Reflex Venoconstriction and Capacity Vessel Pressure-Volume Relationships in Dogs

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ABSTRACT

Reflexogenic control of vascular capacity was studied by measuring the mean circulatory pressure (P_{MC}) at various blood volumes. P_{MC} was obtained by fibrillating the heart for 10 seconds and rapidly transferring blood from the aorta to the vena cava until the pressures equilibrated. It was measured 0.5, 2, and 5 minutes after randomized changes in blood volume of 0 to ± 30% of the control volume in chloralose-urethane anesthetized dogs. Active venoconstriction was suppressed by administering hexamethonium and enhanced by administering norepinephrine. The effective total vascular compliance, expressed as the reciprocal of the slopes of P_{MC} vs. blood volume curves in the controls, was linear. Compliance values differed significantly from each other and increased between 0.5, 2, and 5 minutes after a change in blood volume (2.60, 3.47, and 4.17 ml/kg body weight mm Hg⁻¹, respectively). With ganglionic blockade, only an 8-ml/kg hemorrhage was required to bring P_{MC} from the control level of 7.8 mm Hg to 4 mm Hg within 0.5 minutes. With reflexes intact, a 17-ml/kg hemorrhage reduced P_{MC} from a control of 10.7 mm Hg to 4 mm Hg. To maintain this pressure for 5 minutes, an additional 8.2 and 9.1 ml/kg, respectively, had to be hemorrhaged, suggesting that the compensation after about 30 seconds was mostly from passive viscoelastic creep and fluid shifts. Less than half of the compensation for hemorrhage during the first 5 minutes came from the reflex venoconstriction.

KEY WORDS control of vascular capacity viscoelastic recoil total vascular compliance mean circulatory pressure venous tone blood volume hemorrhage transfusion

Venoconstriction has been assumed to be an effective homeostatic response to hemorrhage. Capacity vessel contraction, acting to transfer blood from the periphery to the heart, restores right ventricular filling pressure and thus maintains cardiac output. Reflex venoconstriction is defined as a neurogenically induced contraction of the smooth muscle in the walls of veins; it causes a reduction in vascular capacity which is seen as a decrease in the volume of blood contained at the same pressure, an increase in the pressure at the same volume, or a combination of both.

The effectiveness of this system is open to question. Gauer et al. (1) have concluded from their studies and a review of the literature that there is an "...absence of any noteworthy venomotor response to moderate fluid volume changes..." They have not changed their 1963 conclusion (2) that changes in capacity vessel tone occur only in emergencies following hemorrhages larger than about 15 ml/kg. Furthermore, neurogenic venoconstriction of skeletal muscle accounts for only a small amount (< 5 ml/kg tissue weight) of the blood mobilized during maximal sympathetic nerve stimulation and constant-flow perfusion (3, 4). Some investigators have reported that the veins have little or no part in the baroreceptor response (5-7). Harris et al. (8) have reported that cutaneous veins of bats dilate in response to hemorrhage. On the other hand, Heymans and Neil (9) have stated that: "The most important change during reflex systemic hypertension of sino-aortic origin is probably that of venoconstriction." A large fraction of the blood in the splanchnic bed is redistributed toward the heart following hemorrhage according to Brooksby and Donald (10, 11). It seems to us that a measure of the pressure-volume relationship of the total vasculature as a function of time with and
without autonomic ganglionic blockade would give an effective measure of the range of reflex venoconstriction.

The pressure-volume relationship of the capacity vessels is influenced by at least five mechanisms. In addition to (a) reflex venoconstriction, the veins (b) also recoil passively in response to a decrease in transmural pressure. Such a passive response will follow a neurogenic arteriolar (resistance vessel) constriction which reduces flow and thus transmural pressure in the area between the capillaries and the heart. Although the resistance to flow in the veins is small, so are the pressure differences; thus, the influence is large. Furthermore, since the veins (c) exhibit time-dependent viscoelastic properties, a simple separation between passive and active responses is not possible. Another complicating factor is (d) the fluid shift to or from the vasculature at the capillary level with changes in capillary pressure following pre- or postcapillary resistance vessel changes or changes in arterial blood pressure or venous pressure. Total tissue weight or plethysmographic measurements in the presence of changes in flow will not give a reliable measure of vascular volume changes—a situation often overlooked by previous investigators. Even if the total perfusion rate is constant, changes in conductance patterns and flow distribution within the tissue will cause changes in transcapillary fluid movements. Finally, the possibility of (e) myogenic activation of the smooth muscle around the veins stimulated by changes in transmural pressure must be considered.

To arrive at a total vascular pressure-volume relationship, we changed the blood volume by hemorrhage or transfusion and assumed that the mean circulatory pressure \( P_{MC} \) was a reasonable estimate of the pressure at the level of greatest vascular volume—the small veins. \( P_{MC} \) was defined as that pressure in the area of the right atrium which occurred when the blood flow in all parts of the cardiovascular system was zero, when the pressures in all parts of the system were equal, and before reflex excitation of the smooth muscle of the capacity vessels occurred. We based our investigation on the following hypotheses. (1) Reflex compensation in response to a change in blood volume alters both the slope and the unstressed vascular volume. (2) The pressure-volume relationships of control and norepinephrine-stimulated dogs coincide under hypovolemic conditions produced by hemorrhage. Maximal activation of the smooth muscle will be present under these conditions in both groups. (3) The pressure-volume relationships of control and areflexic dogs coincide under hypovolemic conditions produced by blood transfusions. Minimal reflex activation of the smooth muscle of the capacity vessels will be present under these conditions in both groups. (4) The slope of the pressure-volume curve decreases with time. Compensation for the volume change will be greater in control dogs that it is in areflexic ones, since only passive compensatory mechanisms will be present after ganglionic blockade.

**Methods**

The mongrel dogs in the control and areflexic groups were anesthetized with sodium methohexital (12.5 mg/kg, iv). Alpha-chloralose (2%) in combination with urethane (12.5%) to increase its solubility was dissolved in distilled water at 60°C and held at 50°C. Within 5–15 minutes, 2 ml/kg of the chloralose-urethane solution was infused to provide 40 mg/kg of chloralose and 250 mg/kg of urethane. Maintenance of anesthesia required infusion of the chloralose-urethane mixture at a rate of 2 ml/kg hour\(^{-1}\). In the norepinephrine series, sodium pentobarbital (30 mg/kg, iv) was used as the anesthetic.

