Autoregulation of Cardiac Output by Passive Elastic Characteristics of the Vascular Capacitance System

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After a change in cardiac output, the magnitude of potential blood volume redistribution was investigated in 10 dogs anesthetized with chloralose. All of the venous return was pumped into a reservoir, using servocontrolled pumps to maintain fixed superior and inferior vena cava pressures. The cardiac output was set at various levels by pumping from the reservoir into the right atrium. Changes in reservoir volume were assumed to reflect the changes in vascular blood volume. After measuring the control responses, cardiovascular reflexes were blocked with hexamethonium. Reducing the cardiac output, for example, from 110 to 80 ml/(min·kg) with reflexes intact, caused a 9.2-ml/kg transfer of blood from the dog to the reservoir. With reflexes blocked, the same change in cardiac output caused 6.8 ml/kg of the blood to be transferred. Under the control conditions, throughout the range of 50–140 ml/(min·kg), an increase or decrease of cardiac output of 1 ml/(min·kg) elicited a 0.304±0.086 (mean±SD) ml/kg change in dog blood volume; with reflexes blocked, the flow sensitivity was 0.239±0.062 ml/kg. Thus, only 21% of the total blood volume redistribution was attributable to active reflex responses. Deterioration of the preparation may have attenuated the magnitude of active reflex activity. Neither the systemic vascular compliance of 1.80±0.35 ml/mm Hg·kg nor the fraction of venous return from the superior vena cava of 26.5±4.6% was significantly changed by reflex blockade.

Passive blood volume redistribution between the peripheral vasculature and the heart after changes in blood flow, such as from changes in cardiac function, provides a more powerful compensatory mechanism to maintain the cardiac output than do active reflex changes in vascular capacitance. (Circulation 1990;81:360–368)

Passive elastic characteristics of the veins, in conjunction with finite venous resistances, provide a powerful, nonreflex mechanism for the control of cardiac output. This mechanism is of great importance for cardiovascular homeostasis, but its magnitude has not been well documented. If the heart weakens so that cardiac output and peripheral blood flow decrease, then there will be a transient decrease in the distending pressure in the systemic veins because of the decreased flow through the peripheral tissue and the decreased pressure gradient across the venous resistances. Passive recoil of the veins then acts to transfer blood to the heart to increase the central venous pressure and cardiac filling, thus restoring cardiac output—an autoregulation of cardiac output that is independent of cardiovascular reflexes. The effect is equivalent to a blood transfusion after a decrease in cardiac function.

The concept of a volume redistribution as a consequence of regional flow changes was described a century ago. Furthermore, Krogh proposed that an increased splanchnic vascular resistance that reduces splanchic blood flow, could lead to an increase in cardiac output because of the transfer of blood from the splanchnic bed to increase filling of the heart. Stene et al. and Stokland and colleagues have further studied the effect of a thoracic aortic occlusion on cardiac output. Rowell has considered splanchic vasoconstriction to be more important than active vasoconstriction as a compensatory mechanism during standing, exercise, or thermal stress.

The concept of interaction between venous return and cardiac output has been thoroughly developed by Guyton et al. Given a cardiac performance curve and a venous return curve, the equilibrium right atrial pressure can be predicted from the analysis of Guyton et al. The analysis, however, does not provide

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an estimation of the magnitude of blood volume increase or decrease that would be required to maintain a constant right atrial pressure after the change in cardiac function. The magnitude of potential blood volume redistribution, after a cardiac output change with cardiovascular reflexes blocked, has been quantified only by Numao and Iriuchijima, Caldini et al., Numao and Iriuchijima, Green and colleagues, and Ogilvie have measured it with reflexes intact throughout a limited range of flows and have reported widely different values. Numao and Iriuchijima reported that a 50% reduction in cardiac output resulted in a 19.7-ml/kg transfer of blood to a venous return reservoir held at a constant venous outflow pressure. After autonomic reflex blockade, a 50% change in cardiac output resulted in a 10.3-ml/kg change in reservoir volume. They concluded that “on a change in cardiac output, the passive change in blood volume is as large as the active or reflexic change.” Even with reflexes blocked, a 50% change in cardiac output led to a blood volume redistribution that is equivalent to the maximum volume redistribution that can be elicited by the carotid baroreceptors, the aortic baroreceptors, or by cerebral ischemia. While we were exploring the possibility of a right atrial volume-receptor mechanism that could control vascular capacitance, using a constant cardiac output, constant central venous pressure, and venous return reservoir technique, we found that small changes in cardiac output induced remarkably large changes in reservoir volume. The primary purpose of our study was thus to further quantify, with and without reflexes, the potential blood volume redistribution in response to cardiac output changes at a fixed central venous pressure.

