Deterioration of Baroreflex by Transient Global Cerebral Ischemia: Its Correlation with the Degree of Ischemia or Post-Ischemic Hypoperfusion in the Medulla Oblongata

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Accepted August 16, 1989

Abstract—In a canine model of transient global cerebral ischemia, the correlation between the decrease in baroreflex sensitivity (BRS) following 5-min ischemia and the degree of ischemia or post-ischemic hypoperfusion was investigated. Although the medulla oblongata and the cerebral cortex suffered a similar degree of ischemia, the extent of post-ischemic decrease in BRS was inversely correlated with the residual blood flow during ischemia in the medulla, but not with that in the cerebral cortex. A similar degree of post-ischemic hypoperfusion occurred in the medulla and the cerebral cortex. However, the extent of decrease in BRS was not correlated with the degree of hypoperfusion, and the cortical EEG was not significantly affected. These results suggest that the decrease in BRS may be due to the functional damage in the medulla and that the selective decrease in BRS without concomitant impairment of the EEG cannot be ascribed to the regional difference in the degree of ischemia or post-ischemic hypoperfusion.

It has been shown in a canine model that global cerebral ischemia of longer than 5 min produces a marked decrease in baroreflex sensitivity (BRS) during the reperfusion period, suggesting that some regions vulnerable to the relatively short duration of cerebral ischemia may be involved in the central pathway of the baroreflex mechanism (1). Then, one of the questions arising from this study was the reason why the decrease in BRS after 5-min ischemia was not accompanied by the impairment of the cortical EEG.

Since the canine model utilized in the previous study was an incomplete type of ischemia caused by the combined occlusions of the brachiocephalic and the left subclavian arteries with preceding ligation of the intercostal arteries, one may speculate that the regional difference in the residual blood flow during ischemia might be one of the reasons. Another possible explanation would be that the extent of post-ischemic circulatory disturbance in the baroreflex pathway might be greater than that in the cerebral cortex, resulting in the selective dysfunction of the baroreflex system, because occurrence of no-reflow phenomenon (2–4) and post-ischemic hypoperfusion syndrome (4–9) are known to be regionally different.

In the present study, therefore, we investigated the correlation of the decrease in BRS with the degree of ischemia or post-ischemic hypoperfusion in the medulla oblongata, which contains the most essential parts of the cerebral baroreflex system, as well as the cerebral cortex.

Materials and Methods

Mongrel dogs of either sex weighing about 10 to 20 kg were anesthetized with sodium pentobarbital (Somnopentyl, Pitman-Moore), 32 mg/kg, i.v. Animals were artificially ventilated and immobilized with suxamethonium chloride (Tokyo Kasei), 2 mg/kg, i.v. Supplemental doses of pentobarbital and suxamethonium, 3.2 and 1 mg/kg/hr, i.v., respectively, were continuously infused throughout the experiment. The $P_{O_2}$ and $P_{CO_2}$ of blood samples drawn from the right saphenous artery were measured by a blood
gas analyzer (Instrumentation Laboratory, 213 and 326), and appropriate volumes of $O_2$ and $CO_2$ gasses were provided via a tracheal tube to maintain $P_{O_2}$ and $P_{CO_2}$ at about 100 and 35 mmHg, respectively. The rectal temperature was maintained at about 38°C. Arterial blood pressure was measured from the left femoral artery by means of a pressure transducer (Nihon Kohden, TP-200T), and heart rate was measured by a heart rate counter (Nihon Kohden, AT-600G) triggered by lead II ECG. The cortical EEG was recorded by means of stainless steel electrodes screwed bilaterally into the parietal skull. EEG frequency analysis was carried out using a frequency analyzer (Nihon Kohden, OEE-7102).