Donor dogs were anesthetized with sodium methohexital. Blood compatibility was assured by cross matching donor cells with recipient plasma and recipient cells with donor plasma. Incompatibility was evidenced by clumping in 29% of all trials.

Body temperatures were maintained at 38–40°C with warm water circulated through channels in the operating table. Commercial oxygen was delivered via a tube opening near the lower end of the endotracheal tube (diameter 0.9 cm). Arterial oxygen tension, monitored with a microcathode polarographic electrode, was maintained above 100 mm Hg.

The right common carotid artery was cannulated for sampling and pressure monitoring. Arterial blood was passed through a densitometer, a three-roller peristaltic pump (Holter model RL-175, Extracorporeal Medical Specialties, Inc.), and a bubble trap and then returned to the dog via a reinfusion line coaxially placed within a polyethylene catheter (3.7 mm, i.d.) in the right external jugular vein. The tip of the catheter was located at the junction of the superior vena cava and the right atrium. From a Plexiglas junction, a Statham P23Dx transducer was connected for measurement of central venous pressure. In addition to the reinfusion line, the jugular catheter also contained a dye injection catheter and a unipolar electrode composed of a silver plug 1 mm in diameter and about 1 cm long at the end of a piece of Teflon tubing, both of which were advanced 2 cm beyond the tip of the jugular catheter.

The placement of the electrode used to produce fibrillation in the right atrium or ventricle was assured by advancing the venous catheter through the right atrium and the tricuspid valve into the right ventricle.
while pressure was monitored. The tip of the electrode was then advanced as the venous catheter was withdrawn to the right atrium or just outside to the junction of the superior and inferior venae cavae. Ventricular fibrillation was achieved by a 3-5-v, 60-Hz stimulus between the sternum and the right atrium. The stimulus strength needed for fibrillation was well below that which causes skeletal muscle involvement and results in artifactual $P_{MC}$-measurements (12).

The right and left femoral arteries and veins were exposed and cannulated with polyethylene tubing (3.2 and 3.8 mm, i.d., respectively). The catheter tips were placed close to the point at which the aorta and the inferior venae cava pass through the diaphragm to minimize aortic collapse during the rapid withdrawal of arterial blood. The locations were judged to lie on the transverse planes which intersect the most caudal point of the last rib and the xiphoid process, respectively. Fluoroscopic placement of the catheter tips was attempted in several pilot experiments but was no better than simple approximation of catheter placement. The placement was routinely checked at autopsy. Short lengths of Silastic or polyethylene tubing (0.25 inches, i.d.) and Plexiglas junction blocks provided the connections to a double-roller pump (Med-Science Electronics) and a one-liter reservoir. Hemostats were used on the tubing for valves. Positive or negative air pressure was applied to the reservoir for rapid (> 1 liter/min) transfusion or hemorrhage. The blood was mixed continuously with a Teflon-coated magnetic-coupled stirrer.

Sodium heparin (5 mg/kg) was given intravenously with supplementary doses infused at a rate of 2.5 mg/kg hour$^{-1}$. Donor blood in the control (reflexic) and areflexic groups was added to the reservoir in amounts sufficient to provide 25.5- and 34.0-ml/kg whole blood infusions, respectively. The pump tubing, connections, and 50 ml of the reservoir were filled with 120 ml of dextran (6% w/v) in saline. To provide an infusion of 17 ml/kg body weight in the norepinephrine series, dextran, rather than whole blood, was mixed with the dog's blood by infusing and withdrawing blood several times. For control conditions, 17 ml/kg of the blood was held in the reservoir.

MEAN CIRCULATORY PRESSURE MEASUREMENTS

For measuring $P_{MC}$, the heart was fibrillated, and within the next 2-5 seconds enough blood was pumped at about 30 ml/sec from the arterial side of the circulation to the venous side to equalize the pressures; then the pump was automatically stopped. The plateau value at the point of equal pressure was taken as $P_{MC}$. The stimulus inducing fibrillation was stopped, and a 100- joule countershock was delivered. Arterial blood pressure was below 80 mm Hg for a period of about 10 seconds. The average time from the initiation of the stimulus until the central venous pressure was within 1 mm Hg of the pressure taken as $P_{MC}$ was 3.2 ± 1.6 seconds. $P_{MC}$ was measured at 5.3 ± 2.2 seconds.

A d-c defibrillator (Electrodyne Co. D-84-M) was used. Defibrillating electrodes 8 cm in diameter were strapped to both sides of the chest using a saline-soaked gauze pad between each electrode and the chest. The dogs were repositioned on their left sides, and transducer pressure reference points were set in a midsternal plane.

BLOOD VOLUME MEASUREMENTS

Red blood cell and plasma volumes of the control dogs were determined using $^{51}$Cr-labeled erythrocytes and $^{131}$I- and $^{125}$I-labeled serum albumin, respectively.

The red cell tagging procedure was a modification of that of Gray and Sterling (13) which used a sodium chromate $^{51}$Cr injection (Mallinckrodt Nuclear) and an acid citrate-dextrose solution special formula anticoagulant (Strumia, Abbott). Ascorbic acid was used to stop the tagging process. For standards, 10.0 ml was diluted to 500 ml with normal saline. Using the same 10.0-ml calibrated syringes, about 150 µc was injected intravenously. Appropriate corrections were made for background, free chromium (average 1.9%) and hematocrit ratio.

For plasma volume, an iodinated $^{125}$I or $^{131}$I human serum albumin injection (Mallinckrodt Nuclear) was used in an intravenous dose of about 15 µc in 10.0 ml. Normal human serum albumin (Courtland Laboratories) was used to inhibit competitively possible glass adsorption of the iodinated serum albumin during preparation and in the standard. Appropriate corrections were made for background, hematocrit of whole blood samples counted, and Compton effect from the $^{51}$Cr.

Duplicate samples of 1.000 ± 0.005 ml were collected, using a constant-delivery sampling syringe, for counting at 10, 20, 30, 45, and 60 minutes after injection. A well scintillation counter (Auto Gamma spectrometer, Packard Instruments) was used. The windows were $8-54$ kev for $^{131}$I, 233-416 kev for $^{51}$Cr, and 228-482 kev for $^{125}$I. Using the $^{131}$I late in the experiments, samples were taken at 6, 9, 12, and 15 minutes after injection. The erythrocytes were separated from the plasma by centrifugation. Counting times were chosen to give counting errors of less than 0.5% for the iodine isotopes and about 1% for the $^{51}$Cr. The data were plotted on semilogarithmic paper for extrapolation to the time of injection for the calculations of volumes.