The magnitude of blood volume redistribution (ΔV), after a change in cardiac output (ΔQ) has been expressed as the ratio of a change in reservoir blood volume to a change in cardiac output at a constant right atrial pressure (ΔV/ΔQ)_{ra} and has been used for subsequent computation of venous resistances and compliances. In the study by Numao and Iriuchijima, a 10.3-ml/kg decrease in dog blood volume, resulting from a 40 ml/(min·kg) decrease in perfusion, resulted in a volume change to flow change ratio (ΔV/ΔF) of 0.26 ml per ml/min in areflexic dogs. The blood volume dependence on flow has been reported to be a linear relation between perfusion rates of 50% and 150% of control flow, but Green reported that the volume-flow relation was reduced at low perfusion rates. A secondary purpose of our study was to evaluate the linearity of the relation throughout a wide range of flows, including zero. We also tested the hypothesis that the magnitude of systemic arterial pressure response to bilateral carotid arterial occlusion (BLCO) is correlated with the magnitude of ΔV/ΔF, and so it may provide a simple index of the reflex responsiveness of the animal.

**Methods**

Random source, hound-breed dogs (held a month by the supplier and free of heartworm and internal and external parasites) weighed 19.6±1.8 (mean±SD) kg and were transiently anesthetized with methohexital sodium 10 mg/kg i.v. and subsequently anesthetized with 80 mg/kg alpha-chloralose (8%, in polyethylene glycol-200). Additional chloralose [13.4±4.4 mg/(kg·hr)] was given to maintain anesthesia. Our study conformed to the guiding principles of the American Physiological Society. Body temperature (rectal) was maintained at 38.8±0.6°C. The dogs were ventilated with a piston-type respirator (model 613, Harvard, South Natick, Massachusetts) set to 20 ml/kg tidal volume, about 15 breaths/min (inspiratory to expiratory duration ratio of 1:3), and an expiratory pressure of 5 cm H₂O. The right chest was opened between the third and fourth and also the sixth and seventh ribs. The inferior vena cava was isolated to permit placement of a snare below the heart. The superior vena cava and ayguses vein were isolated, and the pericardium was opened. The common carotid arteries were isolated for transient occlusion with snare to evaluate the level of general cardiovascular reflex sensitivity. A percutaneous catheter (Angiocath, 22-gauge, 1-in., Deseret Pharmaceutical, Sandy, Utah) was inserted into the left carotid artery to monitor carotid arterial pressure downstream from the occlusion.

Heparin (500 U/kg) was used to prevent blood coagulation. Maintenance dosages averaged 130 U/kg/hr. The femoral veins were cannulated with 2.7-mm i.d. cannulas, which extended into the inferior vena cava and were connected to the venous reservoir by a roller pump. The right femoral artery was ligated, and the left femoral artery was cannulated for monitoring systemic arterial blood pressure.

The extracorporeal circulation system, including three pumps and a reservoir (Figure 1), was soaked overnight in sterile saline, flushed with air, and then filled (420 ml) with dextran (Dextran-70, Abbott Pharmaceuticals, North Chicago, Illinois; or Macrodex, Pharmacia, Uppsala, Sweden) and sodium chloride solution to give an approximately iso-oncotic priming solution (50% of 6% dextran and 50% of 0.9% NaCl). The extracorporeal circulation system included a 20-μm blood filter (product SAF-20, Shiley) and a heat exchanger (pediatric miniprime 5MO337, Travenol Laboratories, Morton Grove, Illinois). The cannula leading from the reservoir and perfusion pump (model 3500, Sarns-Travenol) was placed into the right auricle. Transient increases in splanchic bed venous pressure that might be damaging during inferior vena cava cannulation were prevented by pumping blood from the femoral veins. The inferior vena cava pump and the main perfusion pump were started at about 1,000 ml/min to mix the dextran-saline solution with the dog’s blood. The superior vena cava was cannulated and temporarily drained by gravity to the reservoir. The main perfusion rate was adjusted to keep the reservoir volume constant. The superior vena cava was then connected to the superior vena cava servopump that pumped into the reservoir. The inferior vena cava pump was
then servocontrolled to maintain the inferior vena cava pressure at 3 mm Hg, and the inferior vena cava snare was tightened. The azygos vein was then occluded. All three pump speeds were monitored with tachometer generators and were calibrated before each experiment to relate flow to tachometer output. Reservoir volume was measured in terms of pressure generated at the bottom, using a Statham P23BB pressure transducer (Gould, Cleveland, Ohio), and was calibrated with known volumes of saline.

Pressures were measured with strain-gauge transducers (Statham/Gould P23Db or P23De) held at a constant temperature in an aluminum block heated with water to 33.0±0.2°C. The sidearms of the transducer stopcocks were connected to a common water-filled chamber for setting zero and calibration. The superior vena cava and inferior vena cava pressure catheters were 1.6 mm i.d., closed at the end with a 2-mm plug of epoxy, with two 1-mm holes in the sides, 2 mm from the end, and were coaxial with and extended 1 cm or more beyond the cannula tips. Catheters were continuously flushed with 0.9% NaCl at 0.05 mg/min (model TA4004, Gould Critiflo).

Pressure, reservoir volume, and main perfusion pump flow data were averaged with analog, low-pass, 4-pole Bessel filters (model 730LT-1, Analog Devices, Norwood, Massachusetts) set to a characteristic frequency of 0.18 Hz and then A/D converted at 10 samples/min (series 500 with SOFT500 assembly language algorithms, Keithley DAS).

