Blood Mobilization by Regional Vascular Beds during Cerebral Ischemic Pressor Response in Rabbits

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Abstract The mobilization of blood volume from regional vascular beds during cerebral ischemic pressor response was studied in anesthetized rabbits. The visceral beds of the kidney, jejunum, and liver served as volume reservoirs from which blood was mobilized during cerebral ischemia. The renal bed gave the largest volume decrease, from 24 to 13%. The magnitude of weight change in the renal and intestinal regions varied in parallel to the volemic state of the animal. Superimposition of pressure oscillation on the systemic pressor response was created by progressive restriction of the blood supply to the brain. Regional tissue weights also oscillated with a period equal to that seen in arterial pressure but almost 180° out of phase. Such variations gave evidence of active venoconstriction in the reservoir response of all regional beds except the hind paw. The responses noted in the hind paw were passive except during complete restriction of the blood flow to the brain. Autoregulation of skeletal muscle and especially liver volume was present with moderate elevations in systemic arterial pressure.

Key Words: blood mobilization, regional vascular beds, cerebral ischemic pressor response, hemorrhage, volume loading.

During cerebral ischemic pressor response, blood shifts from the venous to the arterial compartment of the circulatory system. Passive elastic recoil as well as neurogenic constriction of regional venous beds account for the mobilization of blood (GREENWAY and LISTER, 1974; GOW, 1980). BROWN (1956) demonstrated active constriction of the arteries and veins initiated by intracranial pressure elevation. DAMPNey et al. (1979) reported changes in systemic arterial pressure and in femoral and renal conductance with interruption of cerebral blood flow by occlusion of vertebral and carotid arteries. We reported (TAKEUCHI et al., 1979; TAKEUCHI and MIYAKAWA, 1979) that in the normovolemic rabbit the renal and
intestinal vascular beds gave the largest and quickest increase in resistance in a cerebral ischemic pressor response, while in the hypovolemic state, the skeletal muscle bed was the major factor in elevating systemic pressure (TAKEUCHI and MIYAKAWA, 1980).

The blood volume mobilized from a given vascular bed is reported under a few conditions which evoke an increase in neurogenic vasomotor tone. Thus, a shift of 5 ml/kg of the body weight from the splanchnic bed (HAINSWORTH and KARIM, 1976) and 7.5 ml/kg from the entire systemic bed (SHOUKAS and SAGAWA, 1973) was measured in vagotomized dogs when the isolated carotid sinus pressure was changed from high to low levels. With carotid occlusion, 23, 16, and 5.5% of existing organ blood volume were recruited from the spleen, liver, and intestine, respectively (CARNEIRO and DONALD, 1977). Comparable shifts were seen with a non-hypotensive hemorrhage of 9 ml/kg of the body weight (CARNEIRO and DONALD, 1977). Little is known, however, of the reservoir function of regional vascular beds during cerebral ischemia or the variation of their relative importance induced by a change in the blood volume of the preparation. The present studies were undertaken to measure the blood volume mobilized from six regional beds during cerebral ischemia, to assess the degree of mobilization as a function of the blood volemic state, and to characterize the phasic patterns of volume changes during blood pressure oscillation seen with graded cerebral ischemia.

METHODS

Results were obtained from 61 rabbits of both sexes, fasted for 24 hr and anesthetized with urethane (0.9 g/kg i.m.). The rectal temperature was kept at 38°C with a heating pad. The animals were immobilized with gallamine triethiodide (Flaxedil, Teikoku Chemical Industrial Co., 1.4–2 mg/kg i.v.) and were artificially ventilated with a respirator (Shimpo Kogyo Co., TW-65-A). In some rabbits arterial pH, $P_{O_2}$, and $P_{CO_2}$ were measured at regular intervals with a blood gas analyzer (Corning Co., 165).