CARDIAC OUTPUT DETERMINATIONS

Cardiac output was measured by injecting 1.25 mg of indocyanine green with a 0.500-ml syringe injector (14) via a 100 cm long, 0.7 mm, i.d., Teflon catheter inserted in the right atrium without flushing. Blood was drawn at 25 ml/min through a Gilford model 103 IR cuvette den-
sitometer fitted with an 805-nm filter. Transit time from the carotid artery to the densitometer was 3.9 seconds. The densitometer data were recorded on analog magnetic tape for computing using the method of Kunz and Smith (15) as modified by us for a commercial analog computer (Electronic Associates, Inc.: model TR20) (16, 17. Calibration samples contained 0, 5, and 10 mg/liter of dye. Since the computation provides a number representing the minute concentration with extrapolation to infinite time, the flow was calculated as the ratio of the amount of dye injected to this concentration.

**EXPERIMENTAL PROTOCOL**

The time after anesthesia required to complete the setup for a given experiment and to measure blood volume was 1.5-2 hours. After control determinations, the blood volume of the control group was changed ± 8.5, ± 17.0, and ± 25.5 ml/kg corresponding to about ± 10, ± 20 and ± 30% of the total blood volume. Blood volume changes were randomized as to direction of the first volume change. The subsequent change in volume was in the opposite direction, e.g., −17 ml/kg followed by +17 ml/kg. The magnitude of each pair of volume changes was also randomized. Complete randomization was not desirable, since after a series of volume changes in the same direction cumulative passive responses such as fluid shift and viscoelastic behavior probably would occur. The data for zero volume change were from an average of determinations made just before and just after the randomized series.

In the areflexic series of dogs, hexamethonium chloride (Nutritional Biochemicals Corp.) was administered (4 mg/kg, iv) after the initial control run. A supplementary dose (2 mg/kg) was given every half hour. Although Volle and Koelle (19) have reported that ganglionic blockade appears to have a differential effect on the circulation, hexamethonium has been extensively employed as a blocking agent of sympathetic reflexes experimentally and clinically (20-22). An advantage of ganglionic blockade over total spinal anesthesia is that respiration continues without assistance. Positive-pressure lung inflation markedly alters hemodynamics and was deemed undesirable.

The cardiovascular response to hexamethonium was measured about 9 minutes after the administration of the autonomic blocking agent. To compensate in part for the loss of sympathetic tone, 8.5 ml/kg of matched donor blood was then infused. An areflexic, postinfusion control determination was then made (Table 1). Subsequent volume change −17, −8.5, 0, 17, 25.5, and 34 ml/kg were made with respect to the initial blood volume; the 15-minute control periods between volume changes were held at ±8.5 ml/kg.

To check the adequacy of ganglionic blockade, cervical spinal cord conduction was blocked by inflation of a balloon at about 1,200 mm Hg to compress the spinal cord against the wall of the canal. Respiration stopped and was then restored by electrophrenic stimulation (23). No significant changes were seen in PMC, Pcv, cardiac output, total peripheral conductance, or heart rate, but the blood pressure decreased 21 ± 19 mm Hg.

To produce constriction of the vasculature, noradrenaline was diluted to 20 μg/ml in saline and infused at 1.5 μg/kg min⁻¹ for 5.5 minutes, starting 2.5 minutes after volume changes of 0, ± 8.5, ± 17, and −25.5 ml/kg. Although the effective blood concentrations would have changed as the cardiac output changed, the dose was assumed to provide a maximum stimulation under all conditions.

Further details as to methods used have been published previously (16).

**Results**

Mean values are given with the standard deviation as an index of variability unless otherwise stated. If the results of statistical tests indicated a probability of 0.05 or less that the values found could be from random variation, the differences were considered to be significant; if the probability was less than 0.01, the differences were considered to be highly significant. Control values for each series of experiments are given in Table 1. Statistical tests for linearity and differences are discussed in the Appendix. The response of arterial and central venous pressures to fibrillation of the heart is shown in Figure 1. With successive PMC determinations in the control group, no significant change occurred in PMC (Figs. 2 and 5), Pcv (Fig. 5), cardiac output, PA, total peripheral conductance, or heart rate at control volumes, even though the cardiac fibrillation maneuver was repeated three times in 5 minutes (e.g., means of PMC raw data: 10.4 ± 2.7, 10.7 ± 2.8, and 10.4 ± 2.6 mm Hg).
Example of experimental data for determination of mean circulatory pressures (PMC). Defibrillation occurred at 6 seconds. Pressures are in mm Hg. \( P_A \) = arterial pressure, \( Pcv \) = end-expiratory central venous pressure, \( \Delta PA-V \) = the arteriovenous pressure difference. See text for details.

**TABLE 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control*</th>
<th>Areflexic</th>
<th>Norepinephrine*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preblockade†</td>
<td>Postblockade†</td>
<td>Postinfusion§</td>
</tr>
<tr>
<td>No. of expts.</td>
<td>9</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Body wt (kg)</td>
<td>14.5 ± 1.5</td>
<td>13.8 ± 2.1</td>
<td>14.4 ± 1.2</td>
</tr>
<tr>
<td>( P_{MC} ) (mm Hg)</td>
<td>10.5 ± 2.6</td>
<td>8.7 ± 2.5</td>
<td>9.6 ± 2.1</td>
</tr>
<tr>
<td>( Pcv ) (mm Hg)</td>
<td>0.7 ± 1.9</td>
<td>0.8 ± 1.3</td>
<td>-0.2 ± 0.9</td>
</tr>
<tr>
<td>C.O. (ml/min kg(^{-1}))</td>
<td>15.0 ± 37.0</td>
<td>104.0 ± 33.0</td>
<td>128.0 ± 42.0</td>
</tr>
<tr>
<td>( P_a ) (mm Hg)</td>
<td>139.0 ± 14.0</td>
<td>140.0 ± 9.0</td>
<td>139.0 ± 13.0</td>
</tr>
<tr>
<td>( CT_p ) (ml/min kg(^{-1}) mm Hg(^{-1}))</td>
<td>1.00 ± 0.41</td>
<td>1.28 ± 0.26</td>
<td>1.11 ± 0.45</td>
</tr>
<tr>
<td>( CV_R ) (ml/min kg(^{-1}) mm Hg(^{-1}))</td>
<td>13.7 ± 5.4</td>
<td>14.9 ± 2.8</td>
<td>16.0 ± 6.6</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>171.0 ± 34.0</td>
<td>155.0 ± 27.0</td>
<td>185.0 ± 21.0</td>
</tr>
</tbody>
</table>