Protocol

The reservoir pump output was set to provide a control perfusion rate of 110 ml/(min·kg). After the animal was stabilized, the perfusion was changed to 80, 140, 50, and 20 ml/(min·kg), with return to control flow after each change (Table 1, segments 3–6, 9, 10, and 12). Perturbations were applied for 3 minutes, except for segment 12 [20 ml/(min·kg)]. BLCO (protocol segments 1, 2, 11, and 14) were used to evaluate the cardiovascular reflex sensitivity of the animal. We assumed that the magnitude of the reflex component of vascular volume change in response to a change in perfusion paralleled the magnitude of the reflex-induced change in systemic arterial pressure (Psa) during BLCO. Thus, as the Psa response to BLCO was reduced by dog deterioration or reflex blockage, we expected a proportional reduction in the magnitude of the reflex component of AV/ΔF. Additional dextran in saline was added to the reservoir [0.09±0.03 ml/(kg·min)] when the volume in the reservoir approached zero because of uncontrolled hemorrhage or interstitial volume expansion.

Cardiovascular reflexes were then blocked with 10 mg/kg hexamethonium (protocol segment 13) and the perfusion changed to 80, 50, or 20 ml/(min·kg), with return to control after each change (segments 15–21).

For the vascular compliance measurements, central venous pressure (Pcv) was increased 3.0 mm Hg from an average control value of 3.1 mm Hg by changing the pressure set-point of both servo pumps for 3 minutes and then returning Pcv to control (segments 7, 8, 17, and 18). Vascular compliance was computed as the ratio of blood volume change to venous pressure change.

Data Analysis

The changes in reservoir volume, assumed to represent the change in dog blood volume induced by a
perfusion rate change, were evaluated at 0.3, 1, 2, and 3 minutes. The 10 values during the second minute, as well as the third minute, were also averaged to give the second- and third-minute average values.

Means and standard deviations (SD) are given to describe the data. For statistical analysis, multiple regression or a priori paired t tests were used. A probability of 0.05 or less was considered significant.

**Results**

The control perfusion rate was set at 110 ml/ (min-kg). A step change in total body perfusion from control to 80 ml/(min-kg) for 3 minutes, while holding inferior and superior venous pressures (Pivc and Psvc) constant at 3.1 mm Hg, caused a rapid increase in reservoir volume. The dog vascular volume decreased 9.2±3.7 ml/kg by 3 minutes (Figure 2). The response to the return to control perfusion rate [110 ml/(min-kg)] was similar in magnitude, as was the response to an increase in perfusion by 30 ml/(min-kg) (Table 1). When the cardiac output was reduced to 45% of control [50 ml/(min-kg)], with reflexes present (segments 9 and 10 at 3 minutes, Table 1), the dog volume decreased 18.2 ml/kg, but with reflexes blocked (segments 19 and 20), an average of 15 ml/kg blood left the dog. The decrease in mean systemic arterial pressure averaged 36±12 with reflexes intact and 43±10 mm Hg during blockade (Figure 3). Thus, the cardiovascular reflex action associated with the reduced cardiac output and Psa mobilized an additional 3.2 ml/kg blood from the dog. With large changes in flow, more volume left the dogs on reducing flow than was returned by 3 minutes on restoring the cardiac output to 110 ml/(min-kg) (segments 9, 10, 19, and 20, Table 1).

The flow sensitivity (change in dog blood volume per unit change in flow, ΔV/ΔF), obtained by changing the rate of perfusion into the right heart [from control to 50–140 ml/(min-kg) and back to control] averaged 0.304±0.086 ml per min at 3 minutes with reflexes intact (Figure 4). After ganglionic blockade with hexamethonium, the flow sensitivity was significantly reduced to 0.239±0.062 ml per min. Overall, the passive component was 79% of the total, leaving 21% as the active component.

When the perfusion rate was changed from 110 to 20 ml/(min-kg), 25.9±2.5 ml/kg blood entered the reservoir within 2 minutes after the start of flow

