could we be certain in all cases that a pathological thrombus was involved. And, although β-TG seems to be a better marker for platelet activation than PF₄ in vivo, more specific and sensitive tests for in vivo platelet activation are needed.

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References


Hemodynamics In Hemorrhagic Infarction — An Experimental Study

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SUMMARY Using the canine thalamic infarction model, hemodynamics, CO₂ responses and thalamic EEG changes were studied in 7 dogs. Of the 7 animals, 4 showed hemorrhagic infarction and 3 did not, following recirculation after 6 hours of vascular occlusion. 1) The rCBF threshold for producing hemorrhagic infarction when recirculation following 6 hours of vascular occlusion was approximately 50% of the pre-occlusion level. 2) rCBF of the animals showing hemorrhagic infarction included hyperperfusion due to recirculation, and then fell to a level below the pre-occlusion level in a relatively short period. The CO₂ response became disturbed both during occlusion and after release of occlusion. Thalamic EEG was nearly flat during vascular occlusion and recovery was not seen following recirculation. 3) rCBF of the animals not showing hemorrhagic infarction recovered rapidly to the pre-occlusion level due to recirculation. The CO₂ response was somewhat disturbed during occlusion, but recovered following recirculation. Thalamic EEG was well preserved both during occlusion and after release.

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HEMORRHAGIC INFARCTION is one of the most important factors involved in the aggravation of symptoms due to brain infarction. Unfortunately, however, little research has been carried out on the pathophysiology of hemorrhagic infarction¹-² and many areas of uncertainty remain.

We have previously published details of a canine thalamic infarction model³-⁴ in which an ischemic focus confined to the anterior half of the thalamus can be produced with reliability. Moreover, we have reported that hemorrhagic infarction can be produced using that model, when 6-24 hours of vascular occlusion are followed by recirculation⁵-⁶ (fig. 1).

In the current study, we report an investigation on the pathophysiology of hemorrhagic infarction, as
studied from the perspective of thalamic EEG and circulatory dynamics, in relation to the presence or absence of hemorrhagic infarction in the autopsied brain.

Experimental Method

Seven adult mongrel dogs weighing roughly 10 kg each were used. As an experimental model for cerebral infarction, we used the canine thalamic infarction model. Briefly, under the intravenous administration of 35 mg/kg sodium pentobarbital, an endotracheal tube was inserted and, under spontaneous respiration, right temporal craniotomy was performed. After placing the dogs in a stereotaxic apparatus, a deep recording electrode was placed in the anterior portion of the nucleus ventralis of the thalamus, using the stereotaxic atlas of Lim et al. Correct placement of the bipolar electrode was confirmed by the appearance of rhythmic activity of waxing and waning at about 100 μV and 10 Hz. The electrode for EEG recording was a bipolar electrode made of two 0.25 mm stainless steel wires, insulated by 1 mm. For rCBF measurements, a needle-type platinum electrode (0.3 mm diameter) insulated except for the final 0.5 mm, was cemented to the EEG electrode. After implantation of the electrode, a small incision in the dura mater was made over the temporal lobe using a surgical microscope and 4 of the trunk arteries at the base of the brain (internal carotid artery, anterior cerebral artery, middle cerebral artery and posterior communicating artery) were dissected and exposed. Next, the animal was connected to a Harvard respirator. For immobilization purposes, 0.04 mg/kg/hr of pancuronium bromide was administered intravenously and adequate anesthesia was maintained by continuous intravenous administration of 2.5 mg/kg/hr of sodium pentobarbital all over the experiment. Intermittent sampling of arterial blood was also done, and pH, PaO₂ and PaCO₂ levels measured using a blood gas analyzer were maintained within physiological limits. Continuous recordings of systemic blood pressure were made on a strain-gage manometer via a catheter inserted into the abdominal aorta. Rectal temperature was also monitored and maintained within physiological limits.

The value of rCBF was determined from the initial slope method of the clearance curve following 3 minutes of inhalation of 5–10% hydrogen gas. The CO₂ response was evaluated from the rCBF values and the PaCO₂ value obtained during loading of 5–10% CO₂.

The actual procedure was as follows: following the preocclusion rCBF measurement, the 4 intracranial arteries which had previously been exposed were occluded in rapid succession with Scoville clips. The occlusion time was 6 hours and the animals were sacrificed after 6–9 hours of recirculation. During occlusion and after recirculation, rCBF measurements, EEG recordings and CO₂ responses were measured periodically.