All values are means ± SD. \( P_{MC} \) = mean circulatory pressure, \( Pcv \) = end-expiratory central venous pressure, C.O. = cardiac output, \( P_a \) = mean arterial blood pressure, \( CT_p \) = total peripheral conductance, \( CV_R \) = conductance for venous return, and HR = heart rate.

*Average of determinations before and after the randomized changes in volume.
†Average of three determinations per experiment about 100 minutes after anesthesia.
§Mean value 6.6 ± 1.5 minutes after infusion of 8.5 ml/kg of donor whole blood.
volume relationship was 0.385 mm Hg per ml/kg of blood volume change (2.60 ml/kg mm Hg⁻¹, Figs. 2 and 4 and Table 2). With ganglionic blockade (hexamethonium, 4 mg/kg), the slope was significantly steeper (0.460 mm Hg per ml/kg; 2.17 ml/kg mm Hg⁻¹, Figs. 3 and 4 and Table 2); this finding suggests that significant compensation occurred within 30 seconds with an intact autonomic nervous system, since a greater amount of blood had to be removed from the control group than from the areflexic group to attain the same $P_{MC}$. A quadratic plus linear relationship fitted the data (Fig. 4) somewhat better than a simple linear one (Table 2). However, the maximum hemorrhages were so severe that these values were uncertain; they were the prime cause of the nonlinear pressure-volume relationship. Deleting the values for the −25.5-ml/kg volume change for the control group and the −17-ml/kg volume change for the areflexic group (Fig. 4), a linear fit was insignificantly different from a fifth order polynomial least-squares fit through the six mean values for each group. Confidence intervals were computed for linear fit (see Appendix) giving the bands of 5% significant difference shown in Figures 2 and 3.

With both the control and the areflexic dogs, $P_{MC}$ increased with time following hemorrhage and decreased with time following transfusion. The slopes decreased to 0.240 and 0.338 mm Hg per ml/kg (a 38% and 26% decrease), respectively, at 5 minutes (Figs. 2 and 3 and Table 2). The differences in slope were highly significant. Assuming that 4 mg/kg of hexamethonium blocked the reflexogenic response, it is clear that most of the compensation for volume change was not reflexogenic but was passive—transcapillary fluid shifts and viscoelastic creep. Unfortunately, reliable data could not be obtained prior to 0.5 minutes. Furthermore, since a certain amount of fluid will move to or from the vasculature, the actual vascular volume was different at 5 minutes from that at 0.5 minutes. The change in volume, assumed to be constant for the computation of compliance, changes. Thus, we considered the slope coefficient to be a measure of apparent stiffness or its reciprocal to be a measure of apparent compliance. The contribution of viscoelastic creep provided a delayed compliance.

When the blood volume in the areflexic dogs was reduced by 8.5 ml/kg to the level expected in the control group, the $P_{MC}$ was 2.9 mm Hg lower than that in the control group at 0.5 minutes. By 2 minutes the difference was 1.4 mm Hg and at 5 minutes the groups were not significantly different, since the values for the areflexic group had increased to the level of those for the control group, which did not change significantly. The initial response to hexamethonium in the areflexic group was a 4.5-mm Hg decrease in $P_{MC}$ (Table 1).

Alternatively, attainment of a $P_{MC}$ of 10.7 mm Hg at 0.5 minutes in the areflexic group required an infusion averaging 6.3 ml/kg (from equation on line 4,
PARTITION OF CHANGES IN VASCULAR CAPACITY DURING HEMORRHAGE

The importance of reflexogenic activity was our prime concern. To analyze it, data were available to estimate by interpolation, for all groups and times studied, the amount of hemorrhage needed to reduce $P_{MC}$—assumed to be the pressure in the small veins—to 4 mm Hg. At this $P_{MC}$, the cardiac output was about 30% of control and the arterial blood pressure was 62% of control—a severe hemorrhage. (Operationally, the volume was changed and the resulting $P_{MC}$ was measured. By using the confidence bands based on the statistical analysis, a reasonable estimate by interpolation was available.)

We assumed that the 8.3-ml/kg hemorrhage required to bring the areflexic group from 7.8 mm Hg to a $P_{MC}$ of 4 mm Hg at 30 seconds (Table 2) was from passive, elastic, time-independent recoil plus a small component of time-dependent viscoelastic creep. By 5 minutes, in this group, an additional 8.2-ml/kg hemorrhage was required to maintain a $P_{MC}$ of 4 mm Hg. This compensation for hemorrhage is attributed to viscoelastic creep and fluid movement from the tissue into the vasculature. No data were obtained in these experiments to partition these two facets. With the control group, a 17.4-ml/kg hemorrhage brought $P_{MC}$ from 10.7 to 4 mm Hg at 30 seconds. The difference of 9.1 ml/kg

| Table 2 |

Regression Equations of Mean Circulatory Pressure as a Function of Changes in Blood Volume