### Table 1. Response to Change in Rate of Total Body Perfusion

<table>
<thead>
<tr>
<th>Segment</th>
<th>Perfusion flow [ml/(min·kg)]</th>
<th>n</th>
<th>0.3 min</th>
<th>1.0 min</th>
<th>2.0 min</th>
<th>3.0 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>110–80</td>
<td>10</td>
<td>−4.5±1.0</td>
<td>−7.4±2.3</td>
<td>−8.8±3.1</td>
<td>−9.2±3.7</td>
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<tr>
<td>4</td>
<td>80–110</td>
<td>9</td>
<td>4.0±0.8</td>
<td>6.5±1.1</td>
<td>8.6±1.6</td>
<td>9.8±2.1*</td>
</tr>
<tr>
<td>5</td>
<td>110–140</td>
<td>10</td>
<td>5.4±1.7</td>
<td>8.0±2.2</td>
<td>9.2±2.5</td>
<td>10.3±3.0*</td>
</tr>
<tr>
<td>6</td>
<td>140–110</td>
<td>10</td>
<td>−4.4±1.0</td>
<td>−7.1±2.3</td>
<td>−7.6±2.8</td>
<td>−8.0±3.1*</td>
</tr>
<tr>
<td>9</td>
<td>110–50</td>
<td>8</td>
<td>−7.4±3.3</td>
<td>−14.4±1.4</td>
<td>−18.0±2.2</td>
<td>−20.0±3.4*</td>
</tr>
<tr>
<td>10</td>
<td>50–110</td>
<td>8</td>
<td>7.9±1.7</td>
<td>12.7±1.7</td>
<td>16.1±2.8</td>
<td>16.4±2.4</td>
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<tr>
<td>12</td>
<td>110–20</td>
<td>5</td>
<td>−13.2±1.9</td>
<td>−22.0±1.6</td>
<td>−25.9±2.5</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>Hexamethonium (10 mg/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>110–80</td>
<td>10</td>
<td>−4.0±0.7</td>
<td>−5.4±1.1</td>
<td>−6.0±1.5</td>
<td>−6.8±1.6*</td>
</tr>
<tr>
<td>16</td>
<td>80–110</td>
<td>10</td>
<td>3.7±1.0</td>
<td>5.3±0.8</td>
<td>6.2±1.8</td>
<td>7.1±2.4*</td>
</tr>
<tr>
<td>19</td>
<td>110–50</td>
<td>8</td>
<td>−8.6±0.9</td>
<td>−13.6±2.1</td>
<td>−15.6±2.7</td>
<td>−17.9±2.7*</td>
</tr>
<tr>
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<td>7.8±1.6</td>
<td>9.9±1.2</td>
<td>10.8±1.7</td>
<td>12.0±2.0*</td>
</tr>
<tr>
<td>21</td>
<td>110–20</td>
<td>5</td>
<td>−12.7±0.8</td>
<td>−21.2±1.9</td>
<td>−24.0±2.5</td>
<td>−25.6±3.4</td>
</tr>
</tbody>
</table>

Values are mean±SD for measurements at 0.1-minute intervals at the times indicated. Segment is the protocol segment as defined in the "Methods." All dog blood volume changes were significantly different from zero by 0.3 minutes. *Volume change at 3.0 minutes significantly (p<0.05) greater than at 2.0 minutes.

![Figure 2. Plot of change in dog blood volume (ml/kg body wt) as a function of time in response to changes in perfusion rate from the control of 110 ml/(min·kg). Central venous pressure (inferior and superior venae cavae) held at 3.1 mm Hg throughout. Protocol segment numbers and changed flows given with each curve. O, values before hexamethonium reflex blockade; □, values after (n=8 dogs).x, Second-minute average values of data obtained between 1.1 and 2.0 minutes (n=10). Index of variability are standard deviations.](http://circ.ahajournals.org/content/363/11/e65.full.html)
Figure 3. Plot of systemic arterial pressure response to changes in perfusion rate before (○) and after (□) reflex blockade with hexamethonium (10 mg/kg).

reduction (segment 12, Table 1), and the ΔV/ΔF was 0.28±0.03 ml per ml/min. After reflex blockade, the ΔV/ΔF was 0.26±0.02 ml per ml/min, which is an insignificant difference.

The total circulatory stressed volume of these dogs was estimated, at the end of the experiment during ganglionic blockade, by stopping the main perfusion pump and both vena cava pumps. The Pvc and Psvc increased to a stop-flow-vascular pressure of 12.7±4.7 mm Hg and to 13.3±5.0 mm Hg at 6 and 12 seconds, respectively. Both vena cava pumps were then restarted (but not the main perfusion pump) to return the Pvc and Psvc to 3.1 mm Hg. The subsequent increase in reservoir volume was assumed to be the stressed volume between the distending pressure at control flows (estimated by the stop-flow-vascular pressure) and that at 3.1 mm Hg. It averaged 29.1±6.4 ml/kg, and the ΔV/ΔF averaged 0.26±0.06 ml per ml/min. The value fell along the linear volume-flow line with reflexes blocked (Figure 4). Assuming a compliance of 1.8 ml/(mm Hg·kg) (as found at control flows and pressures), the remaining stressed volume was 5.6 ml/kg (1.8×3.1), giving a total stressed volume of 34 ml/kg. We attributed the high stop-flow-vascular pressure, compared with an expected mean circulatory filling pressure of 7–10 mm Hg, to a transient continuation of cardiac pumping from the cardiopulmonary bed, even when right heart inflow was zero, and to an increased blood volume associated with the control cardiac output forced to 110 ml/(min·kg).

During the experiments, a plateau in response to flow change seemed to be apparent by about 2 minutes, and therefore, the flow was returned to control after 3 minutes. However, after plotting the average data (Figure 2), it became obvious that the response was usually not complete by 2 minutes (see also Table 1).

The systemic vascular compliance during the control periods averaged 1.83±0.40 ml/(mm Hg·kg), and after blockade, it averaged 1.78±0.34 ml/(mm Hg·kg).