The autopsied brain was fixed in 10% formalin and the right anterior portion of the thalamus was studied for hemorrhagic infarction. A comparison was then made of the degree of fall in rCBF due to occlusion, the hemodynamics following recirculation, the CO₂ response and the thalamic EEG in the animals with and without hemorrhagic infarction.

Results

rCBF values of the anterior thalamus were between 26.0 and 45.5 ml/100 g/min in all 7 animals prior to vascular occlusion. Four of the animals showed hemorrhagic infarction at autopsy and three did not. None of those three without hemorrhagic infarction showed signs of anemic infarction.

1. The Hemorrhagic Infarction Group — 4 Dogs

(i) rCBF

The pre-occlusion rCBF values in the four dogs were each taken as the respective 100% level and the mean and standard deviation were recorded. After occlusion, the rCBF fell to 40 ± 13% and after 2, 4 and 6 hours of occlusion, the rCBF values were 44 ± 12%, 42 ± 12% and 40 ± 6%. After release of the vascular occlusion, a wide range of values were seen, but they were in general large (159 ± 63%). Thereafter, rCBF values fell rapidly. After 2, 4 and 6 hours, rCBF values were 84 ± 31%, 56 ± 21% and 45 ± 18%, respectively (fig. 2).

(ii) CO₂ Response

The CO₂ response was measured in 3 animals during occlusion and in 2 animals following release. In all 3 cases, loss of CO₂ responsiveness was found both during occlusion and after release. The data of the CO₂ response was published elsewhere.

(iii) Thalamic EEG

Due to vascular occlusion, there was attenuation of voltage and loss of fast wave components in 3 dogs. Recovery of normal EEG was not seen either during the occlusion or following recirculation. In the other dog, voltage became attenuated and there was an increase in slow wave components due to occlusion, and immediately following recirculation there was com-
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The Group without Hemorrhagic Infarction — 3 Dogs

(i) rCBF

Taking the pre-occlusion rCBF level as 100%, the blood flow following recirculation was 68 ± 13% and measurements during occlusion showed values of 67 ± 16%, 70 ± 14% and 67 ± 6% after 2, 4 and 6 hours. Immediately following release of the occlusion the rCBF was slightly low at 82 ± 8%, but after 2, 4 and 6 hours of recirculation, the rCBF levels were 94 ± 20%, 101 ± 25% and 93 ± 17%, respectively — that is, at levels near to those prior to occlusion (fig. 2).

(ii) CO₂ Response

The CO₂ response was somewhat disturbed during vascular occlusion and after 1 hour of recirculation, but after 2 hours of recirculation it had returned to nearly normal — i.e., to the pre-occlusion level. The data of CO₂ response was published elsewhere.

(iii) Thalamic EEG

In 2 dogs, there was a slight attenuation of voltage and an increase in slow wave activity due to vascular occlusion. There was further attenuation over the ensuing six hours of occlusion, but fast wave activity recovered following recirculation. In the other dog of this group, occlusion produced attenuation of voltage, but there was little effect on the frequency components of the EEG. After 6 hours of occlusion, there was a slight decrease in the amount of fast wave activity, but the electrical activity returned to the pre-occlusion state after recirculation (fig. 4).

Discussion

Together with the advances in microsurgery in recent years, surgical reconstruction, such as STA-MCA anastomosis, has been actively undertaken. There have also been, however, reports concerning the dangers of causing severe symptoms due to brain edema or hemorrhagic infarction in the acute period following reconstruction. Unfortunately, there have been few experimental studies which address questions concerning the pathophysiology of hemorrhagic infarction, and particularly few reports on circulatory dynamics. One reason for this lack of experimental work has been the fact that there has not been a suitable model for producing hemorrhagic infarction at a defined site with reliability.

Recently, we have shown that a high incidence of hemorrhagic infarction can be produced using the canine thalamic infarction model. With that model, hemorrhagic infarction is confined to the anterior half of the thalamus and it is technically easy to make repeated measurements of the rCBF within the hemorrhagic focus. Furthermore, since the size of the focus is relatively small, there is little or no swelling of the brain during the experimental procedure.

Using this thalamic infarction model, we have made a series of studies on the effects of occlusion and recirculation on brain tissue. It has been found that in brain samples obtained after 30 min — 24 hours of vascular occlusion without subsequent recirculation, no hemorrhagic infarction occurs. In contrast, however, hemorrhagic infarction...
tion is produced when recirculation is allowed after 6–24 hours of vascular occlusion. These results are thought to indicate the importance of both the period of vascular occlusion and the period of recirculation in the development of hemorrhagic infarction.

