Compensatory Adjustment in Blood Flow of the Rabbit Cerebral Cortex during Graded Cerebral Ischemia

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Abstract The role of the bilateral internal carotid and vertebral arteries in supplying cerebral cortex tissue blood flow (CTF) and the compensatory adjustment in CTF during graded cerebral ischemia were studied to determine the relationship to the increase in systemic arterial pressure (SAP) in anesthetized rabbits. CTF was recorded continuously by using Peltier stacks placed on both sides of the surface of the cerebral parietal cortex. Occlusion of the bilateral internal carotid arteries caused a decrease in CTF to 81.9% of the control value for the right hemisphere, and 83.5% of that for the left. Occlusion of the bilateral vertebral arteries produced no appreciable change in CTF. Compensatory adjustment in CTF was incomplete, i.e., CTF was reduced to a lower level, in the range of internal carotid flow (ICF) from 2 to 6 ml/min, and was severely reduced at 1 and 0 ml/min. The relationships between ICF and SAP, and ICF and CTF formed rectangular hyperbolic curves. No significant difference was observed between the decreases in CTF obtained before and after bilateral sectioning of the cervical sympathetic trunks. The relationship between SAP and CTF was described by a linear regression equation. These results indicate that the internal carotid arteries play a much more important role in supplying CTF than the vertebral arteries, that SAP rises in inverse proportion to the decrease in CTF, and that the cervical sympathetic trunks do not influence the compensatory adjustment in CTF caused by cerebral ischemia.

Key words: cerebral ischemia, internal carotid flow, vertebral artery flow, cerebral cortex tissue flow, compensatory adjustment.

Decreases in internal carotid blood flow and perfusion pressure produce an intense elevation in systemic arterial pressure (SAP) (SAGAWA *et al.*, 1961; LITTLE and ÖBERG, 1981; TAKEUCHI *et al.*, 1989), and cause significant redistribution of blood flow to different cerebral regions (MUELLER *et al.*, 1977; MARCUS and HEISTAD,

1979; SADOSHIMA *et al.*, 1981). In studies examining the effect of sympathetic nerves on cerebral blood flow (CBF) during cerebral hypotension, MUELLER *et al.* (1977), GROSS *et al.* (1979), and SADOSHIMA *et al.* (1981) found no significant effect on CBF in anesthetized animals, but MARCUS and HEISTAD (1979) reported a small but significant effect on CBF in awake animals. The effect of hypotension on CBF has usually been studied by means of hemorrhagic hypotension (MUELLER *et al.*, 1977; MARCUS and HEISTAD, 1979; TUOR and FARRAR, 1984) or increased intracranial pressure (SADOSHIMA *et al.*, 1981). In these studies, CBF is measured intermittently by the injection of radioactive microspheres (MUELLER *et al.*, 1977; MARCUS and HEISTAD, 1979) and the hydrogen clearance technique (TUOR and FARRAR, 1984). There have been almost no studies in which the relationship between reductions in CBF such as cerebral cortex tissue blood flow (CTF) and the rise in SAP was determined directly. Further, no studies have continuously measured the effects of selective, graded reductions in CBF on CTF or examined the influence of sympathetic nerves on the relationship between them.

The purposes of this study were 1) to measure the relationship between CTF and SAP; 2) to determine the compensatory adjustment pattern of CTF when the blood supply to the brain is reduced to various low levels, and at the same time 3) to determine the influence of sympathetic nerves on CTF during graded cerebral ischemia. To achieve these goals, it was necessary to establish a method to control cerebral circulation.