When we blocked the autonomic ganglia by infusing hexamethonium chloride (10 mg/kg), the mean Psa decreased from 116±11 to 60±9 mm Hg within 1–2 minutes, and total peripheral resistance (TPR) decreased from 1.08±0.13 to 0.75±0.11 mm Hg·min/kg/ml. The Psa before ganglionic blockade was reflexively regulated by changes in TPR (Figure 3) as expected. During the first 2 minutes of blockade, as Psa decreased, the total dog and reservoir blood volumes did not change (0.6±1.3 ml/kg) as blood was transferred from the arterial to the venous bed. The dog blood volume then significantly increased to 5.6±3.2 ml/kg by 4 minutes when the Psa had increased to 76±14 mm Hg. The systemic arterial pressure changed in a linear manner with changes in perfusion rate during reflex blockade (Figure 3) and could be extrapolated to a zero-flow pressure of about 12 mm Hg.

**Bilateral Carotid Arterial Occlusion**

The responses to 3-minute periods of BLCO were measured during control flows to assess the degree of cardiovascular reflex depression induced by anesthesia, surgery, and the periods of low total body perfusion. In the last four dogs of the study, before opening the chest and with cardiac output uncontrolled, the mean Psa increased 42±12 mm Hg in response to BLCO (protocol segment 1). During the first BLCO with perfusion held at 110 ml/(min·kg) (segment 2), the Psa response in nine dogs was 32±7 mm Hg, and just before ganglionic blockade (segment 11), the response had decreased to an average of 16±7 mm Hg. During these periods, control Psa averaged 153±12, 124±15, and 119±17 mm Hg, respectively. After ganglionic blockade (10 mg/kg hexamethonium), Psa decreased to 73±11 mm Hg, but the response in Psa to BLCO (segment 14) remained significantly greater than zero (9.7±5.1 mm Hg, p<0.01). We attribute these small Psa responses to BLCO, with a fixed cardiac output and reflex blockade, to the increased vascular resistance from occluding the carotid arteries.
During BLCO, the downstream carotid artery pressure (Pca) decreased markedly and then increased in parallel with the increase in Psa as expected.20 Within 3 minutes of BLCO with reflexes intact, Pca increased and averaged 67.8±2.0, 68.0±8.1, and 66.7±9.4% of the Psa during occlusion for segments 1, 2, and 11, respectively. After blockade, the equilibrium downstream Pca, during BLCO, was 50±18% of the Psa. The BLCO induced no significant change in reservoir volume (−0.17±0.92 ml/kg in segment 2, and 0.08±0.65 in segment 11), in part because the blood volume that was needed to distend the arterial bed, as Psa increased, was apparently supplied almost completely by a baroreceptor-induced venoconstriction. After reflex blockade, the reservoir volume decreased 1.03±1.19 ml/kg (p=0.05) (segment 14) during BLCO.

The magnitude of the sensitivity of vascular volume change to changes in perfusion flow rate (ΔV/ΔF) was significantly correlated to the magnitude of changes in mean Psa during the bilateral carotid occlusion just before or after the cardiac output change. We therefore computed a reflex sensitivity equation to quantify the relation and to evaluate the general reflex status of the preparation. The equation obtained by a least-squares fit of available data, without and with hexamethonium treatment (segments 2–4, 9–11, and 14–16) obtained 3 minutes after the flow change was (ΔV/ΔF)=0.227+0.0027ΔPsa (n=45, root mean square error=0.080 ml per ml/min, r=0.360, p=0.014). The equation predicts that the flow sensitivity (ΔV/ΔF) would be 0.349 ml per min if the response in Psa to BLCO were 45 mm Hg. It also predicts that with reflexes blocked (as assessed by only a 9-mm Hg Psa response to BLCO), the flow sensitivity would be 0.251 ml per ml/min flow change, which is a value similar to that which we obtained. The equation does not imply cause and effect, but it relates the magnitude of the reflex component of flow sensitivity to the reflex response to BLCO.

Flow Distribution
The superior vena cava supplied 26.5±4.6% (n=51) of the total venous return under control conditions. This fraction was not significantly changed with cardiac outputs set at 50 (28.8±5.1%), 80 (27.7±4.7%), or 140 (28.4±5.9%) ml/(min·kg), or during BLCO. Ganglionic blockade with hexamethonium also did not alter the flow distribution (27.1±2.0%), but the variability was about half that without ganglionic blockade.

Discussion
The ratio of change in volume resulting from a change in flow includes units of time. Because the focus of our study is the vascular blood volume change in response to flow perturbation, we prefer to use units of milliliters per milliliter divided by minutes for ΔV/ΔF rather than the simpler time unit.