<table>
<thead>
<tr>
<th>Line</th>
<th>Group</th>
<th>No. of</th>
<th>$P_{MC}$ (mm Hg)</th>
<th>Zero intercept $P_{MC}$ (mm Hg)</th>
<th>Slope (mm Hg per ml/kg)</th>
<th>Standard error of slope</th>
<th>$\Delta V$ for $P_{MC}$ of 4 mm Hg</th>
<th>Root of mean square error (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control*</td>
<td>0.5</td>
<td>9  6  61</td>
<td>$P_{MC} = 10.70 + 0.385 \Delta V_{ol}$</td>
<td>0.0161</td>
<td>-17.4</td>
<td>1.81</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Control</td>
<td>2.0</td>
<td>9  7  68</td>
<td>$P_{MC} = 10.84 + 0.288 \Delta V_{ol}$</td>
<td>0.0131</td>
<td>-23.8</td>
<td>1.78</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Control</td>
<td>5.0</td>
<td>9  7  68</td>
<td>$P_{MC} = 10.35 + 0.240 \Delta V_{ol}$</td>
<td>0.0131</td>
<td>-26.5</td>
<td>1.50</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Areflexic†</td>
<td>0.5</td>
<td>7  6  42</td>
<td>$P_{MC} = 7.81 + 0.460 \Delta V_{ol}$</td>
<td>0.0321</td>
<td>-8.3</td>
<td>2.49</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Areflexic</td>
<td>2.0</td>
<td>7  6  39</td>
<td>$P_{MC} = 9.41 + 0.380 \Delta V_{ol}$</td>
<td>0.0277</td>
<td>-14.2</td>
<td>3.27</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Areflexic</td>
<td>5.0</td>
<td>7  6  40</td>
<td>$P_{MC} = 9.57 + 0.338 \Delta V_{ol}$</td>
<td>0.0276</td>
<td>-16.5</td>
<td>3.26</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Control‡</td>
<td>2.0</td>
<td>10 6  58</td>
<td>$P_{MC} = 10.00 + 0.310 \Delta V_{ol}$</td>
<td>0.0202</td>
<td>-19.4</td>
<td>1.99</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Norepinephrine§</td>
<td>5.0</td>
<td>10 6  59</td>
<td>$P_{MC} = 14.68 + 0.408 \Delta V_{ol}$</td>
<td>0.0201</td>
<td>-26.2</td>
<td>2.23</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Norepinephrine</td>
<td>8.0</td>
<td>10 6  59</td>
<td>$P_{MC} = 13.77 + 0.367 \Delta V_{ol}$</td>
<td>0.0201</td>
<td>-26.6</td>
<td>2.36</td>
<td></td>
</tr>
</tbody>
</table>

Since the variances within each group were homogeneous, the error mean squares were pooled for the computation of the standard error of slope (see Appendix). $\Delta V$ for $P_{MC}$ of 4 mm Hg was calculated from regression equation. The linear fits through all available data were included for comparison; the fits are unsatisfactory.

*Chloralose (40 mg/kg) plus urethane (250 mg/kg) anesthetic.
†Reflexes blocked with 4 mg/kg of hexamethonium. Control volume was +8.5 ml/kg by transfusion of matched donor dog blood.
‡Pentobarbital (30 mg/kg) anesthetic.
§Norepinephrine was infused at 1.5 µg/kg min⁻¹ starting 2.5 minutes after the volume change.

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between the control and the areflexic groups at 0.5 minutes represents a combination of rapid reflexogenic venoconstriction and a basal tone in the control group.

By 5 minutes the control group could sustain a 26.5-ml/kg hemorrhage. Note that the 9.1-ml/kg compensation between 0.5 and 5.0 minutes after hemorrhage is similar to the 8.2-ml/kg compensation in the areflexic group, suggesting little further reflex compensation after 30 seconds. A maximum reflexogenic venoconstriction was apparently present in the control group hemorrhage to a Pmc of 4 mm Hg, for the degree of hemorrhage required was the same as that in the group given norepinephrine (Fig. 3 and from equations on lines 3 and 8, Table 2). The difference in blood volumes at a Pmc of 4 mm Hg between the areflexic group and the control or norepinephrine groups of about 10 ml/kg represents the range of reflexogenic activity following hemorrhage. With respect to a control Pmc of 10.4 mm Hg (from equation on line 3, Table 2), the difference is about 13 ml/kg (from equations on lines 6 and 8, Table 2).

Since the compliances of the norepinephrine-stimulated and the hexamethonium-relaxed groups were similar at 5 minutes after a volume change (about 2.7 ml/kg mm Hg−1), it would appear that sympathetic activity primarily changed the unstressed vascular volume rather than the slope and that the marked increase in apparent compliance at 5 minutes in the control group (4.2 ml/kg mm Hg−1) represented differences in sympathetic activity; transfusions led to reduced sympathetic activity following hemorrhage. With respect to a control Pmc of 10.4 mm Hg (from equation on line 3, Table 2), the difference is about 13 ml/kg (from equations on lines 6 and 8, Table 2).

Thus, at 5 minutes at least 31% (100 × 8.3/26.5) of the rapidly hemorrhaged volume is from passive elastic recoil, nearly 31% (100 × [16.5 - 8.3])/26.5) is from passive viscoelastic creep and fluid shifts from the tissue, and 38% (100 × [26.5 - 16.5])/26.5) is attributable to reflexogenically induced activity.

**MEASURED BLOOD VOLUME**

The blood volume in the control group was 96.5 ± 7.5 ml/kg. Total blood volume measured after 4-5 hours of experimentation equaled 82.3 ± 10.8 ml/kg. The red blood cell volume, determined by concentrations of 81Cr in samples taken prior to the injection of 131I-labeled human serum albumin, did not decrease significantly (−2.1 ± 3.5 ml/kg). Blood taken for samples was 4.5 ml/kg. However, the decrease in plasma volume was highly significant (−12.1 ± 3.4 ml/kg).

The loss of plasma may have resulted from an increase in capillary permeability with subsequent loss of plasma proteins and fluid. In contrast to the average disappearance of 9.4 ± 4.2%/hour of the 131I activity at the beginning of the experiments (70-130 minutes after anesthesia), the average disappearance of 131I activity at the end of the experiments (370-385 minutes) occurred at the rate of 27.6 ± 13.6%/hour. In all but one experiment, all four 131I sample concentrations (at 6, 9, 12, and 15 minutes after injection) plotted on semilogarithmic paper fell on a straight line.

The duration of the experiment had a significant effect on Pmc. The highly significant change in Pmc (12.0 ± 2.1 mm Hg about 135 minutes after anesthesia vs. 9.1 ± 2.4 mm Hg 3 hours later) that occurred at the control blood volume represents the primary rationale for having randomized all volume changes from experiment to experiment. Changes also occurred in the responses to hypovolemia. The initial runs at ±17.0 ml/kg were randomized over the 3-hour interval along with all of the other volume changes. At the end of the randomized changes in blood volume, final runs at the control blood volume and at +17 ml/kg and −17 ml/kg were again made. Except for the 0.5-minute values at ±17.0 ml/kg, which did not differ statistically between the early and late runs, all other Pmc values were also significantly lower late in the experiments. The decrease in Pmc could reflect a decrease in sympathetic tone. More likely, however, the decrease in pressure reflected the 14.2-ml/kg decrease in blood volume over the 4-hour intervening period between volume measurements.