In the present study we have investigated the relationship between the degree of fall in rCBF due to vascular occlusion and the appearance of hemorrhagic infarction, when recirculation has been permitted following 6 hour occlusion. It was seen that in the group of animals which developed hemorrhagic infarction, the level of ischemia during occlusion averaged 40 ± 13%, whereas in the animals which did not develop hemorrhagic infarction, the level of ischemia averaged 68 ± 13%. These findings are thought to indicate that rCBF must fall to below approximately 50% for six hours for hemorrhagic infarction to develop.

In order to determine the nature of the hemodynamics at the focus of hemorrhagic infarction, a comparison was made between the circulatory condition following recirculation in the animals with hemorrhagic infarction and those without hemorrhagic infarction. By taking the pre-occlusion rCBF value as 100%, it was found that immediately following recirculation, rCBF was at 159 ± 63% among the animals which ultimately showed hemorrhagic infarction, whereas it was 82 ± 8% in the animals without hemorrhagic infarction. Two hours after the start of recirculation, the two groups showed similar levels of rCBF, but after 4 and 6 hours of recirculation, the hemorrhagic infarction group has relatively low rCBF levels, whereas the animals without hemorrhagic infarction showed a return of rCBF to the pre-occlusion condition. These findings suggest that a characteristic feature of the animals showing hemorrhagic infarction is that transient hyperperfusion arises immediately following recirculation and such hyperperfusion is followed by a fall in rCBF; after 2 hours of recirculation, rCBF levels are below the pre-occlusion level.

Details of the CO₂ response were published elsewhere, but it is worth noting that there were disturbances of the CO₂ response both during and following vascular occlusion among the animals which ultimately showed hemorrhagic infarction.

With regard to thalamic EEG, it was found that the electrical activity following recirculation recovered to normal in all of the dogs which did not ultimately show foci of hemorrhagic infarction, whereas none of the animals which showed hemorrhagic infarction demonstrated recovery of normal EEG activity following recirculation.

These experimental findings are thought to indicate that a fall in rCBF due to vascular occlusion to below one half the level found prior to vascular occlusion and continuation of such a hemodynamic state for 6 hours using this model brings about disturbances in the regulation of cerebral circulation, as indicated by the disturbances of CO₂ response. As has been observed under the electron microscope, dehiscence of tight junctions in capillaries are recognized. By means of a sudden increase in perfusion pressure due to recirculation, transient hyperperfusion is brought about and blood components leak from the cerebral vessels at all weak point, resulting in hemorrhagic infarction. Consequently, a rise in tissue pressure is invited, there is a sharp fall in rCBF and severe damage to the surrounding brain tissue is brought about by prolonged ischemia.

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Chronological Changes in Spontaneous Intracerebral Hematoma — An Experimental and Clinical Study

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SUMMARY A model of intracerebral hematoma that closely resembles the state in humans after spontaneous intracerebral hematoma was developed. Sequential changes in experimental intracerebral hematomas were compared with the in vivo findings in spontaneous intracerebral hemorrhage.

The clinical series consisted of 28 patients with spontaneous intracerebral hemorrhage observed by CT during their natural course from 1976 through 1978. The experimental series consisted of 26 adult mongrel dogs with intracerebral hematoma near the basal ganglia studied by CT and histological examinations.

In neither the clinical nor the experimental series was the time of decrease in density beginning in the periphery of the hematoma or the first appearance of ring enhancement and its concentric concentration toward the center of the hematoma affected by the size of the hematoma. In the experimental series, the tissue reaction near the periphery of the intracerebral hematoma showed constant processes: First, a necrotic layer appeared; this was then replaced by immature connective tissue with newly formed vessels and argentophil fibers, and finally the immature layer was gradually transformed into mature connective tissue with collagenous fibers. Ring enhancement was accompanied by the appearance of immature connective tissue and capillaries. This process of change was also unrelated to the size of the hematoma.

The following correlations were suggested from the chronological observation of CT images and the histological appearance: 1) acute stage — homogeneous high density extending to the periphery and formation of ring enhancement, appearance of immature connective tissue with collagenous fibers; 2) subacute stage — decreased density spreading from the periphery and formation of ring enhancement, appearance of immature connective tissue with argentophil fibers; 3) chronic stage — concentric concentration of ring enhancement and development of mature connective tissue with collagenous fibers.

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