The passive flow sensitivity of peripheral blood volume (ΔV/ΔF) of 0.24±0.06 ml volume change per ml/min flow change, which we observed after reflex blockade with hexamethonium, was closely similar to the 0.26 ml per ml/min calculated from the data of Numao and Iriuchijima.9 From data shown in their Table 1, a ΔV/ΔF of 0.49 ml per ml/min for reflexes intact can be estimated, which is also consistent with the data shown in their Figure 5. The reflex-intact flow sensitivity of 0.30±0.09 ml per ml/min that we found was 61% of that found by Numao and Iriuchijima.9 By extrapolation, if the cardiac output had been decreased from 80 to 0 ml/(min·kg), the reflex intact estimate of 0.49 ml per ml/kg predicts a total (active and passive) blood volume change of 39.2 ml/kg (80×0.49). By using the areflexic value (0.26 ml per ml/min), a passive volume change of 20.6 ml/kg (80×0.26) is predicted. The difference of 18.8 ml/kg is attributable to reflex activity and is higher than any reflex component reported by others.1,14–17

The flow sensitivity with reflexes intact may be less at flow less than 40 ml/(min·kg). Indeed, in our study, by changingflow to 20 ml/(min·kg), we obtained similar values, with or without reflexes. We do not have estimates of the ΔV/ΔF with reflexes intact below flows of 20 ml/(min·kg) because 2 minutes of almost zero cardiac output would have seriously traumatized the dogs. Furthermore, the primary purpose of the study was to quantify the basic, passive response of the system.

Before major surgery and total-body perfusion, BLCO caused the mean Psa to increase 42±12 mm Hg, which is a response similar to that reported for conscious dogs.21,22 However, the extensive surgery required to collect all of the venous return and to provide a constant perfusion likely caused the attenuation of the carotid reflex that we report as well as attenuation of the reflex component of the capacitance system. The relation between the flow sensitivity (ΔV/ΔF) and the increase in systemic arterial pressure (APsa) during BLCO (equation above) suggests that if the cardiovascular reflexes were more normal, so that the Psa response to BLCO was 45 mm Hg, the flow sensitivity would have been about 0.35 ml/kg per ml/(min·kg). On changingflow from 110 to 50 ml/(min·kg), the predicted total response would be 21 ml/kg rather than the 18.2 ml/kg that we report and thus a 6 ml/kg reflex component (21.0–15.0). Because reflex blockade caused a 5.6 ml/kg increase in dog blood volume, there must have been a significant venous tone under the control conditions. The total response to 11.6 ml/kg (6±5.6) for reflex changes in vascular capacitance is similar to that reported by Shoukas and colleagues14–16,23 from the baroreceptor reflex. Nonetheless reflex activity would appear to account for less than half of the total potential blood volume redistribution in response to peripheral blood flow changes.

Some of the responses may be a result of transcapillary fluid shifts. We used a parameter-fitting routine24 to fit a monoexponential plus ramp equation to the data in four to six experiments in which the flow was changed within less than 2 seconds. The ramp coef-
ponents averaged about 1.2 ml/(min-kg) and were in the same direction as the dog blood volume change. Although significant, the magnitude is relatively small. Transcapillary fluid shifts could explain the larger volume change on reducing flow (segments 9 and 19) compared with restoring flow to control (segments 10 and 20). Additional explanations for a continuing slow change include a second, slower exponential response\textsuperscript{10} or stress relaxation.

The magnitude of $\Delta V/\Delta F$ with reflexes intact has not been well defined. Other investigators have reduced cardiac output while holding $Pcv$ constant, measured the blood volume change in a venous return reservoir by 3–5 minutes, and then estimated $(\Delta V/\Delta Q)_{Pcv}$. Under control conditions, with reflexes intact and the right heart bypassed, the flow sensitivity has been reported, or could be computed as $0.23^{10}, 0.31^{13}, 0.44^{12}$ and $0.49^{9}$ ml per min. Green\textsuperscript{11} forced the cardiac output to equal the venous return at a fixed central venous pressure and changed cardiac output by changing the blood volume. To reduce to zero, on the average, the initial 49-ml/(min-kg) cardiac output of the 20.2-kg dogs anesthetized with pentobarbital, the derived quadratic equation predicted that 14.3 ml/kg would have to be removed, which is a volume-flow relation of 0.29 ml per ml/min. At a flow of 100 ml/(min-kg), Green's equation predicted a $\Delta V/\Delta F$ of 0.57 ml per ml/min for the dogs anesthetized with pentobarbital and 0.44 ml per ml/min for dogs anesthetized with methoxyflurane and nitrous oxide. The variability was large in that the quadratic coefficient of the equations varied by a factor of 1:48.

The vascular volume responses to changes in cardiac output tended to be linear with reflexes either intact or blocked (Figure 4). A quadratic equation of the blood volume versus flow change data [20–140 ml/(min-kg)] for each experiment was not significantly better ($p=0.07$–0.89) than a linear fit. Our data thus confirm the report of Numao and Iriuchijima\textsuperscript{9} and Green et al\textsuperscript{12} but not that of Green.\textsuperscript{11}

We conclude that the $\Delta V/\Delta F$ relation, with or without reflexes, is generally linear (Figure 4), in contrast with the nonlinear resistance characteristics with reflexes intact (Figure 3).

Vascular compliance was not changed by blockade nor was the relative flow distribution between the inferior and superior venae cavae. Thus, we hypothesize that capacitance vessel smooth muscle was stimulated to contract and expel added blood by changes in unstressed volume with but little change in compliance\textsuperscript{14,15} or venous resistance, and thus would account for the larger $\Delta V/\Delta F$ seen with reflexes intact, compared with that in areflexic animals. To test this hypothesis would require a radically different experimental approach than used in our present study.