Although the duration of the experiments caused a significant change in Pmc, the factors involved had much less of an effect on Pcv. Although Pcv decreased over the intervening period of time, the average pressures at corresponding times and volumes were generally not significantly different.

Differences in control values of Pmc for the dogs in the three groups (Table 1) are attributable to the anesthetic used and the duration of anesthesia before initiation of experimentation (16). It would appear that the normal Pmc in the supine, lightly anesthetized dog is on the order of 12.6 ± 2.3 mm Hg, the result of 45 early observations from the control and areflexic groups.
Other cardiovascular variables were measured to evaluate the condition of the dogs in each group and to provide comparable data on sensitivity to volume change.

The effects of the various maneuvers on \( P_{CV} \) are shown in Figure 5. The patterns are similar to but lower in magnitude than those for \( P_{MC} \). The data are clearly nonlinear, in contrast to those for \( P_{MC} \). These differences might be expected, since \( P_{CV} \) is modified by cardiac function and is dependent on \( P_{MC} \) and the conductance for venous return.

The changes in cardiac output and \( P_A \) expressed as a percent of control (Table 1) are shown in Figure 6. A ±17-ml/kg change in blood volume in the control group produced comparable changes in \( P_{MC} \) (146 ± 18 and 58 ± 17%) and cardiac output (168 ± 46 and 62 ± 27%). Above 90% of the control blood volume, \( P_A \) showed little change from control at 1.5 minutes and no difference at 4.5 minutes, suggesting good regulation. After ganglionic blockade (Fig. 6) the decreases in cardiac output and \( P_A \) from the control mean value were highly significant. Increasing the blood volume by about 10% partially restored both variables. Norepinephrine had a marked effect on \( P_A \) (Fig. 6); the effect on cardiac output was less with respect to control as the blood volume was decreased.

Cardiac power as a function of mean \( P_{CV} \) provided an indication of the degree of sympathetic blockade or stimulation. A positive inotropic effect was clearly demonstrated by the infusion of norepinephrine. Ganglionic blockade had a negative inotropic effect which was particularly noticeable at the higher venous pressures, e.g., at a \( P_{CV} \) of 6 mm Hg; the power developed was only about half that found during norepinephrine infusion.

Total peripheral conductance, \( G_{TP} = \frac{C.O.}{(P_A - P_{CV})} \), and conductance for venous return, \( G_{VR} = \frac{C.O.}{(P_{MC} - P_{CV})} \) (where C.O. = cardiac output and \( P_A \) = arterial blood pressure), were computed and plotted in Figure 6. The constancy of the total peripheral conductance in the areflexic group as volume was changed is prime evidence that the autonomic reflexes were blocked. The slope for the conductance for venous return, \( G_{VR} \), was also reduced in this series compared with control. The decrease in conductance with decreased blood volume is attributable to both reflex and passive factors in the control group. With the areflexic group some decrease would also be expected, since...
a reduction in internal pressure permits elastic recoil and viscoelastic creep which not only reduce the volume but also the conductance.

The heart rate was highly variable and higher than normal for an unanesthetized dog (Table 1). With ganglionic blockade or hemorrhage the heart rate tended to increase; norepinephrine resulted in a decrease.

**Discussion**

The data presented support three of our hypotheses. (1) With severe hemorrhage, the control group and the catecholamine-infused group have similar values of P_M C . (2) With transfusion, the control group and the ganglionic reflex-blocked group have similar values of P_M C . (3) With time, various compensatory mechanisms act to bring PMC toward a control level. However, with a change in blood volume, reflex compensation alters the unstressed vascular volume relatively more than the slope of the vascular pressure-volume relationship. The range of reflexogenic compensation taken as the difference between the areflexic and norepinephrine groups at 5 minutes and equivalent pressures appears to be about 13 ml/kg (Fig. 3) with an even greater range with hypervolemia.

The nearly linear pressure-volume relationship which we found is in stark contrast to the conclusions of Gauer et al. (1, 2) that the vascular tone of the capacity vessels changes only in response to severe hemorrhage. The basis for their conclusions came mostly from studies of the venous beds of the extremities. Although our dogs were anesthetized, the total body response including the splanchnic bed suggests that venomotor activity is involved with fine as well as coarse emergency circulatory homeostasis. Harlan et al. (18) found a linear relationship, also.

Guyton et al. (25) state that P_M C is 6.9 ± 0.9 mm Hg—a much lower value than that which we found. However, they used sodium pentobarbital anesthesia at a depth sufficient to suppress the hyperventilatory response which accompanied their P_M C maneuver (26). This procedure probably reduced sympathetic activity (27) and venomotor tone and decreased P_M C . Furthermore, their procedure was to continue pumping blood from the arterial to the venous side of the circulation and to take the pressure at which central arterial and central venous pressure crossed as P_M C . At that instant, however, flow is occurring, and so the pressure in the periphery is close to but not the same as the measured value, although Guyton et al. (26) reported an error of less than 1 mm Hg when they investigated this source of error. These two factors—anesthetic and technique—may account for the difference.

Reflex venoconstriction might have started between the initiation of fibrillation and the stabilization of the system to the pressure taken as P_M C , since sympathetic nerve activity to the tissue increases within a fraction of a second (28). However, the response of smooth muscle is slow, and only 3.2 ± 1.6 seconds was required to attain a value within 1 mm Hg of the plateau pressure. Guyton et al. (26) and Harlan et al. (18) give a value of 7–8 seconds before venomotor reflexes become apparent. Shoukas and Sagawa (24) reported a 10–15-second lag in the onset of a vascular volume shift after a change in isolated carotid sinus pressure; the lag in the arterial blood pressure response was 2–5 seconds.