METHODS

General procedures. Sixteen rabbits of either sex were selected by weight (2.75 ± 0.02 (mean $\pm$ S.E.M.) kg), anesthetized with urethane (1.0 g/kg, i.m.), immobilized with gallamine triethiodide (1–2 mg/kg) and kept in mechanically ventilated room air by a Harvard closed circuit respirator. The ventilation rate (30–36 cycles/min) and tidal volume (7–10 ml/kg) were adjusted to maintain arterial blood gases within the physiological ranges (P_{O_2} , 85–100 mg; P_{CO_2} , 35–40 mmHg; pH, 7.35–7.45). The heads of the animals were fixed in a stereotaxic frame. Their rectal temperature was kept at 38°C by means of a heating pad. Dehydration and metabolic acidosis were prevented during the experiment by continuous intravenous infusion of 10% dextran and a 10% sodium bicarbonate solution ($0.3\text{--}1.0\text{ ml kg}^{-1} \cdot \text{h}^{-1}$).

After exposing the bilateral ventral surfaces of the second vertebra, a hole about 2 mm in diameter was drilled with a dental burr through each surface into the cervical canal (MIYAKAWA, 1966; TAKEUCHI *et al.*, 1989). Snare loops were placed around the bilateral vertebral arteries in the opened cervical canal. In 3 rabbits, a snare loop was also placed around the anterior spinal artery through a hole about 2.5 mm in diameter opened in the median part of the third vertebra by drilling with dental burr into the spinal cavity.

As illustrated in Fig. 1, polyethylene tubes placed in the left external jugular

Fig. 1. Schematic illustration of methods. EJVP, external jugular venous pressure; RICP, LICP, right and left internal carotid artery pressures; RICE, LICE, right and left internal carotid artery blood flow; RCTF, LCTF, right and left cerebral parietal cortex tissue blood flow; SAP, systemic arterial pressure; T, pressure transducer; F, flowmeter; A, DC amplifier.

vein and the bilateral internal carotid arteries through the left facial vein and bilateral external carotid arteries and connected to pressure transducers (Statham, P23ID) were used to measure pressure in the respective vein and arteries. Also, a polyethylene tube was placed in the abdominal aorta via the left femoral artery for measurement of SAP. The aortic and carotid sinus nerves were sectioned bilaterally. After ligation of all small branches of the common carotid arteries and the carotid sinus region except for the internal carotid arteries, the blood flow of the bilateral internal carotid artery was measured simultaneously by placing electromagnetic flow probes connected to the flowmeters (Nihon Kohden, MFV-1200 Japan) around the common carotid arteries. A hole (about 6.5 mm in diameter) was cut in the cranium over the parietal cortex by using a saline-cooled dental drill. The position of the craniectomy was selected so as to locate the rostral edge of the hole about 1.5 mm caudal to the coronary suture and its central edge about 2 mm lateral to the central line of the skull. Symmetrical holes were made on the two sides of the skull. Thermal diffusion probes 6.0 mm in diameter and 4.1 mm in height incorporating Peltier stacks were placed on the surfaces of the bilateral cerebral

parietal cortex through the holes after complete extirpation of the dura mater. The probes were connected to flowmeters (Biomedical Science, BGT-41, Japan) and covered completely with bone wax to a thickness of about 1 cm together with the surface of the surrounding skull in order to avoid alkalosis of the cerebrospinal fluid (KUSCHINSKY and WAHL, 1980). The temperature of the brain was kept at 38°C by wrapping it with a warm jacket. The voltage differences between the thermocouples were calibrated with CTF measured by electrochemically generated hydrogen gas (Biomedical Science, RBF-2, Japan), as tested by CARTER *et al.* (1981, 1982). All variables were displayed simultaneously in mean values on a thermal recorder (NEC Sanei, RECTIHORI-8K, Japan) using a 2-s time constant integrator. At the end of the experiments, the 0 value of CTF was measured by completely stopping the ascending aortic blood flow by pulling the snare loop placed around the ascending aorta. After the animal was killed by infusion of about 5 ml of a saturated potassium chloride solution into the femoral vein, the whole brain was removed from the skull and its wet weight was measured.