*Components of the Total Body Flow Sensitivity*

A $\Delta V/\Delta F$ of 0.25 ml per ml/min per kg body wt during reflex blockade (our study and that of Numao and Iriuchijima\textsuperscript{9}) is about three times the 0.061 ml per ml/min reported for the intestinal bed,\textsuperscript{25} the 0.07 ml per ml/min computed for the hindlimb,\textsuperscript{26} and the 0.066–0.075 ml per ml for the highly compliant liver.\textsuperscript{19,27,28} Brooksby and Donald\textsuperscript{29} found the vascular volume sensitivity to flow changes for the isolated splanchic bed of dogs to be 0.19±0.10 ml/kg body wt per 1 ml/(min-kg), which is a value somewhat lower than the $\Delta V/\Delta F$ of 0.24±0.06 ml per ml/min for the whole body computed from the data of our study. At a mean venous pressure of 7 mm Hg and under control conditions, Mitzner and Goldberg\textsuperscript{30} reported time constants for the tissues drained by the superior vena cava of about 5 seconds, for the splanchic bed of about 7 seconds, and for nonsplanchnic tissues drained by the caudal inferior vena cava of about 6 seconds. Mitzner and Goldberg\textsuperscript{30} did not consider the time constants to be an index of regional blood volume change as a function of flow, but by converting the time constants to minutes, the values may be considered\textsuperscript{10,31} to correspond to flow sensitivities of 0.08, 0.12, and 0.10 ml per ml/min, respectively. The time constants were dependent upon mean venous pressure and were increased by epinephrine infusions. None of the flow sensitivities of these parallel circuits were of the magnitude of $\Delta V/\Delta F$ that we or Numao and Iriuchijima\textsuperscript{9} found for the total body.

The higher $\Delta V/\Delta F$ for the total body compared with individual organs may be from other series elements such as the arterial bed or the heart and lungs. Numao and Iriuchijima\textsuperscript{9} suggested that 33% of the volume shift [3.4 ml/kg of the 10.3 ml/kg from a 40 ml/(min-kg) flow change] came from the arterial bed with reflexes blocked. However, in our study, the $Psa$ decreased about 0.6 mm Hg per ml/(min-kg) change in perfusion (Figure 3). Assuming an arterial bed compliance\textsuperscript{32} of 0.04 ml/(mm Hg-kg), only 0.024 ml per ml/min (0.6×0.04) or 10% of the $\Delta V/\Delta F$ was contributed by the arterial bed. A significant part of the blood may have come from the cardiopulmonary bed as total body perfusion was changed. Mitzner et al\textsuperscript{33} provided data from one dog that suggested an appreciable increase in cardiopulmonary volume as the perfusion rate to the right atrium was increased. Furthermore, from the data of Muller-Ruchholz et al,\textsuperscript{34} the total body $\Delta V/\Delta F$ may be calculated to be about 0.1 ml per ml/min, when the entire cardiopulmonary bed is bypassed. However, Numao and Iriuchijima\textsuperscript{9} reported a $\Delta V/\Delta F$ of the right heart and lung bed of only 0.05-ml per ml/min change in flow [2.2 ml/kg for a 40-ml/(min-kg) flow change], and Pouleur et al\textsuperscript{35} reported less than a 1-ml/kg change in central blood volume during the first 10 seconds of a sudden change in right heart perfusion rate. The flow sensitivity of the total cardiopulmonary bed, including the left heart, may thus be as high as 0.1 ml per ml/min. The discrepancy between a $\Delta V/\Delta F$ for the areflexic total body of 0.24 ml per ml/min and that of about 0.1 ml per ml/min for the specific organs studied is large and is yet unresolved. To the extent that blood is transferred from the cardiopulmonary bed during the determination of $(\Delta V/\Delta Q)_{Psa}$,
the assumption of Caldini et al\textsuperscript{10} that all of the
volume change is from the systemic vasculature will be in
error, as will estimates of vascular parameters
using their approach. Because of the relatively large
blood volume of the splanchic bed, the reflex respons-
siveness of its capacitance system in the dog,\textsuperscript{14,36} and
its unusual vascular characteristics,\textsuperscript{10,37} the vascular
volume of the splanchic bed may be particularly
sensitive to changes in blood flow. The liver is not.\textsuperscript{19}

Venocostriction During Bilateral Carotid
Arterial Occlusion

In conscious dogs, BLCO results in a 40–
50-mm Hg increase in mean systemic arterial
pressure.\textsuperscript{21,22} Corcondillas et al\textsuperscript{22} found no significant
change in right atrial pressure, cardiac output, or
cardiopulmonary blood volume during bilateral carotid
occlusion and concluded that there was no wide-
spread constriction of systemic veins. We found no
significant changes in reservoir volume, either. How-
ever, the increased systemic arterial pressure would
have distended the arterial bed by about 2 ml/kg
body wt. This volume presumably came from the
systemic veins. With a constant flow and central
venous pressure, this volume transfer would have
required an active venocostriction, leaving a zero
net transfer of blood to the reservoir.

