitative role of the veins during prolonged hypotension is not known. We therefore continued our previous studies of the capacity of the vascular system to hold blood—its capacitance—beyond 5 minutes after hemorrhage. We used similar techniques but a much different protocol.

By vascular stiffness (S in mm Hg per ml/kg) we mean the ratio of the change in mean circulatory pressure (ΔPmc in mm Hg, as herein measured) to a change in blood volume (ΔV in ml/kg of body weight), or S = ΔPmc/ΔV. Compliance was calculated as the reciprocal of stiffness. Because the pressure-volume relationship becomes nonlinear at a Pmc of less than about 5 mm Hg (Fig. 4 of Drees and Rothe), the unstressed volume is defined as the vascular volume at zero Pmc obtained by linear extrapolation of the pressure-volume relationship in the range of Pmc from 5 to 20 mm Hg. Active reflex venoconstriction can reduce the capacity of the vasculature by reducing the unstressed volume without a change in compliance.

Our hypotheses were that after hemorrhage: (1) most of the active (reflex) venoconstriction occurs early (within the first 2 minutes); (2) the volume compensation which occurs after the first few minutes is mostly by fluid shifts into the vasculature; (3) the vascular capacitance is then relatively constant, with no significant loss of venous tone. The hypotheses are not rejected by our data. However, our experiments support the observation that, in the dog, after about an hour of severe (arterial pressure of 40 mm Hg) hemorrhagic hypotension there is then a progressive loss of fluid from the vasculature.

Methods

Mongrel dogs weighing 17.6 ± 1.5 (SD) kg were transiently anesthetized with sodium methohexital (Brevital, Lilly), 12.5 mg/kg, iv, followed with 2 ml/kg of a solution (held at 50°C) of 2% α-chloralose (Nutritional Biochemicals) and 12.5% urethane (ethyl carbamate, Fisher). The maintenance dosage was less than 1 ml/kg per hour. Sodium heparin (Nutritional Biochemicals) was given in an initial dose of 5 mg/kg followed by a dose of 2.5 mg/kg at hourly intervals.

After standardized prehemorrhage measurements were completed each dog was randomly assigned to one of four groups of eight dogs each: (1) control (no sustained hemorrhage), (2) bled by 17 ml/kg (approximately 20% of the blood volume), (3) by 34 ml/kg, or (4) hemorrhage to an arterial pressure of 40 mm Hg and servo-controlled at a mean arterial pressure (Pa – 40 mm Hg) by further hemorrhage or reinfusion. The dogs were intubated and occasionally ventilated with 100% oxygen, especially after defibrillation and severe hemorrhage. The dogs were bled or transfused via the femoral arterial cannulae at rates up to about 100 ml/kg per min.

Techniques for cardiac output and arterial blood sampling were similar to those used before, as were the procedures for fibrillation, determination of mean circulatory pressure (Pmc), and defibrillation. The fibrillatory stimulus (5 V, 60 Hz between the sternum and right atrium) was applied continuously throughout the Pmc procedure to ensure continuation of fibrillation. Turning this weak stimulus off did not significantly influence the pressure. The aorta to inferior vena cava pump rate was about 2 liters/min until the pressure difference was 20 mm Hg, when it was automatically slowed to 1 liter/min, and then to about 0.3 liter/min for pressures between 5 and 0 mm Hg. It then automatically was stopped at zero difference by a third relay incorporated...
in the roller pump (Med-Science Electronics). The pump rotor was manually turned to hold the systemic arterial pressure equal to the central venous pressure. Systemic arterial and venous pressure, monitored near the heart, were within 1 mm Hg of each other by 2.7 ± 0.9 (SD) seconds after initiation of fibrillation. The Pmc was measured as the end-expiratory central venous pressure 5.0 seconds after start of fibrillation. Fibrillation was continued for only 10.5 ± 4.1 seconds. It was terminated with a transthoracic d.c. countershock (Electrodyne, model D-84-M). Between 5 and 9 seconds, the pressure increased by only 0.21 ± 0.35 mm Hg/sec (n = 382; many fibrillations were terminated before 9 seconds). This rate of increase, though small, was significantly greater than zero (P < 0.001). The heart rate and arterial blood pressures were not different from the prefibrillatory values by 1.5–2 minutes after defibrillation. The reservoir (for holding the hemorrhaged blood), pump, and tubing were primed with 106 ml of 6% dextran (Abbott, No. 1505; average molecular weight = 75,000).