Production of cerebral ischemia: Thoracotomy was performed at the fifth intercostal space. In 11 animals, 14 to 16 intercostal arteries descending along the thoracic aorta were permanently ligated to severely obstruct the collateral blood flow to the brain. In another 5 animals, only 8 intercostal arteries were ligated to produce a mild obstruction. Furthermore, ligation of the intercostal artery was not performed in 2 animals. Transient global cerebral ischemia was produced by the 5-min occlusion with clamps of the left subclavian artery and the brachiocephalic artery as close as possible to the aortic arch.

Measurement of cerebral blood flow: The head of the animal was rigidly fixed in a stereotactic apparatus in a sphinx-like position, and the head was tilted down at an angle of 30 to 45 degrees to easily manipulate the medulla. Cranitomy was performed at the parietal region about 1 cm frontal to the external meatus. The foramen magnum was enlarged by removal of the caudal edge of the occipital bone. Regional cerebral blood flow (rCBF) was continuously measured by a tissue flow monitor (Unique Medical, UMW-101) using plate type thermocouple electrodes placed on the surface of the left marginal gyrus and on the left fasciculus cuneatus in the dorsal medulla oblongata close to the obex. In some animals, platinum electrodes were further inserted contralaterally to the thermocouple electrodes to a depth of 1 to 2 mm, and rCBF was measured by the hydrogen clearance method (10).

In order to evaluate the degree of ischemia, the residual blood flow during ischemia was calculated, as shown in Fig. 1, using the thermocouple electrodes. Blood flow level just before ischemia was regarded as 100%, and zero flow was obtained by killing the

![Fig. 1. Method for calculation of the residual blood flow during ischemia.](image-url)
animal with saturated KCl at the end of each experiment. Blood flow during ischemia was plotted at 30 sec intervals, and the percent ratio of the integrated residual blood flow (hatched area in Fig. 1) to the total integrated flow (area of the square ABCD) was calculated as a measure of the residual blood flow during ischemia.

**Measurement of baroreflex sensitivity (BRS):** The baroreceptor reflex was assessed by the bolus injections of 4 to 5 doses of 1-phenylephrine hydrochloride (Sigma) within the dose range of 0.3 to 10 μg/kg, i.v. Phenylephrine-induced increase in pulse interval (msec) was correlated with the increase in mean arterial blood pressure (mmHg) by the method of least squares. Then, the slope of the regression line (msec/mmHg) was utilized as a measure of BRS, because no parallel shift of the regression line was observed following transient global cerebral ischemia as shown in our previous report (1).

**Statistical analyses:** Differences between the values before and after ischemia were analyzed by the paired Student's t-test. Analysis of differences between two groups was performed by the analysis of variance and unpaired Student's t-test. The regression line was analyzed by the analysis of covariance. Differences giving P<0.05 were regarded as statistically significant.

**Results**

**The residual blood flow during ischemia:** The residual blood flow was generally dependent on the number of ligation of the intercostal arteries, as shown in Fig. 2. In the case of animals which received 14 to 16 ligations, mean residual blood flow in the dorsal medulla and the cerebral cortex was 45.4±7.2 and 39.8±6.3% (n=11), respectively, and the difference between them was not statistically significant.

**The correlation between the residual blood flow during ischemia and BRS during reperfusion period:** As shown in Fig. 2A, BRS during the reperfusion period correlated well with the residual blood flow in the dorsal medulla; smaller residual blood flow produced more marked decrease in BRS, and the

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**Fig. 2.** Correlation between the residual blood flow during ischemia and baroreflex sensitivity during reperfusion period. Baroreflex sensitivity during the reperfusion period of 60 to 210 min is correlated with the residual blood flow in the dorsal medulla (A) and the cerebral cortex (B). ○ none, △ 8 and ● 14 to 16: number of ligations of the intercostal arteries. *P<0.05: significantly different from the corresponding value in Fig. 2A.
correlation was linear. There was no time-dependent difference in this correlation during the reperfusion period of 60 to 210 min. Although the residual blood flow in the cerebral cortex during ischemia also linearly correlated to BRS during the reperfusion as shown in Fig. 2B, the correlation coefficient (r) was significantly lower than that in Fig. 2A. Furthermore, in the case of animals that received 14 to 16 ligations of the intercostal arteries (closed circles in Fig. 2), the post-ischemic BRS was linearly correlated with the residual blood flow in the medulla (n=27, r=0.774, P<0.001), but not with that in the cerebral cortex (n=27, r=0.275, P>0.1).