Servo-controller. An actuator of the servo-controller used is illustrated in Fig. 2. A pair of actuators was fixed at the rostral side of the electromagnetic flow probes, as shown in Fig. 1, and used to compress the bilateral common carotid arteries. When rod A in Fig. 2 was rotated manually, the rotating movement was converted mechanically into linear movement of cylinder B in box C. The common carotid artery was compressed with cylinder B, which was operated by cam D, with a minimum discriminable drive length of 1.6 μm , and driven by a small pulse motor controlled by the servo-controller. The total amount of bilateral internal carotid flow (ICF) was displayed on the panel of the servo-controller. The servo-controller frequently memorized the real 0 value of the total amount of bilateral ICF which was obtained by completely compressing the common carotid arteries with the actuators and regulating the blood flow under reference of the memorized real 0 value.

The study consisted of the following two experiments.

Experiment 1: The role of the respective arteries to the brain in supplying CTF. Ten rabbits were used in this experiment. The arteries were successively occluded by pulling the snare loops that had been placed around the vertebral arteries and compressing the common carotid arteries by means of the actuators in the following two series: 1) the right and left internal carotid arteries (RIC, LIC), right and left vertebral arteries (RV, LV); 2) RV, LV, RIC, and LIC.

Fig. 2. Schematic representation of an actuator connected to the servo-controller. For details see the text.

Experiment 2: Compensatory adjustment in CTF during graded reduction of blood supply to the brain. Seven rabbits were used in this experiment. After the bilateral vertebral arteries were completely occluded at the second cervical vertebra by pulling the snare loops that had been placed around the arteries, the bilateral common carotid arteries were compressed to regulate the total blood flow through the bilateral internal carotid arteries at nine different reduced levels—0, 1, 2, 3, 4, 6, 8, 10, and 12 ml/min—by the actuators connected to the servo-controller. Each level of blood flow was maintained for about 1 min to allow for a steady state except for 0 ml/min which was maintained for 30 to 50 s to achieve a nearly steady state in CTF. A period of 2 to 10 min was allowed after each reduction in ICF for recovery of the measured values. Maximum care was taken to prevent any damage to the cervical sympathetic trunks during surgery of the neck.

Complete interruption of the blood supply to the brain was confirmed by the following two criteria. If either of these criteria was not satisfied, the data obtained were not used. First, after complete occlusion of the bilateral vertebral arteries, when the bilateral internal carotid arteries are occluded completely, respiratory movement should stop within about 10 s. Second, the value of CTF recorded by Peltier stacks should be of the same magnitude during occlusion of both the internal carotid arteries and the ascending aorta.

Data analysis. The mean values of the left external jugular vein, bilateral internal carotid pressure (ICP) and ICF, bilateral CTF and SAP were measured before and after successive occlusion of the 4 arteries to the brain in experiment 1, and before and during graded reduction of ICF in experiment 2. CTF values after successive occlusion of the arteries and during graded reduction in ICF were measured at about 1 min after the occlusion of each artery and after the beginning of reduction in ICF, except for complete occlusion of ICF, when the lowest value was used. Student's *t*-test was used to determine the statistical significance of the differences, and regression equations and coefficients were calculated with the aid of a microcomputer (NEC Co., PC-9801F).

RESULTS

The mean wet weight of the whole brain was 9.9 ± 0.1 g (mean $\pm$ S.E.M., $n=16$). The mean CTF of the parietal region under control conditions was 38.3 ± 1.7 ml/(100 g $\cdot$ min) ($n=12$).