At the end of the experiment, the wet weights of the left kidney, jejunal segment, muscles of the right foreleg and left hind leg, the caudate process of the liver, and skin of the right hind paw with hair completely removed were measured. The total wet weights of the liver, intestine, and skeletal muscles were measured in six rabbits. The values are referred to in discussion.

Production of cerebral ischemic pressor response. The blood supply to the brain was surgically restricted to one common carotid artery (MIYAKAWA, 1966a, b). The common carotid artery through which the brain was perfused was compressed by side pressure using the device shown in Fig. 1. As the side pressure was elevated in steps, corresponding stepwise increases in systemic arterial pressure occurred invariably, with oscillations superimposed on it.

Changes in organ weight. The vascularly isolated (except for the renal and

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superior mesenteric arteries and veins) but innervated left kidney and a segment of the empty jejunum having a length of 31.5 ± 1.5 cm (mean ± S.E.) were weighed with force-displacement transducers (Shinko Communication Industrial Co., UL-20-240) at nearly their original positions. Less than 1 cm of the artery and vein of the organs was included in the weight. This was checked by applying droplets of physiological saline solution to various sites of the exposed connecting vessels and monitoring if any weight change resulted. The organs were wrapped with Saran wrap and sealed with a plasticized hydrocarbon gel (Plastibase, Taisho Pharmaceutical Co.). The surface temperature of the organs was maintained at 38°C with infrared lamps.

Changes in organ blood volume (plethysmography). The skeletal muscles of the left hind leg and right foreleg, the right hind paw, and the caudate process of the liver were placed in plastic boxes and sealed with Plastibase as shown in Fig. 1. Ultimate care was taken to avoid any possible impedance to venous outflow. Two systems were used to measure the organ weight. The plastic boxes containing the tissue to be studied were filled with Krebs-Ringer solution and fitted with a silicone tube (i.d. 4 mm). The end of one tube was placed in a thin-walled 6-cm diameter plastic container filled with Ringer solution, which was placed on top of an electronic top loader (Hansen Scientech 3300). The scale accuracy was 1 mg. The other was in a similar container which was hung from a force-displacement transducer of similar accuracy. The surface level of the solution in the containers was adjusted with a lab jack. The pressure of the plethysmograph was kept at atmospheric. The output of the electronic top loader and force-displacement transducer was amplified with a DC amplifier (Sanei Instrument Co., 1117 and 1205D) and together with systemic arterial pressure recorded on a Rectigraph (Sanei Instrument Co., 13-8D) which had 1-sec time constant. The accuracy and dynamic responses of the plethysmograph systems were checked.

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with a microsyringe by displacing volumes of 0.05 to 1 ml. The temperature of the Ringer solution in the boxes was monitored with thermisters (Nihon Kohden Co., MGA 111-219) and was kept at 38°C, except for the hind paw which was held at 22°C. The superior mesenteric and femoral venous pressures were recorded.

Side pressure and blood volume changes. The side pressures on the common carotid artery were elevated in 10-mmHg steps up to a value of 200 mmHg which caused complete interruption of the blood supply to the brain. The side pressure was maintained at each level for 1–3 min to allow the measured variables to reach a steady state.

In order to change the blood volume, rapid hemorrhages and infusions of Dextran 70-Ringer solution were performed. The volume changes were 0.3 and 0.6% of the body weight of the animal. These procedures will be referred to as 0.3 or 0.6% hemorrhaging and 0.3 or 0.6% volume loading. The side pressure was applied approximately 1 min after hemorrhaging or volume loading. A period of 15 to 18 min was allowed between each experiment for recovery of the measured values.

Data analysis. The mean values of systemic arterial pressure and organ weight were measured before and during the application of side pressure on the common carotid artery. The steady-state change in renal weight had the longest time constant and was read at the end of each step of side pressure application. When arterial pressure oscillated and organ weight undulated, the values were obtained by levelling off the oscillation and the undulation. The difference between the top and bottom of the undulation constituted the wave height. The Student's t-test was used to determine the statistical significance of the differences.