**Comparison with Other Studies**

Using a small volume perturbation and measuring changes in P_ CV , Shoukas and Sagawa (29) reported a total systemic vascular compliance of 2.44 ml/mm Hg kg^-1 body weight 2 minutes after a change in volume. They assumed that the systemic vascular volume was about 70% of the total blood volume. Thus, an estimate of the total body circulatory compliance would be 3.49 ml/mm Hg kg^-1 (2.44/0.70). Converting our apparent stiffness values to compliance by taking the reciprocal of the slopes (Table 2) gives a closely similar value of 3.47 ml/mm Hg kg^-1 . Their value at 30 seconds was 2.96 ml/mm Hg kg^-1 (2.07/0.70), and ours at 30 seconds was 2.60 ml/mm Hg kg^-1 . In a more recent paper (24) steady-state control values for the systemic circulation were reported as 2.05 ml/mm Hg kg^-1 at 2 minutes and 1.52 ml/mm Hg kg^-1 0.5 minutes after a change in carotid sinus pressure, giving total circulatory values of 2.93 and 2.17 ml/mm Hg kg^-1 , respectively. Although they found no further increase in compliance between 2 and 3 minutes in either study, our values between 2 and 5 minutes increased significantly by about 20%.

Richardson et al. (30) have provided data suggesting a lower value for the compliance than ours. They failed to indicate the average blood volume of the dogs they used, but if 85 ml/kg is assumed, the reciprocal of their slope is 1.78 ml/mm Hg kg^-1 (14.7% of 85/7.0).

If one assumes from the data of Harlan et al. (18) that an extremely rapid 15-ml/kg hemorrhage brings P_M C from the normal value of 6.9 mm Hg re-
ported by Guyton et al. (25) to zero, then the total compliance of the vasculature is 2.17 ml/mm Hg kg⁻¹ (15/6.9), a value identical to that which we obtained at 0.5 minutes under the areflexic condition (2.17 ml/mm Hg kg⁻¹, Table 2). The data were claimed to represent the initial pressure-volume response (within a few seconds after the change in volume) of the intact circulation. Unfortunately, we were not able to attain such large volume changes and equilibrium within the 7 seconds available before the effects of reflexes are likely to occur. Guyton et al. (26) reported 4.9 mm Hg as the \( P_{MC} \) during total spinal anesthesia; we found 8.7 mm Hg with hexamethonium. They also found, during 1.5-\( \mu \)g/kg min⁻¹ epinephrine infusions, a mean systemic pressure of about 15 mm Hg, a value similar to the one we found when we infused norepinephrine at the same rate. Thus, the normal value of \( P_{MC} \) and the pressure-volume relationships reported by these investigators may have been obtained from dogs in which the reflexogenic venoconstrictor tone was greatly reduced by the anesthetic level used. On the other hand, our value may be abnormally high because of abnormally high sympathetic activity.

Gauer et al. (1, p 555) give a value of 5.7 ml/mm Hg kg⁻¹ for the compliance of the vascular bed of dogs, a value much larger than that which we found. A delay in measurement allowing extensive transcapillary fluid shifts and reflexogenic compensation may account for much of the discrepancy. On the other hand, a value of 0.7 ml/mm Hg kg⁻¹ may be calculated from the data of Ross et al. (31, Fig. 2), normalized by the average weight of the dogs they used. Lutz (32) has provided a useful literature review and a value of 2.06 ml/mm Hg kg⁻¹ for the mesenteric vascular compliance at low (0–15 cm H₂O) pressures.

Our data, showing decreased unstressed vascular volume on the order of 10 ml/kg with norepinephrine infusion, confirm studies using different techniques (31–34). Vascular relaxation of similar magnitude after ganglionic blockade was noted by Trapold (22) and Rose and Freis (21). Trapold (22) noted that when the pump output was reduced following blockade to parallel the reduction in venous return and prevent a shift of blood from the reservoir, venous return had decreased to 50% or less of the predrug level, a value close to the 55% of control cardiac output observed with no change in blood volume after ganglionic blockade in our experiments. These results suggest that under normal resting conditions a tonic discharge of sympathetic impulses exists which maintains a tonic level of venoconstrictor activity. Inhibition of sympathetic activity may thus result in an increased vascular capacity of up to 10 ml/kg body weight due to a reduction in venoconstrictor tone.

From the data presented in Figure 6, it is apparent that in the absence of compensation removal of only 20% of the blood volume (17 ml/kg) would cause the arterial blood pressure to fall to 40 mm Hg or less. However, in earlier studies (35) we found that 60 ± 8 ml/kg of blood must be removed from the intact dog to maintain an arterial blood pressure of 35 mm Hg for 1–2 hours. During oligemic hypotension (\( P_A = 35 \) mm Hg), Banet and Smith (36) observed a \( P_{MC} \) of 2.0 mm Hg after a maximum hemorrhage of 45% of the control blood volume. Our data (Fig. 2) suggest that continued compensation for a similar hemorrhage of 43.4 ml/kg (45% of our control blood volume) might well result in a \( P_{MC} \) of 2 mm Hg or even higher, depending primarily on the extent of viscoelastic creep and the inward shift of fluid. What fraction of this volume comes from continued venoconstriction, in comparison to that from viscoelastic creep and fluid shifts into the vasculature, has yet to be determined, but it is clear from our data that venoconstriction provides for but a minor fraction of the compensation to hemorrhage.

In addition to the reduction in apparent unstressed vascular capacity following norepinephrine infusion, we also found an increase in vascular stiffness, as have others at low (physiological) pressures (32, 34, 37). If higher, nonphysiological venous pressures are imposed by the measurement technique (e.g., venous occlusion), then a decrease in stiffness may be seen following catecholamine infusion or severe hemorrhage (31, 32, 37, 38). Because of the nonlinearity of the relationship above venous pressures of about 20 mm Hg, the determinations under these conditions do not provide a reliable measure of the situation at the normal operating point.

**EXTRAPOLATION**

Although the vascular pressure-volume relationship is linear over the physiological range, it is obvious from the data presented in Figures 5 and 6 that linear extrapolation of pressure and other cardiovascular variables as a function of extreme reduction in blood volume to confirm the study of Harlan et al. (18) is fraught with uncertainty. Thus, because of this uncertainty and the likely nonlinearity at a \( P_{MC} \) less than about 4 mm Hg, we
have chosen a value of 4 mm Hg to permit interpolation, rather than extrapolation, for comparisons following hemorrhage.

Extrapolation above the physiological range (about 15 mm Hg) is also uncertain, as suggested from the highly nonlinear curves reported by Alexander (37) and Lutz (32). The veins of the extremities may have different characteristics than those of the trunk.