The blood volume was measured by isotope dilution using 125I-albumin and 45Cr-erythrocytes, as described in the earlier study.1 Determinations were made 65 minutes before and 30 minutes after hemorrhage with samples taken as indicated in Figure 1. Each blood sample was 5 ml; this provided two samples of 1.000 ± 0.005 ml for measurement of isotope activity and 3 ml for determination of the hematocrit, plasma protein concentration, and oncotic pressure. The concentration of plasma 125I, extrapolated to the time of injection, was based on a least squares fit to the natural logarithm of isotope activity of six samples taken between 10 and 60 minutes after the first injection (Fig. 1). Corrections were made for activity in the reservoir but not for loss of radioactivity in sampling. The 5-minute sample deviated by −4.0 ± 3.1% from the value predicted from the least squares-fitted, semilogarithmic line, whereas the deviation at 10 and 60 minutes averaged +0.47 ± 0.88% and +1.4 ± 1.0%, respectively; this finding suggests that mixing was nearly complete by 10 minutes. Plasma dilution resulted from the addition of 56 ml of hyperoncotic oncotic pressure about 60 mm Hg) dextran from the pump at 25 minutes and 50 ml from the reservoir at 39 minutes. Corrections for isotopically held in the tubing and reservoir were made by increasing the isotope activity of the 45-minute sample by 5% and that of the 60-minute sample by 6%. The loss of 125I during the control period was expressed as 100 × 60 times the exponential rate constant (in minutes). It averaged 17.4 ± 5.3% (RMSE) per hour. [Index of variability is the root of the mean square error (RMSE) of a one-way analysis of variance of the four groups.]

The extrapolated concentration for the second 125I-albumin injection was based on samples taken at 9, 12, and 15 minutes after isotope injection. The background was based on samples taken 2, 12, and 22 minutes before the second isotope injection. The slopes are given as the tag loss rates in Table 1. The extrapolated concentration of 45Cr in the erythrocytes was based on 17 samples taken between 30 and 210 minutes after 45Cr injection (Fig. 1). The coefficient of variation based on the squared deviation of each datum from the least squares-fitted line was only 1.36 ± 0.43% with no significant deviations, even during the hemorrhage periods. At 30 minutes after injection, the deviation from the single exponential line was +0.48 ± 1.93%, suggesting good mixing throughout the entire vascular system by this time. The 45Cr loss averaged 1.8 ± 1.2% (RMSE) per hour. (See Table 1 for each group.) A second 45Cr injection was not made for determination of the posthemorrhage blood volume, because it was reasonable to assume a constant circulating erythrocyte mass. This was supported by the constancy of the exponential decay of 45Cr activity throughout the experiment. Frank loss of erythrocytes into the gastrointestinal tract or sequestration in tissue after the original injection of isotope would not be detected by this approach, however.

The cardiac output and Pmc determinations were taken when indicated in Figure 1. Arterial and central venous pressures and heart rate (from a cardiotachometer, Beckman 9857) were those taken immediately before the cardiac output measurement.

To assess the vascular compliance, we used the following procedure: A test volume of blood of 0, 8.5, or 17 ml/kg was infused into the hemorrhaged groups (or removed from the control group). In our previous study,1 we found that hemorrhage or transfusion gave data falling on the same straight pressure-volume line in the range of at least ±17 ml/kg. At 30 seconds after the start of the rapid (10–20 seconds) volume change, the Pmc was determined. This gave a pressure and volume pair of data. The blood volume of the dog was then immediately restored to its nominal value, so that the duration of the test volume maneuver was less than 1 minute. Three to six pairs of pressure and volume values thus were obtained for a least squares estimation of the pressure-volume slope during the 50 (30–65 minutes), 90 (75–110 minutes), or 135 (120–150 minutes) intervals. Two or three of the determinations (e.g., at 55, 65, and 80 minutes) (Fig. 1) were added in the last half of the study to