Possible Errors From Ignoring Flow Sensitivity

If the $\Delta V/\Delta F$ phenomenon is disregarded, signifi-
cant error in the estimation of arterial compliance
may occur. Arterial bed compliance has been esti-
mates by using a constant cardiac output, constant
central venous pressure preparation, and pumping
blood from an artery to the reservoir at such a rate as
to reduce the mean arterial pressure a known
amount.\textsuperscript{15,23,38} The subsequent change in reservoir
volume divided by the change in arterial blood pres-
sure provided an estimate of arterial compliance.
The estimate of arterial bed compliance\textsuperscript{38} of 0.20±0.06
ml/(min-kg) is much higher than the 0.037 ml/(mg-kg)
estimated from the data of Guyton et al\textsuperscript{39} the 0.027
ml/(mm Hg-kg) of Mitzner and Goldberg,\textsuperscript{30} the 0.081
ml/(mm Hg-kg) of Shoukas and Brunner,\textsuperscript{23} or our\textsuperscript{32}
previously estimated value of 0.036 ml/(mm Hg-kg).
Because the arterial bypass-pump technique not only
reduces arterial blood pressure, but also reduces flow
through the peripheral tissue, some of the recorded
reservoir volume increase was also from passive
peripheral venous recoil associated with the flow
reduction. Because the rate of bypass flows (to
estimate arterial bed compliance) was not given,\textsuperscript{15,23,38}
we cannot estimate the magnitude of error associated
with the peripheral flow change. Because
arterial pressure is normally much higher than venous
pressure, even a small compliance represents a rela-
tively large stressed volume under normal conditions.
Indeed, using the arterial bed compliance estimate\textsuperscript{38}
of 0.20 ml/(mm Hg-kg) at a mean arterial pressure of
120 mm Hg, the stressed volume of the arterial bed
alone would be 24 ml/kg, which is an unreasonably
high value. If the constant cardiac output, constant
central venous pressure, reservoir technique is used
to evaluate vascular capacitance or compliance, rig-
orous control of peripheral blood flow is essential.

We conclude from our data and those of others
that the potential blood volume redistribution within
the cardiovascular system from changes in cardiac
output, the passive flow sensitivity ($\Delta V/\Delta F$), is quan-
titatively even more important than active reflex
mechanisms for maintaining cardiovascular homeo-
stasis. It provides a potent mechanism for maintain-
ing a normal cardiac output in response to changes in
cardiac function.

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References

1. Rothe CF: Reflex control of veins and vascular capacitance.
Physiol Rev 1983;63:1281–1342
2. De Jager S: Experiments and considerations on haemodynam-
ics. J Physiol (Lond) 1986;7:130–215
3. Krogh A: The regulation of the supply of blood to the right
heart. Skand Arch J Physiol 1912;27:227–248
cardiac output following carotid occlusion of the descending thoracic
5. Stokland O, Thorvaldsen J, Ilebekk A, Kiil F: Contributions of
blood drainage from the liver, spleen and intestines to cardiac
effects of aortic occlusion in the dog. Acta Physiol Scand
1982;114:351–362
7. Rowell LB: Human Circulation: Regulation During Physical
Stress. New York, Oxford University Press, 1986
8. Guyton AC, Jones CE, Coleman TG: Circulatory Physiology:
Cardiac Output and its Regulation. Philadelphia, WB Saunders
Co, 1973
9. Numao Y, Iriuchijima J: Effect of cardiac output on circula-
12. Green JF, Jackman AP, Parsons G: The effects of morphine
on the mechanical properties of the systemic circulation in the
13. Ogilvie RI: Comparative effects of vasodilator drugs on flow
distribution and venous return. Can J Physiol Pharmacol
1985;63:1345–1355
carotid sinus baroreceptor reflex on blood flow and volume redistribution in the total systemic vascular bed of the dog.
15. Shoukas AA, Sagawa K: Control of total systemic vascular
capacity by the carotid sinus baroreceptor reflex. Circ Res
1973;33:22–33
16. Shoukas AA, Brunner MJ, Greene AS, MacAnespie CL:
Aortic arch reflex control of total systemic vascular capacity.
Am J Physiol 1987;253:H598–H603
17. Stein PM, MacAnespie CL, Rothe CF: Total body vascular
capacitance changes during high intracranial pressure in dogs.
18. Guyton AC, Lindsey AW, Abernathy B, Richardson T: Venous
return at various right atrial pressures and the normal venous
19. Bennett TD, Rothe CF: Hepatic capacitance responses to
changes in flow and hepatic venous pressure in dogs. Am J
Physiol 1981;240:H18–H28
20. Chungcharoen D, Daly Mde B, Neil E, Schweitzer A: The effect of carotid occlusion upon the intrasinusosal pressure with special reference to vascular communications between the carotid and vertebral circulations in the dog, cat and rabbit. J Physiol (Lond) 1952;117:56–76
22. Corcondilas A, Donald DE, Shepherd JT: Assessment by two independent methods of the role of cardiac output in the pressor response to carotid occlusion. J Physiol (Lond) 1964; 170:250–262

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