Extrapolation to zero time after the volume change would permit a measure of the elastic recoil which is not time dependent, but this extrapolation is uncertain, since the time between the start of hemorrhage and the attainment of pressure equilibration throughout the vasculature is almost certainly longer than the time before vascular smooth muscle responses occur as a result of the sympathetic activity engendered by the hemorrhage. If the smooth muscle is paralyzed and viscoelastic creep can be characterized, then a nonlinear extrapolation may be feasible.

Our results thus suggest that sympathetic activity can alter the total vascular capacity of the body by about 13 ml/kg. These results suggest that sympathetic venoconstriction must occur to a far greater extent in tissues of the body other than skeletal muscle (3, 4), e.g., the splanchnic bed (10, 11). Even if the splanchnic bed can provide a relatively large fractional change in its volume by active venoconstriction, the degree of volume compensation for the benefit of the entire body is modest, as suggested by Gauer et al. (1, 2). However, the reflexogenic decrease in vascular capacity provides the circulation with a limited, but rapid, method for restoring the filling pressure for the heart following even a small loss of blood or fluid, pooling of blood in the extremities, or extravasation of fluid into the tissue.

Appendix

Statistical Analysis

The statistical analysis is not simple nor is the approach outlined in the literature. The procedure developed is powerful and so is explained in some detail here.

Each of the three groups—control, areflexic, and norepinephrine—was studied at three times (0.5, 2, and 5 minutes) after each of the six or seven volume changes. The primary hypotheses to be tested were as follows. (1) At a given change in blood volume, does reflexogenic venoconstriction or relaxation influence $P_{\text{MC}}$? (2) With a given volume change, what is the time course of changes in $P_{\text{MC}}$? (3) Is the pressure-volume relationship linear? Unfortunately, about 0–5% of the data were missing in each group. Program X64 from the BMD statistical package (39) entitled "General Linear Hypothesis" using orthogonal polynomials and tolerant of missing data was used. Appropriate polynomial coefficients representing the changes in volume were chosen. Since the changes in volume about zero were asymmetrical for some groups, appropriate transformations were made from the computed independent variable to scale to actual blood volume. It was essential to be able to assume that the volume changes were integer multiples of 8.5 ml/kg. Each component of the basic statistical model used is represented by a combination of dummy variables. In addition to the standard hypotheses for the analysis of variance (mean, animal, volume, and none [a five or six polynomial fit]), we included tests for a linear fit to volume, a deviation from linear fit, a linear plus quadratic fit, and a deviation from the linear plus quadratic fit.

Except for the 0.5-minute determinations in the control and areflexic groups, the deviation from the linear fit was not significant, i.e., the $F$ ratio of the deviation-from-linearity mean square to the error mean square was not significant. In these two groups, we found that the linear plus quadratic fit was satisfactory (Table 2, lines 10 and 11) but that deletion of the greatest hemorrhage data permitted the assumption of linearity; therefore, this procedure was followed to simplify the comparisons. As can be seen, the effect is small. The linear fits for all data (Table 2, lines 12 and 13) were not as good and were included only for comparison.

From regression coefficients supplied by the X64 print-out, we computed the slope and the zero-volume change intercept (Table 2). In our tests for differences, we explored the possibility of pooling all of the error mean squares but found inhomogeneity of variance between groups; those within groups were satisfactorily homogeneous. Thus, at the three times for each group, the error sums of squares were summed and divided by the sum of their degrees of freedom to give $MS_{\text{ERROR (pooled)}}$.

\[ F_b = \frac{MS_{\text{VOLLIN}}}{MS_{\text{ERROR (pooled)}}} = t_b^2 = \frac{b_i^2}{s_b^2}, \]  

(1)

where $MS_{\text{VOLLIN}}$ is the mean square for the linear fit of $P_{\text{MC}}$ to volume, we obtained the standard error of the slope, $s_b$, for each time by manipulating Eq. 1. Thus,

\[ s_{bij} = \sqrt{\frac{MS_{\text{ERROR (pooled)}} b_{ij}^2}{MS_{\text{VOLLIN}}}}, \]  

(2)

where $i$ is the time and $j$ is the group. For comparison of slopes, $t$ values were calculated:

\[ t = \frac{b_i - b_j}{\sqrt{s_b^2 + s_a^2}}. \]  

(3)

When comparing between the three groups, a Satterthwaite approximate degrees of freedom (40) was calculated; otherwise, the degrees of freedom for the pooled error mean square were used (153, 85, and 131, respectively).

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Assuming a linear relationship, the predicted $P_{MC}$ at a given change in volume ($\Delta V$) was calculated as:

$$P_{MC} = P_{MC(AV)} + b(\Delta V). \tag{4}$$

The standard error of the estimated pressure for each group, time, and volume change was calculated as:

$$s_{PMC(AV)} = \sqrt{s_{PMC}^2 + s_{\Delta V}^2 (\Delta V - \bar{\Delta V})^2}, \tag{5}$$

where $\bar{\Delta V}$ is the mean of the volumes used, $s_{PMC}^2 = (MSE_{B-Pooled})/n$, and $n$ = number of observations in this set (Table 2, column 4). Eq. 3 was used with appropriate changes in symbols for the calculation of $t$ values.

Finally, to provide estimates to show the confidence intervals (C.I.) of Figures 2 and 3, the deviation expected by chance (5%) was calculated as:

$$C.I. = t \cdot s_{PMC(AV)}, \tag{6}$$

where $t$ is the $t$ value at 0.05 probability and the pooled degrees of freedom, $s_{PMC(AV)}$, is the standard error from Eq. 5 at each volume. So that significant differences would be apparent by lack of overlap of the bands, the predicted value $\pm C.I.$ was plotted rather than the more conventional confidence interval. The standard errors were similar (Table 2).

As a check of the computation of the linear regression equation, a simple linear regression was computed for each group and time. Differences in slope and intercept of up to 2.4% were attributed to the handling of missing data by X64. Using the more complex approach, the errors were similar (Table 2).

As a check of the computation of the linear regression equation, a simple linear regression was computed for each group and time. Differences in slope and intercept of up to 2.4% were attributed to the handling of missing data by X64. Using the more complex approach, the standard errors for the slopes and the means were reduced by about one third, and the degrees of freedom were nearly tripled.

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