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**FIGURE 1 Example of experimental protocol.** Isotopes were injected before and after hemorrhage at the times indicated. Arterial blood samples were then taken as indicated. Three cardiac output (C.O.) determinations were made during the prehemorrhage period at the times shown, with arterial and central venous pressures and heart rate taken a few seconds before. The magnitudes of the test volume changes were zero ( ), 8.5 ml/kg, or 17 ml/kg. For this experiment, during the experimental period infusions (lasting 1 minute) of the indicated magnitude were used. The mean circulatory pressure (Pmc) determinations were made 30 seconds after the start of the test hemorrhage or infusion. (During the prehemorrhage periods for all groups, and during the experimental periods for the control group, blood was removed as the test volume change.) As indicated by a brace, the data obtained between 30 and 65 minutes were used to obtain the pressure-volume estimate for 50 minutes, with a similar pooling used for the 90-minute and 135-minute estimate. Within the 50-, 90-, and 135-minute intervals, the magnitude of the test volume changes were randomly varied.
provide more data for the estimate of vascular compliance. As an example, during the 90-minute interval for experiment 28 (Fig. 1), the Pmc was obtained with no test volume change at 75, 90, and 105 minutes, giving the Pmc estimates of 4.2, 3.5, and 3.5 mm Hg at -17 ml/kg. At 80 minutes, 17 ml/kg were infused (giving an apparent hematocrit of zero) and the Pmc was determined (14 mm Hg). Finally, 8.5 ml/kg were transiently infused at 95 and 110 minutes, giving values of 7.5 and 7.5 mm Hg at -8.5 ml/kg. The vascular stiffness for the 90-minute interval was defined as the computed slope (b) of the line through these six pairs of data for Pmc and change in blood volume using an equation of the form: Pmc = a + bΔV. The order of the 8.5 and 17 ml/kg volume change was random.

To reduce the complexity and uncertainty resulting from mixing the dog's blood with the reservoir blood, no Pmc determinations were made while the second second sample was mixing in the dog (30–50 minutes after hemorrhage).

Plasma oncotic pressure was measured with a Friedman oncotic pressure system using a semipermeable membrane (Amicon, PM-30; cut-off at 30,000 molecular weight) and a centrifuge and model CR reader) after 5 minutes of centrifugation.

The RMSE is the average over the entire experiment (usually 14 times, as indicated in Figures 2–5) of the root (R) of the one-way analysis of variance, within group mean square (MS) error (E) for each time period. A two-way analysis was precluded by about 5% missing data. RMSE values were similar enough to suggest homogeneity of variance by the Fmax test and so were simply averaged. The value is an estimation of variability (pooled standard deviation) with the group effects removed. Since the degrees of freedom from a pooled standard error at each time period was 28, t = 2.048 at the 5% level. The standard error of the difference is 2/2n times the RMSE. Since n = 8, 2/2n  = 0.5, and so the least significant difference (LSD) is (2.048) (0.5) (RMSE). The RMSE is thus approximately equal to the LSD or the 5% confidence interval for these experiments.

Results

Control values for and major changes in the variables measured are given in Table 1.

The mean circulatory pressure during the prehemorrhage control periods averaged 11.4 ± 2.1 (RMSE) mm Hg and was similar to that found in our earlier study (12.0 ± 2.1 at 135 minutes after anesthetization). The Pmc decreased

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There were eight dogs in each group, as follows: control (no sustained hemorrhage); —17 and —34 (bled by 17 and 34 ml/kg, respectively); Pa = 40 (hemorrhage to an arterial pressure of 40 mm Hg). Results are expressed as mean ± SD except for overall average column, where root of the mean square error (RMSE) is given.

* Average values during the prehemorrhagic period.
† Compliance in ml/kg × mm Hg × 1/ vasstiffness.
‡ Significant difference between groups; P < 0.05.
§ Increase in total plasma volume 30 minutes after hemorrhage calculated as: (Plasma vol by 2nd isotope injection plus plasma in reservoir) minus (plasma vol by 1st injection plus 106 ml dextran minus 30 ml plasma in samples).
¶ Based on the exponential rate constant used for extrapolation for the plasma and erythrocyte volume determinations. Times given relative to the start of hemorrhage.
progressively in the control group that had no sustained hemorrhage during the experimental periods (Fig. 2), but even at 2.5 hours after time zero it was above the 7.0 ± 1.0 (sd) found by Guyton and associates,14 who use somewhat different techniques and deeper anesthesia. In group "—17," hemorrhaged by 20% of the estimated blood volume, the Pmc decreased to about half the control value. In group "—34," the Pmc initially was reduced to nearly zero. Indeed, in four dogs only about 28 ml/kg were removed in the first 30 seconds because the arterial pressure otherwise was less than about 30 mm Hg. Over the next 15 minutes, the Pmc increased markedly (Fig. 2). In group "Pa = 40," the hemorrhaged volumes were 29.3, 36.7, and 38.5 ml/kg at 0.5, 2, and 5 minutes, respectively. By 15 minutes the hemorrhaged volume was 39 ml/kg (the values in parentheses at the bottom of Fig. 2). Throughout the hemorrhagic hypotensive period the Pmc of this group was less than 1 mm Hg, a value required to reduce the cardiac output enough to result in the arterial pressure of 40 mm Hg. Except in the control group, the Pmc was relatively constant after the first half-hour. If one assumes that the experimental groups had the same declining trend in Pmc as the nonhemorrhage control group, then, in relation to this trend, the Pmc of the "—17" and "—34" groups increased progressively, especially during the first hour.