RESULTS

Changes during progressive cerebral ischemia at varied volemic states

Three groups of rabbits were used. The mean body weight of 23 rabbits used to study the renal and intestinal vascular beds was 2.66±0.06 (S.E.) kg. Another group of 24 rabbits studied for the hind leg muscle and hind paw weighed 2.63±0.07 kg on average. The third group of 14 rabbits used for the foreleg muscle and liver weighed 2.55±0.05 kg on average. Examples of the responses to the stepwise reduction to cerebral blood flow in the six vascular beds are shown in Figs. 2, 3, and 4. As the cerebral blood flow was reduced, systemic arterial pressure (SAP) oscillated with clearly noticeable oscillations in blood volume of the regional beds at all volemic states. The undulations in organ weight were out

Fig. 2. Recording of superior mesenteric venous pressure (MVP) and weight variations of left kidney (RW) and jejunal segment (JW) during elevation and oscillation of systemic arterial pressure (SAP) produced by stepwise elevation of side pressure (SP) exerted on common carotid artery in varied volemic states. Dotted line in each panel indicates phasic relation among curves.

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Fig. 2

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Fig. 3. Recording of weight variations of right hind paw (CWP) and right hind leg muscle (MW) during elevation and oscillation of systemic arterial pressure (SAP) in varied volemic states.

of phase with SAP waves reflecting a phasic increase in blood volume of the regional vascular beds with an increase in arterial pressure. These oscillations in regional organ weight superimposed on a gradual decline in weight as the cerebral
blood flow was progressively restricted. The only exception to this general response pattern was the hind paw where the oscillation in weight was in phase with arterial pressure waves in spite of a reduction in paw weight with severe cerebral...
ischemia. As shown in Fig. 2, especially in Fig. 2C, the level of renal weight undulation indicated a slow reduction with cerebral ischemic pressor response and was the only exception among the vascular beds studied; it required approximately 140 sec to reach a steady-state.

Upon resumption of the blood flow to the brain, the systemic pressure returned
to the preischemic level in 2 to 3 min. Most of the regional tissues regained the original weight or volume within the same range of time and displayed an evidence of reactive hyperemia. Exceptions to such recovery patterns were the renal and intestinal beds. The kidney required 395±38 sec to recover the weight loss, whereas the intestinal segment regained the weight extremely quickly, in 57±19 sec.

**Capacitance of regional vascular beds**

The intestinal segments, kidney, and liver showed an initial decrease in weight when SAP rose slightly in response to a modest restriction of the cerebral flow (Fig. 5A, B, F). The initial fall was prominent in the jejunum. The kidney and the liver showed an accelerated rate of volume loss as the severity of cerebral ischemia increased. Similarly accelerated volume changes were noted in the jejunum only with the greater degree of volume loading. The volume changes in the kidney and intestinal segment were directly proportional to the volemic state of the animal. Thus, the greatest mobilization of volume from the renal and intestinal beds as well as the largest per cent change was observed after 0.6% volume loading (Table 1).

In normovolemia and hypovolemia the liver weight decreased much less than the kidney or jejunum with the onset of systemic pressor response. Indeed a rapid change in hepatic volume was seen only at SAP above 100 mmHg. SAP's lower than 100 mmHg were mainly obtained at control and reduced circulatory blood volumes. All of which suggests that a neurogenic decrease in the blood volume capacity of the liver is hindered by an inherent mechanism which begins to operate when the perfusion pressure is below 100 mmHg.

In contrast the three somatic regions showed an initial increase in vascular volume at the onset of cerebral ischemic response. The two muscle beds displayed a small to modest expansion in volume only to have a rapid decrease that ensured as ischemia progressed (Fig. 5C, E). In the hind limb, the onset of rapid volume loss was fixed at nearly 110 mmHg SAP regardless of the animal's volemic status (Fig. 5C). Except in hypovolemia the vascular reservoir of the paw passively increased in volume as SAP rose (Fig. 5D). The volume of the paw decreased only with severe restriction of the blood flow to the brain.