Experiment 1

As shown in Fig. 3, occlusion of the right internal carotid artery produced a compensatory increase in the left ICF. Occlusion of the internal carotid artery on either side caused a transient and slight decrease in the respective ipsilateral CTF, but produced almost the same magnitude of decrease in CTF in both hemispheres at the steady state. After bilateral occlusion of the internal carotid arteries, the pressure in the bilateral internal carotid arteries decreased but still remained

Fig. 3. Polygraphic record showing the effects of successive occlusions of the right and left internal carotid arteries (RICO, LICO), and right and left vertebral arteries (RVO, LVO) of external jugular vein pressure (EJVP), right and left internal carotid artery pressures (RICP, LICP), right and left internal carotid artery blood flow (RICF, LICF), right and left cerebral parietal cortex tissue blood flow (RCTF, LCTF), and systemic arterial pressure (SAP).

relatively high (50 to 70 mmHg) due to vertebral artery blood flow to the brain. Final occlusion of the left vertebral artery produced a sharp decrease in the bilateral CTF and SAP elevation. As shown in the left panel of Fig. 4, occlusion of the bilateral internal carotid arteries produced a decrease in CTF to $81.9 \pm 3.7\%$ of the control value for the right hemisphere, and $83.5 \pm 3.6\%$ of that for the left. Occlusion of the bilateral vertebral arteries caused no appreciable change in CTF. In the left panel of Fig. 4, when the route of the blood supply to the brain was restricted to only the left vertebral artery, CTF showed a large and significant decrease to $64.6 \pm 7.1\%$ of the control value for the right side and $58.0 \pm 6.7\%$ of that for the left. In contrast, when the route of the blood supply to the brain was restricted to only the left internal carotid artery, CTF decreased slightly but significantly ($p < 0.05$) to

Fig. 4. Percent decrease in cerebral cortex tissue blood flow of the right and left parietal regions and mean systemic arterial pressure rise produced by successive occlusions in the order of the right and left internal carotid arteries (RICO, LICO), and of the right and left vertebral arteries (RVO, LVO) in the left panel and by successive occlusions of RVO, LVO, RICO, and LICO in the right panel. The cortical blood flow decreased significantly ($p < 0.01$) and systemic arterial pressure rose significantly ($p < 0.01$) after completion of RICO and LICO (left panel) and also after finishing RVO, LVO, and RICO (right panel). Values, mean $\pm$ S.E.M. n , the number of animals used.

$96.2 \pm 1.3\%$ of the control value for the right side and $97.1 \pm 1.7\%$ of that for the left. SAP rose in inverse proportion to the CTF changes, as shown in both panels. SAP under control conditions was 85.6 ± 4.0 mmHg. Occlusion of the anterior spinal artery had no effect of CTF and SAP ($n=3$).

Experiment 2

As seen in Fig. 5, when the bilateral ICF was reduced to 4 ml/min, CTF on both sides showed a rapid but transient decrease followed by a compensatory increase. The compensatory increase was not large enough to reach the control values during bilateral ICF reduction to 4, 3, and 2 ml/min. A slight compensatory increase in CTF could still be seen when bilateral ICF was reduced to 1 ml/min. CTF did not show this compensatory increase; rather, it showed an initially sharp decrease followed by a slow reduction, reaching a steady-state level when bilateral ICF was reduced to 0 ml/min. Bilateral ICP decreased nearly in proportion to the decrease in ICF. The magnitude of the rise in SAP especially increased at ICF of 1 and 0 ml/min. External jugular venous pressure showed a slight increase only at ICF of 1 and 0 ml/min.

Rectangular hyperbolic curves were obtained between SAP and ICF, and CTF

Fig. 5. Polygraphic record of the effect of decreasing RICF and LICF on EJVP, RICP, LICP, RCTF, LCTF, and SAP. Numbers 0–4 ml/min indicate the respective decreased values in the total amount of RICF and LICF. Abbreviations are the same as in the legend for Fig. 3.