The changes in central venous pressure (Fig. 3, top) were similar in pattern to those of the Pmc, but the changes were only about 30% as great. Even though the Pmc of the Pa = 40 group was nearly zero (0.4 mm Hg), the central venous pressure of -4.1 mm Hg provided a pressure gradient of 4.5 mm Hg for venous return that was about 40% of the prehemorrhage pressure gradient [11.3 - (—0.5) = 11.8 mm Hg].

The cardiac output (Fig. 3, middle) showed a significantly greater decrease in response to hemorrhage from control to 20% of the blood volume (0 group vs. —17 group) than from 20% to 40% (—17 group vs. —34 group). The progressive decline of cardiac output in the control group followed that of the central venous pressure and Pmc. There also were increases in cardiac output in the —17 and —34 groups during the first half-hour that were similar to the patterns of the mean circulatory pressures.

The arterial pressure (Fig. 3, lower panel) did not change proportionally as much as the previously described cardiovascular variables. The high (>120 mm Hg) mean arterial pressure in the control group possibly can be attributed to the use of a minimal level of anesthesia or to the use of methohexital and urethane. The arterial pressure before the first cardiac fibrillation was not lower than the pressures that followed this intervention. In the group hemorrhaged by 20% of their blood volume and subjected to up to 23 fibrillations and procedures to measure Pmc, the arterial pressure averaged more than 100 mm Hg. This suggests that the dogs were in good condition and that the techniques were not extremely traumatic.

The heart rate during the control period was 145 ± 27 beats/min. Only the —17 group showed a significant increase, to about 175 beats/min, after the first hour of hemorrhagic hypotension.

The total peripheral conductance [cardiac output/(arterial – venous pressure)] (Fig. 4) decreased to about half of the control value in the experimental groups. Progressive vasoconstriction in dogs of the control group accounts for the maintenance of their arterial pressure, because the cardiac output of this group decreased (see Fig. 3).

The conductance for venous return [cardiac output/(mean circulatory – central venous pressure)] (Fig. 4, lower panel) decreased by half in the —34 and Pa = 40 groups. This increased resistance is attributable to both elastic recoil, which reduces venous radius because of the reduced transmural pressure, and to active vasoconstriction.

Hemodilution was seen as a reduction in plasma oncotic pressure, plasma protein concentration, and hematocrit (Fig. 5). All three methods showed similar patterns of change. The Pa = 40 group, however, showed a progressive trend toward hemoconcentration after the first 45 minutes of hemorrhage.

Fluid shifts accounted for a recovery of approximately 15% of bled volume by 30 minutes (Table 1). Whereas the control group showed no significant change in blood volume
between the first and second injections of isotope, there was a significant increase of 2.9, 4.2, and 8.6 ml/kg in plasma volume in the -17, -34, and Pa = 40 groups, respectively.

We do not present our attempts at estimating the changes in blood volume after hemorrhage, using changes in plasma protein concentration or oncotic pressure, because of the likelihood that an unknown but significant amount of protein entered the vasculature in response to severe hemor-
rhage. Calculating the total blood volume based on the erythrocyte volume by $^{46}$Cr dilution and the arterial hematocrit is fraught with uncertainty for the ratio of the arterial to total body hematocrit (the f$\text{eM}_8$ ratio) may not be one or may change (Table 1). The total body hematocrit was calculated as the ratio of the erythrocyte volume to the sum of plasma plus erythrocyte volumes using the isotope dilution data. During the prehemorrhage period it averaged 1.045 ± 0.066 (RMSE), as expected for the four groups of dogs with intact spleens. During the period of hemorrhagic hypotension it was significantly reduced to 0.944 ± 0.093 (RMSE) in the control, -17, and Pa = 40 groups by paired comparisons, but at this time there were no significant differences between the groups (Table 1) by one-way analysis of variance.