The correlation of the post-ischemic hypoperfusion with BRS and the cortical EEG during reperfusion period: In the animals that received 14 to 16 ligations of the intercostal arteries, as shown in Table 1, the decrease in BRS was accompanied by the significant decrease in rCBF in the dorsal medulla. However, there was no linear correlation between the extent of the post-ischemic hypoperfusion in the medulla and BRS at the corresponding period of reperfusion (n=18, r=-0.286, p>0.1). Furthermore, as shown in Fig. 3, the residual blood flow in the medulla of these animals during ischemia was linearly correlated to BRS, but not to post-ischemic.

Table 1. Influence of 5-min cerebral ischemia on the regional blood flow in the dorsal medulla (rCBF) and baroreflex sensitivity (BRS)

|                      | Before ischemia | 60 | 120 | 180 |
|----------------------|-----------------|----|-----|-----|
| rCBF (ml/min/100 g)  | 34.1±5.2        | 24.8±4.5* | 22.5±4.8* | 21.2±3.6* |
| (%)                  | 100             | 71.9±5.3* | 64.2±6.3* | 63.0±5.8* |
| BRS (msec/mmHg)      | 2.77±0.37       | 1.36±0.53* | 1.28±0.45* | 1.07±0.41* |
| (%)                  | 100             | 43.7±13.6* | 43.7±11.1* | 35.5±10.2* |

Data from 6 animals that received 14 to 16 ligations of the intercostal arteries are indicated as the mean ±S.E.M. rCBF was measured by the hydrogen clearance method. *P<0.01: significantly different from the value before ischemia.

Fig. 3. Correlation between the residual blood flow in the dorsal medulla during ischemia and baroreflex sensitivity (A) or blood flow in the medulla (B) during the reperfusion period.
Table 2. Influence of 5-min cerebral ischemia on the regional blood flow in the cerebral cortex (rCBF) and the cortical EEG power spectrum

|                  | Before ischemia | Reperfusion (min)  |
|------------------|-----------------|-------------------|
|                  |                 | 60                | 120               | 180               |
| rCBF (ml/min/100 g) (%) | 37.5±2.8 | 21.6±2.7** | 21.1±2.1** | 21.1±2.9** |
| EEG              |                 | 58.1±5.5**       | 56.9±4.6**       | 55.9±4.9**       |
| Delta (1–3.5 Hz) | 25.4±4.2       | 24.2±5.0          | 24.2±5.3          | 22.6±5.6          |
| Theta (4–7.5 Hz) | 41.9±2.3       | 46.3±4.4          | 47.0±5.1          | 47.6±4.4          |
| Alpha (8–12.5 Hz)| 25.1±2.0       | 22.6±3.9          | 21.7±4.4          | 24.4±3.7          |
| Beta (13–32 Hz)  | 7.6±2.1        | 6.9±3.3           | 7.1±3.1           | 5.4±2.8           |

Data from 6 animals that received 14 to 16 ligations of the intercostal arteries are indicated as the mean±S.E.M. rCBF was measured by the hydrogen clearance method. EEG data represent the percent ratio of each component of the power spectrum to the total power. *P<0.01, **P<0.001; significantly different from the value before ischemia.

rCBF in the medulla. The extent of post-ischemic hypoperfusion was relatively constant in spite of a considerable variation in the degree of ischemia as shown in Fig. 3B. Additionally, no significant decrease in rCBF was observed in the animals that received 8 ligations of the intercostal arteries. Table 2 summarizes the post-ischemic hypoperfusion in the cerebral cortex and the result of the frequency analysis of the cortical EEG. rCBF in the cerebral cortex during the reperfusion period of 60 to 180 min was significantly lower than that before ischemia, and the extent of hypoperfusion was statistically similar to that in the dorsal medulla. In spite of this reduction of rCBF, the frequency characteristics of the cortical EEG was not significantly affected by 5-min global cerebral ischemia.