and ICF before and after bilateral sectioning of the cervical sympathetic trunks (Fig. 6A, B). In Fig. 6A, SAP under control conditions before and after bilateral sectioning of the sympathetic trunks was 84.3 ± 3.6 and 85.7 ± 3.7 mmHg, respectively. As shown in Fig. 6A and B, the patterns of increase in SAP and decrease in CTF obtained before bilateral sectioning of the cervical sympathetic trunks did not differ significantly from those of SAP and CTF obtained denervation of the sympathetic trunks. In Fig. 6B, CTF was not reduced significantly either before or after denervation accompanying the decrease in ICF in the range of ICF between 8 ml/min and the control (10.8 ± 1.4 ml/min). As ICF was reduced from 6 to 2 ml/min, the slope, i.e., the CTF/ICF ratio, increased gradually. As illustrated in the lower part of Fig. 6B, the initial rapid decrease in CTF was followed by a compensatory increase. The compensatory increase was not large enough to return completely to the control values in the range of CTF from 6 to 2 ml/min. CTF still showed a weak compensatory increase during extreme reduction of CTF by 59.7% at an ICF of 1 ml/min. CTF showed a sharp decrease followed by slow reduction

Fig. 6. A: The relationship between mean systemic arterial pressure and total internal carotid artery blood flow before and after denervation of the bilateral cervical sympathetic trunks. B: The relationship between the total amount of bilateral cortex tissue blood flow and total internal carotid artery blood flow before and after denervation of the bilateral cervical sympathetic trunks. Patterns of compensatory adjustment in the cortex tissue blood flow caused by the rapid decrease in RICF and LICF as shown in Fig. 5 are illustrated in the lower part of the figure. Compensatory adjustment was complete above total internal carotid artery blood flow at 8 ml/min, incomplete in the range of total internal carotid artery blood flow from 1 to 6 ml/min and absent at 0 ml/min. For details see the text. Values, mean $\pm$ S.E.M. n , the number of animals used.

to 0% at an ICF of 0 ml/min, indicating complete interruption of blood supply to the brain. In Fig. 7, the relationship between CTF(X) and SAP(Y) is described by a linear regression equation: $Y = -0.94X + 192$. The correlation coefficient ($r = -0.931$) indicates that the decreases in CTF are inversely correlated with SAP changes.

In Fig. 8, a regression equation, $Y = 122 \log X - 139$, having a correlation coefficient of 0.921, was obtained for the relationship between ICP(X) and CTF(Y)

Fig. 7. Variation in mean systemic arterial pressure as an inverse linear function of cortex tissue blood flow. Solid and open circles indicate values obtained before and after bilateral sectioning of the cervical sympathetic trunks, respectively.

Fig. 8. Cortex tissue blood flow plotted against mean internal carotid artery pressure. Solid and open circles indicate values obtained before and after bilateral sectioning of the cervical sympathetic trunks, respectively.

before bilateral sectioning of the cervical sympathetic trunks. ICP under control conditions before and after bilateral sectioning of the sympathetic trunks was 82.0 ± 2.7 and 82.1 ± 2.9 mmHg, respectively. As shown in Figs. 3 and 5, external jugular venous pressure maintained a nearly constant value during graded cerebral ischemia, which may indicate that cerebral perfusion pressure changes in parallel with ICP.

DISCUSSION

Considerations regarding the methods. In our methods, CTF was recorded continuously by using thermal diffusion probes incorporating Peltier stacks fixed on the surface of the bilateral cerebral parietal cortex without any injury to the cortex tissue. We used a servo-controller to reduce ICF, so that the rate of reduction in ICF could be kept at a constant value, which would result in our always obtaining a similar pattern of compensatory adjustment in CTF. The intracranial pressure during progressive hemorrhagic hypotension decreased by only 3 mmHg, from 9 to 6 mmHg, accompanying a fall in mean SAP from 113 to 23 mmHg (TUOR and FARRAR, 1984). The previous authors calculated cerebral perfusion pressure as mean SAP minus intracranial pressure and described its relationship to CBF. ICP in the present study changed in parallel with cerebral perfusion pressure, so that the relationship between ICP and CTF is thought to be nearly the same as that between cerebral perfusion pressure and CTF.