The vascular pressure-volume (P/V) relationships 0.5 minute after initiation of the test volume change are shown in Figure 6. The average parameter values are given in Table 1 for the control and 50-minute period for each group. All volume data are normalized to 1 kg of body weight. The “change in blood volume,” plotted on the abscissa of Figure 6, is the blood volume hemorrhaged into and measured in the reservoir at the times indicated at the top of each panel. The data are not corrected for fluid shifts. The closed symbols are the averaged Pmc of each group during the four time periods calculated for the nominal bled volume. These derived data were based on the least squares fit through the 0.5-minute test volume data (Table 1), and are similar (shown as asterisks in Fig. 2) to the Pmc data found without making a test volume change. The open symbols (Fig. 6) were calculated from the derived slope (vascular stiffness; Table 1) and the maximum change in test volume (17 ml/kg). The P/V relationships during the prehemorrhage period were closely similar (Fig. 6 and Table 1), especially when dogs were bled by 17 ml/kg. During the experimental periods, a hemorrhage into the reservoir totaling about 20 ml/kg would have brought both the 0 and -17 groups to a Pmc of 4 mm Hg (Fig. 6). Note, however, the steeper (stiffer) P/V curve of the -17 group. The P/V relationships of the -34 and Pa = 40 groups were displaced to the left, suggesting the occurrence of significant compensatory changes in addition to changes in compliance.

The Pa = 40 group, after 2 hours of hemorrhagic hypotension, appeared to show an increase in unstressed...
VASCULAR CAPACITANCE AFTER HEMORRHAGE

PLASMA ONCOTIC PRESSURE

PLASMA PROTEIN

HEMATOCRIT

FIGURE 5 Indices of hemodilution and plasma volume shifts. Symbols have same meaning as in Figure 2.

volume (less hemorrhaged volume at the same "near zero" Pmc and so more volume in the dog), but this is only apparent since the plasma protein concentration, oncotic pressure, and hematocrit progressively increased (Fig. 5) as blood was reinfused from the reservoir to maintain Pa = 40 mm Hg. Fluid was being lost from the vasculature.

If the P/V relationship at 50 minutes is corrected for the measured fluid shifts (Table 1) into the vasculature, the apparent degree of capacity vessel compensation to hemorrhage is less—the P/V curves of the experimental groups are closer to that of the control group. If the blood deficits were restored (Fig. 7)—a true hemorrhage of zero—the hemorrhaged groups would have had a Pmc much greater than that of the control group (Pmc = 9.8 mm Hg). For example, the Pmc of the control group averaged 9.8 mm Hg with no change in blood volume, but in the group bled by 17 ml/kg an infusion of only 11 ml/kg would have brought the -17 group to the same Pmc of 9.8 mm Hg at 50 minutes after hemorrhage (Fig. 7); this amounts to a compensation of 6 ml/kg, since 6 ml/kg could have been left in the reservoir. An even larger compensation was seen after a hemorrhage of 34 ml/kg, for only about 15 ml/kg would have been required to restore the Pmc to the control level for this group (Fig. 7, the -34 group, heavy line at 9.8 mm Hg), leaving 19 ml/kg in the reservoir.

The slopes of the P/V relationship (total vascular stiffness) of the experimental groups were greater (compliance less) than that for the control group during the experimental periods (Figs. 6-8). By one-way analysis of variance, the differences between the control and experimental groups are significant at the 5% level or less at 50 and 135 minutes (Fig. 8). Even after more than 2 hours of hemorrhage which caused an arterial pressure of 40 mm Hg, there was no evidence of decreasing total vascular stiffness.