**Venous pressure**

The mean venous pressure measured from the superior mesenteric vein decreased in the final stage of restricted flow to the brain regardless of the animal's volemic state (Fig. 2). Oscillations occurred in venous pressure which had the same period as SAP waves. Like the regional vascular volume, except for the paw, the pressure undulations in the superior mesenteric vein and femoral vein were out of phase with the SAP waves.

The mean venous pressure decreased or increased after hemorrhaging or
<table>
<thead>
<tr>
<th>Volemic state (%)</th>
<th>+0.6</th>
<th>+0.3</th>
<th>Control</th>
<th>−0.3</th>
<th>−0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial weight (g)</td>
<td>Change (%)</td>
<td>Initial weight (g)</td>
<td>Change (%)</td>
<td>Initial weight (g)</td>
</tr>
<tr>
<td>Jejunum (23)</td>
<td>8.75</td>
<td>-2.5</td>
<td>8.64</td>
<td>-2.4</td>
<td>8.53</td>
</tr>
<tr>
<td>Liver (14)</td>
<td>10.64</td>
<td>-7.1</td>
<td>10.20</td>
<td>-8.4</td>
<td>9.68</td>
</tr>
<tr>
<td>Hind leg muscle (24)</td>
<td>44.88</td>
<td>-1.0</td>
<td>44.83</td>
<td>-1.0</td>
<td>44.77</td>
</tr>
<tr>
<td>Foreleg muscle (14)</td>
<td>24.48</td>
<td>-0.7</td>
<td>25.43</td>
<td>-0.7</td>
<td>25.35</td>
</tr>
<tr>
<td>Hind paw (24)</td>
<td>9.43</td>
<td>-0.5</td>
<td>9.41</td>
<td>-0.4</td>
<td>9.37</td>
</tr>
</tbody>
</table>

Control, −0.3, −0.6, +0.3, and +0.6% represent normovolemic state, 0.3% hemorrhaging, 0.6% hemorrhaging, 0.3% volume loading, and 0.6% volume loading, respectively. Numbers in parenthesis indicate the number of animals used.
The important findings of the present study are that volumes of blood are mobilized from the kidney, liver, and intestinal vascular beds as part of and in all stages of the cerebral ischemic response, that the phasic undulations of organ volume are out of phase with the SAP wave caused by the restricted cerebral blood flow, and that cutaneous vascular regions, as represented by the hind paw, change the blood volume in phase with the SAP wave when cerebral ischemia is mild to moderate, but decrease the level of blood volume undulation when the ischemia is moderate to extremely severe. Additionally, we observed that during the initial pressor response with modest restriction of the cerebral blood flow, the vascular beds of the skeletal muscle and especially that of the liver maintained the blood volume constant. From the present study, however, it is not possible to determine separately the blood volume mobilized from passive depletion of blood due to decreased pressure in the venular and venous vascular beds and that from neurogenic vasoconstriction.

As previously reported (TAKEUCHI and MIYAKAWA, 1980), the renal blood flow decreased to nearly zero with maximum cerebral pressor response induced by interruption of the blood flow to the brain. Thus a marked passive decrease...
in blood volume in capacitance vessels may result from neurogenic constriction of the renal arterioles. At the same time, renal glomerular filtration will decrease, and interstitial fluid in a renal tissue space will move slowly into capillaries and venules until the tissue pressure becomes equilibrated with plasma and interstitial fluid colloid osmotic pressures and the decreased hydrostatic pressure of the capillaries. This series of events speculated for the kidney could account for slow reduction of the renal weight. This passage of fluid from tissues into capillaries may accelerate reabsorption of water in the renal tubules. The suppressive effect of 0.6% volume loading on the initial reduction of the renal weight may partially be the result of the cardiopulmonary mechanoreceptor reflex, which is known to exert strong control on the renal vasculature (Mancia et al., 1975; Lloyd and Friedman, 1977; Purtock et al., 1977; Weaver, 1977).