Compensatory adjustment in CTF. Blood flow in the rabbit cerebral cortical gray matter is reduced as the intracranial pressure is increased (SADOSHIMA *et al.*, 1981). TUOR and FARRAR (1984) reported that autoregulation in rabbit CBF during hemorrhagic hypotension was complete at perfusion pressures higher than 65 mmHg, incomplete between 35 and 65 mmHg and abolished at less than 35 mmHg. In the present study, as already mentioned, the routes of blood supply to the brain were surgically restricted to only the bilateral internal carotid arteries, so that the total amount of bilateral ICF indicates nearly the amount of blood supply to the brain. Although there is a difference in parameters, blood flow and pressure, this study showed a relationship between CTF and ICF similar to that between cerebral blood flow and perfusion pressure presented by TUOR and FARRAR (1984). In our study, compensatory adjustment in CTF was complete in the range of ICF between 8 ml/min and the control value and incomplete in the range between 2 ml/min and 6 ml/min, as shown by the compensatory adjustment patterns in the lower part of Fig. 6B. At an ICF of 1 ml/min, compensatory adjustment in CTF was not entirely abolished but was diminished markedly, as shown in Fig. 6B, results which seem to be slightly different from those of TUOR and FARRAR (1984) that compensatory adjustment in CTF was abolished at perfusion pressure less than 35 mmHg. Compensatory adjustment was entirely abolished only at an ICF of 0 ml/min, a finding which is in agreement with Tuor and Farrar's results. That is, a perfusion pressure of 65 mmHg in Tuor and Farrar's results may correspond to ICF of slightly

higher than 6 ml/min in our results and 35 mmHg to 1 ml/min. The relationship between CTF and ICP shown in Fig. 8 of this paper is also generally in agreement with the relationship between CBF and perfusion pressure reported by TUOR and FARRAR (1984).

The functional role of the sympathetic nerves in cerebral circulatory regulation is minor (GROSS *et al.*, 1979; MARCUS and HEISTAD, 1979) or undetectable (MUELLER *et al.*, 1977; SADOSHIMA *et al.*, 1981) during cerebral hypotension. The present study shows that the sympathetic nerves have no significant role in CTF regulation in anesthetized rabbits when the brain is exposed to ischemia. This result can probably be explained as follows: sympathetic constriction of cerebral vessels might be opposed by the dilator action of cerebral hypoxia and hypercapnia caused by cerebral ischemia.

Linear correlation between SAP and CTF. SAGAWA *et al.* (1961) reported a rectangular hyperbolic curve relationship between SAP and CBF in dogs, a result that is in agreement with our present data showing a relationship between SAP and ICF in rabbits before and after bilateral sectioning of the cervical sympathetic trunks. The present results indicate that the decreases in ICF were correlated with those in CTF and inversely correlated with changes in SAP. Thus the function of the quantitative relationship between SAP(Y) and CTF(X) was described by a linear regression equation: $Y = -0.94X + 192$ ($r = -0.931$). As far as we know, there are no previous reports of such data. Such a pressor response which increased inversely as CTF decreased would be an important mechanism for recovery from reduced CTF. The main region in the brain responsible for increasing sympathetic nerve activity and producing the pressor response when the brain is exposed to ischemia has been considered to be the pressor area of the medullary vasomotor center (TAKEUCHI *et al.*, 1969; DAMPNEY *et al.*, 1979; DAMPNEY and MOON, 1980; FARLOW *et al.*, 1984). The relationship between the degree of ischemia in the medulla and the magnitude of the ischemic pressor response should be studied in the near future.

In summary, we have shown that in rabbits 1) the internal carotid arteries make a much greater contribution to supplying CTF than the vertebral arteries; 2) during extreme reduction of CTF by 59.7%, CTF still showed a compensatory increase; 3) SAP rose in inverse proportion to the decrease in CTF; and 4) the cervical sympathetic trunks did not influence significantly the compensatory adjustment in CTF caused by cerebral ischemia.

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