Discussion

The total vascular pressure-volume (P/V) relationship, corrected for fluid shifts and shown in Figure 7, suggests a large capacity-vessel compensation in response to hemorrhage. The group hemorrhaged by 34 ml/kg (about 40% of blood volume) attained mean circulatory pressures equal to those of the control group on reinfusion of about 15 ml/kg, leaving about 19 ml/kg still apparently out of the dog (light line, Fig. 7). Fluid reabsorption amounted to about 4 ml/kg for this group. The change in vascular capacity thus accounts for the difference of about 15 ml/kg. Most of this is attributable to a change in vascular stiffness, for if the P/V had the same slope as the control, starting from the -30 ml/kg change at 3.8 mm Hg, a reinfusion of 24 ml/kg would have been required to attain the control Pmc.
Because we could not instantaneously hemorrhage the dog and also expect cessation of flow throughout the vasculature—a primary assumption of the Pmc determination—we do not have data concerning the active venomotor response during the first 30 seconds following initiation of hemorrhage and, especially, we do not know the instantaneous vascular stiffness. Although our data confirm the finding of Guyton et al. that there is no significant venomotor response before 7 seconds, as tested by noting the equilibrium pressure (Pmc) with flow presumably equal to zero and volume constant, the possibility must be considered that much of the active venomotor constriction occurs between 10 and 30 seconds, and so would be missed by comparing our control and hemorrhaged groups 30 seconds after a test volume change. With hemorrhage, there is an increased sympathetic outflow and so, we contend, a venoconstriction which causes the Pmc to increase; this starts at about 7 seconds and continues for at least 5 minutes (see Fig. 2, groups -17 and -34). Since the contained volume is constant, the change in Pmc (ΔP) at 30 seconds will be less, since the Pmc is increasing, than it would have been, if it could have been measured, at zero time. Compensation thus would cause a return of Pmc toward control (less ΔP), with a given volume change (ΔV). Therefore, the calculated stiffness (S = ΔP/ΔV) would be less than 30 seconds than the instantaneous stiffness. Thus, we suggest, the total vascular stiffness, without reflex compensation, is probably greater than the average control values of 0.289 ± 0.124 (S0) mm Hg per ml/kg (and the total vascular compliance of dogs is lower than 3.5 ml/kg per mm Hg). (Fig. 8 and Table 1). Indeed, in reflex-blocked dogs in our previous study the stiffness was 0.460 mm Hg per ml/kg, a value similar to that of the experimental groups (Fig. 8). The vasculature of the hemorrhaged groups may not have had time to show a similar degree of reverse change (smooth muscle relaxation) when transfused quickly with the test volume. We and others have reported a vascular stiffness of control animals of more than 0.4 mm Hg per ml/kg (a compliance less than 2.5 ml/kg per mm Hg). The possibility must be considered that surgical trauma, blood losses, or anesthetics attenuated any reflex compensation by the time the measurement was made.

The true, instantaneous vascular stiffness thus may not be changed appreciably by active venous smooth muscle contraction, but only the unstressed volume. Put another way, the low stiffness (0.3 mm Hg per ml/kg) during the prehemorrhage periods and in the control group may be a result of venomotor compensation during the first 30 seconds. Neither our data, those of Shoukas et al., nor those of Richardson et al. conclusively test this hypothesis, because it seems to be physically impossible to change the vascular volume instantaneously and obtain an accurate, composite measure of the intravascular pressure of the microvasculature (vessels less than 1 mm in diameter) where most of the blood is located.

Time-dependent changes in the P/V relationship also must include viscoelastic creep of the vascular wall after changes in transmural pressure, in addition to fluid shifts and smooth muscle contraction. By 2 hours after expansion of blood volume by 30% (about 21 ml/kg), Prather et al. reported a 13% (about 9 ml/kg) stress relaxation. As a first approximation, it is reasonable to assume a corresponding viscoelastic recoil after hemorrhage. Our current studies (Bruce Johns, personal communication) suggest that most viscoelastic creep occurs within the first 7 minutes and, in total, is much less than the purely elastic recoil. Slow viscoelastic relaxation probably would have lowered the Pmc in the hemorrhaged groups that had a test volume changes.
reinfused (Fig. 7), if the volume restoration had been continued beyond 1 minute. On the other hand, this viscoelastic recoil provides a significant, but undetermined, part of the compensation to hemorrhage.

The hemorrhaged volume increased from 29.2 to 36.7 ml/kg between 0.5 and 2 minutes after the start of hemorrhage in the Pa = 40 group. This difference, of 7.5 ml/kg, is attributable to reflex smooth muscle venoconstriction and viscoelastic recoil, but not to fluid shifts which occur much more slowly. (Between 2 and 5 minutes the change was only 1.8 ml/kg.) During the first 30 seconds the major source of the 29.2 ml/kg is from passive elastic recoil following the reduction in flow due to a reduced cardiac output and arteriolar constriction and an undetermined amount of active venoconstriction. Furthermore, the increased sympathetic outflow after hemorrhage would likely increase cardiac vigor and so tend to increase cardiac output if the cardiac filling were constant (we have no data before 5 minutes). Hemorrhage to contribute to the 29.2 ml/kg would then be needed to maintain Pa = 40 mm Hg.