Discussion

In a model of incomplete cerebral ischemia, the residual blood flow level during ischemia may be a critical determinant of a post-ischemic cerebral dysfunction. In this regard, the present study demonstrated that the extent of decrease in BRS during the reperfusion period following 5-min global cerebral ischemia was inversely correlated with the residual blood flow in the dorsal medulla oblongata. Considering the poor correlation between the decrease in BRS and the residual blood flow in the cerebral cortex, the present results may suggest that the site of damage responsible for the decrease in BRS may exist in the medulla. This is well consistent with the fact that the medulla contains some essential parts of the central pathway of the baroreflex mechanism (11). Since the vagal efferent fibers in dogs arise from the nucleus ambiguous and the dorsal motor nucleus in the medulla (12), these regions may be the candidates for the functionally damaged site. Alternatively, the nucleus tractus solitarius, which contains the first synapses from the baroreceptive afferent fibers, as well as the sympathetic center might be involved.

The present study also demonstrated that there was no significant difference between the residual blood flow in the medulla and that in the cerebral cortex. Therefore, selective attenuation of the baroreflex without concomitant impairment of the cortical EEG could not be explained by the regional difference in the residual blood flow during ischemia.

Another possible determinant of the post-ischemic cerebral dysfunction would be the extent of post-ischemic circulatory disturbances, because the cerebral function is known to be greatly dependent on the energy source supplied by cerebral blood flow (13). In this regard, Paschen et al. (14) suggested that the selective hypoperfusion may contribute to the focal metabolic impairment of the boundary zone between the major cerebral arteries in the cat. In the present study, however, the extent of decrease in BRS was not correlated with
the extent of hypoperfusion in the medulla, suggesting that the decrease in BRS cannot be ascribed to the post-ischemic hypoperfusion. Furthermore, the hypoperfusion in the cerebral cortex was not accompanied by a significant abnormality in the frequency characteristics of the cortical EEG. Since there was no difference between the extent of the hypoperfusion in the medulla and the cerebral cortex, the selective decrease in BRS without concomitant impairment of the cortical EEG could not be explained by the regional difference in the extent of post-ischemic hypoperfusion. These results are consistent with the previous literature (6, 7, 15–18), in which many investigators have failed to find the correlation between the degree of hypoperfusion and the degree of metabolic or histological changes in several models of transient cerebral ischemia. It has also been suggested that the post-ischemic hypoperfusion may occur secondarily to the primary cellular damage by ischemia itself (14, 18, 19). Additionally, it is unlikely that the decrease in BRS might be ascribed to the focal no-reflow phenomenon within the central pathway of the baroreflex, which could not be detected by the method used in the present study, because 5-min ischemia seems to be too short to produce no-reflow as shown by Kågström et al. (4) and Ginsberg et al. (6).

In conclusion, the present results exclude the possibility that the regional difference in the degree of ischemia or post-ischemic hypoperfusion might be the reason why BRS is decreased by 5-min global cerebral ischemia without accompanying the impairment of the cortical EEG. Since the extent of decrease in BRS was closely correlated with the extent of ischemia in the medulla, the decrease in BRS seems to be due to the functional damage in the medulla. Although the precise mechanism of the selective decrease in BRS is still unknown, exaggeration of energy deficiency by the functional excitation of the medulla during ischemia (20–23) may be one of the promising explanations.

Acknowledgments: The authors express their thanks to Mr. Hiroshi Tomita and Miss Kumi Tamai for their skilful technical assistance.

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