Marked neurogenic venoconstriction (Takeuchi and Miyakawa, 1979), in addition to passive elastic recoil (Greenway and Lister, 1974; Gow, 1980), may be associated with the consistently intense blood volume mobilization from the jejunum by a mild initial ischemic pressor response. Judging from the pattern of renal weight decrease with a systemic pressor response, neurogenic venoconstriction seems somewhat less marked in the kidney than the jejunum (Mellander, 1960). The well-known autoregulatory adjustment of the renal vascular resistance may also participate in producing the differences in the pattern of weight decrease between the kidney and jejunum (Källskog et al., 1975).

The response of the hepatic vascular bed was characterized by a trend to hold the hepatic blood volume constant at the onset of initial pressor response. This trend faded away as SAP rose further with more severe cerebral ischemia. In the present study, an average blood volume of 8.4 ml/100 g of tissue was mobilized from the liver by maximum cerebral ischemic pressor response in a normovolemic state, but this value was slightly lower than the results obtained in dogs by hepatic nerve stimulation (Greenway and Oshiro, 1972). Slight expansion of the skeletal muscle vascular volume during the initial pressor response with a modest reduction of cerebral blood flow regardless of the volemic status in animals may be attributed to the following. First, we have reported the specific behavior of the skeletal muscle vascular bed that tends to increase blood flow with an increase in SAP during cerebral ischemic pressor response (Takeuchi and Miyakawa, 1980). Secondly, β-adrenergic receptors in muscle vascular walls may exert an effect in producing dilatation of muscle vascular beds. The present study showed that the blood volumes mobilized from the hind leg skeletal muscle and from the foreleg muscle during maximum cerebral ischemic pressor response amounted to 0.85 and 0.65% of the muscle weights, respectively. These values are fairly consistent with the data shown by Mellander (1960), Hajiminas and Öberg (1968), and Lesh and Rothe (1969).

The following two factors may be responsible for the passive volume expansion of the hind paw with SAP elevation in this study. One is that constric-
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SAP elevation, thereby causing a transient increment of the blood flow in the hind paw in correspondence with the pressor response. TAKEUCHI et al. (1979) found that the abdominal skin vascular bed was constricted with a considerable delay after the start of SAP elevation induced by complete interruption of the blood flow to the brain. The other is that neurogenic constriction of the hind paw vascular bed is weaker than that of the visceral vascular beds.

Bleeding decreased and volume loading increased the blood volume mobilized from the kidney and jejunum with cerebral ischemic response. In contrast, bleeding and volume loading produced far less effect on the amount mobilized from the foreleg and hind leg skeletal muscles, hind paw, and liver during cerebral ischemic response.

GREENWAY and LISTER (1974) reported that hemorrhage of 8 ml/kg in cats caused decreases in intestinal, hepatic, and splenic blood volumes by 1.7, 1.7, and 1.5 ml/kg, respectively. The present study revealed that hemorrhage of 6 ml/kg in rabbits caused decreases in intestinal, hepatic, left renal, and skeletal muscle blood volumes by 1.2, 1.2, 0.45, and 2.0 ml/kg, respectively. The volume losses of intestinal and hepatic beds in our results agree with the data of GREENWAY and LISTER (1974) in spite of the difference in animal species. Our data shown above were calculated by extrapolating the blood volume mobilized from a small portion of these organs presented in results to that for the wet weight of the entire organs. The value of skeletal muscle blood volume shown above is the mean blood volume from the foreleg and hind leg skeletal muscles.