FLUID SHIFT

Because of unknown rates of gain or loss of plasma protein and/or 131I loss caused by the change in blood volume, estimates of the changes in plasma volume after hemorrhage, based on the rate of change of radioisotope activity before and after hemorrhage, are in doubt. An estimate of the background isotope activity remaining and a second isotope injection are necessary to determine the posthemorrhage blood volume. This we did.

Chien et al., using repeated injections of 131I-labeled albumin in dogs with intact spleens and hemorrhaged to an arterial pressure of 40 mm Hg, found the dog plus reservoir plasma volume was about 10% (fluid shift = 5 ml/kg) more than the prehemorrhage volume by 20 minutes (bled volume = 40 ml/kg), and by 80 minutes it was about 22% (fluid shift = 11 ml/kg) larger than the prehemorrhage value in those dogs which survived for 24 hours after the 3 hours of hemorrhagic hypotension. The maximum increase in plasma volume in our dogs held at Pa = 40 mm Hg averaged 8.6 ± 3.6 ml/kg at 30 minutes, with an average hemorrhaged volume of 42.5 ml/kg, a 20% replacement for this group. In an earlier study of fluid shifts in normal vs. dehydrated dogs, we found a fluid shift of about 8 ml/kg in the normal dogs hemorrhaged to an arterial pressure of 40 mm Hg for 30 minutes (average bled volume = 47 ml/kg). The dehydrated dogs showed a fluid shift of only 5 ml/kg. Dunn et al. found about 7 ml/kg to be added to the circulation of hemorrhaged dogs. Deavers et al. found 8.6 ml/kg were added to the circulation after 1.5–2.5 hours of hemorrhagic hypotension, whereas Allen et al. reported 10 ml/kg. Chien, in an early study, reported that hemodilution was completed by about 15 minutes after a hemorrhage of more than 40% of the initial blood volume in splenectomized dogs. The fluid replacement amounted to about 26% of the hemorrhaged volume (equivalent to about 10 ml/kg for our dogs).

The rate of loss of 131I (Table 1) was higher than expected during the prehemorrhage period. In our previous study the loss rate was 9.4% per hour and, in another, 7.5%. The addition of the hyperoncotic (about 60 mm Hg) dextran would cause some fluid reabsorption and so plasma dilution. Since fresh, radiiodinated human serum albumin (RISA-125, Abbott) was used, the amount of free iodine was expected to be low. We did not dialyze it, however. We would expect that much of the free iodine would be lost within the first 9 minutes and so not contribute to the extrapolation. Since the effective amount of isotope injected would be less with such loss, our calculated volumes would be low, but the average blood volume, 84.1 ± 7.2 (SD) ml/kg, and arterial hematocrit of 0.402 ± 0.055 for the dogs were the expected values. Removal of the foreign protein by the body might also explain the somewhat rapid rate of loss of tracer. The increased loss rate of tracer during hemor-
rhagic hypotension is attributable to increased capillary permeability and to plasma dilution by the fluids that move into the vasculature.

Banet and Smith found a prehemorrhage pressure gradient for venous return of about 8 mm Hg (11.5 mm Hg in our study) in their study of Pmc in hemorrhagic shock. During hemorrhagic hypotension (Pa = 30 mm Hg) the gradient was about 4.0 mm Hg (ours was 4.5 mm Hg at Pa = 40 mm Hg). Because of difficulties in defibrillating the heart during hypotension, they made only one determination of Pmc on each dog during this phase of the experiment and so could not provide detailed information about the pattern of change in Pmc during hypovolemic shock. They were unable to draw any conclusions as to changes in vascular stiffness or blood volume during hemorrhagic hypotension.

Further studies will be needed to partition the approximately 35 ml/kg hemorrhaged during the first 2 minutes between passive elastic recoil, viscoelastic recoil, and active capacity vessel constriction.

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References

Vascular capacitance and fluid shifts in dogs during prolonged hemorrhagic hypotension.
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