With the maximum cerebral ischemic pressor response in a normovolemic state, the blood volume reductions in the kidney, total intestine, skeletal muscle, and liver were estimated to amount to 0.64, 1.1, 2.9, and 2.8 ml/kg, respectively. Expressing these values per 100 g of tissue, the blood volume mobilized from the intestine amounted to 2.1 ml/100 g. Assuming the blood volume contained in the intestine is approximately 12.2 ml/100 g (CARNEIRO and DONALD, 1977), it corresponds to approximately 17% of the regional blood volume. The liver and skeletal muscle mobilized 8.4 and 0.77 ml/100 g, respectively. Assuming that the total blood volumes contained in the liver and muscle amount to 25 ml/kg (CARNEIRO and DONALD, 1977) and 2.5 ml/100 g (MELLANDER, 1960) respectively, the mobilized blood volumes correspond to 33 and 31% of the organ blood volume.

CARNEIRO and DONALD (1977) showed an 83% greater blood mobilization from the intestine in dogs after hemorrhage of 9 ml/kg than during bilateral carotid occlusion. In contrast, blood mobilization from the liver after hemorrhaging was only 11% greater than during carotid occlusion. The present study showed similar results. In contrast to comparatively stronger constriction of the intestinal vascular bed after hemorrhage than during cerebral ischemic pressor response, the hepatic vascular bed incurred a greater reduction in blood volume during ischemic pressor response relative to the reduction during hemorrhage.

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Comparison between our and those of Carneiro and Donald (1977) on the same weight basis shows that the blood volumes mobilized from the intestine and liver during maximum ischemic pressor response were larger by 27 and 94%, respectively, in rabbits than by carotid sinus occlusion in vagotomized dogs.

Shoukas and Sagawa (1973) reported that pressure change from 200 to 75 mmHg in the isolated carotid sinuses of vagotomized dogs resulted in a total blood mobilization of approximately 7.5 ml/kg from the total systemic vascular beds. By either decrease or increase in intrasinus pressure in a 50–125 mmHg range, the blood volume change in the total systemic vascular bed was 7.3 ml/kg (Shoukas and Brunner, 1980). Hainsworth and Karim (1976) and Karim et al. (1978) demonstrated that by decreasing the isolated carotid sinus pressure from approximately 220 to 60 mmHg, the blood volume mobilized from the abdominal vascular bed in vagotomized dogs was approximately 5.0 ml/kg. Hainsworth and Karim (1976) further found that stimulation of the efferent splanchnic sympathetic nerves on both sides immediately above the diaphragm at 5 Hz induced a response quantitatively similar to the data cited above. The present study provided an estimation of the total splanchnic volume change to be 5.5 ml/kg and that of the whole body skeletal muscles to be 2.9 ml/kg during maximum cerebral ischemic pressor response. These values do not include the volume changes of the stomach, spleen, and other small organs. The volume changes in the latter organs may, however, be assessed as considerably small in comparison with those obtained in this study. It seems reasonable that the higher values obtained in the present study than those reported in the reflex investigations may be attributed mainly to a much stronger effect of severe cerebral ischemia in rabbits than carotid sinus reflex in vagotomized animals on the capacitance vessels. Chen et al. (1980) described that in rats severe brain ischemia produced dramatic pulmonary venous hypertension and acute increase in pulmonary blood volume as a result of decrease in cardiac output and marked blood mobilization from peripheral vascular beds.

The present study demonstrated the presence of non-uniform blood mobilization patterns from regional vascular beds by graded cerebral ischemic pressor response. Of great interest are the factors and mechanisms involved in the production of such differential responses peculiar to different vascular beds, but further information awaits future studies.

The authors gratefully acknowledge the valuable suggestions of Prof. J. W. Manning, Department of Physiology, Emory University School of Medicine, Prof. K. Sagawa, Department of Biomedical Engineering, The Johns Hopkins Medical School, and Prof. J. T. Shepherd, Department of Physiology and Biophysics, Mayo Medical School, Mayo Foundation. This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan (No. 448094).

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Physiol., 185: 510-514.


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