EDITORIAL REVIEW

The Cerebral Ischemic Penumbra

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When neuronal activity is suppressed by ischemia of sufficient severity, maintained for a long enough period of time, permanent clinical deficit can be accompanied by radiographic signs of cerebral infarction and histological evidence of ischemic damage. Recent work suggests that this is not an all-or-none event. Between the most densely ischemic region and the more normally perfused brain, an intermediate zone exists where blood flow is reduced to a level that interrupts neuronal function and the consequent electrical activities such as somatosensory evoked potentials (SEP) and electroencephalography (EEG), yet permits maintenance of membrane pumps and preservation of ion gradients.[1,2] This area is referred to as the ischemic penumbra. This intermediate zone has two characteristics that explain its potential clinical importance: 1) the interruption of clinical and electrical function that characterizes this zone is fundamentally reversible, but 2) the reversibility is time-limited.

This description of the penumbra suggests that complete understanding of its properties and its potentially successful management may minimize the clinical deficit resulting from an acute cerebral infarct.

Table 1: Some Characteristics of the Ischemic Penumbra*

	Severe Ischemia	Penumbra	Normal
CBF, ml/100g/min	< 12	12-18	>18
$CMRO_2$, μmol/100g/min	< 60	60-80	110
CMRGlc, μmol/100g/min	12	17+	25
pH	≤6.6	6.7	7.0
K^+, mM	60-100	4-10	4
SSEP	abolished	reversible attenuation	preserved
Histology	infarction	neuronal dropout	normal

*The values given are approximate and are intended to apply in the acute phase of ischemia in human patients. Some of the information is obtained through extrapolation from animal data.

Abbreviations: CBF, cerebral blood flow; $CMRO_3$, cerebral metabolic rate for oxygen; CMRGlc, cerebral metabolic rate for glucose; K^+ extracellular potassium concentration: SSEP, somatosensory evoked potential.

+May be considerably higher very acutely.

Characteristics of the Ischemic Penumbra

The primary definition of the ischemic penumbra is electrical. It is the para-ischemic zone which loses electrical excitability, as measured by EEG and SEP, but maintains the membrane potential of the neurons within it. At a practical level, however, this definition is unwieldy. If the study of the penumbra eventually is to benefit the patient, EEG and SEP measurements which suffer from imprecise localization and time constraints must be replaced by metabolic measurements that can be evaluated rapidly and precisely.

Perfusion, metabolism and time limits of the penumbra

Table 1 summarizes the salient points of our present understanding of the characteristics of the penumbra as they differ from both normal and severely ischemic brains. Evidence from several laboratories has contributed to the knowledge of the perfusion limits within which the penumbra exists. In baboons with the middle cerebral artery (MCA) occluded, Symon and his colleagues showed that cerebral blood flow (CBF) above 18 ml 100g/min sustained normal SEP while CBF below 12 led to histologically evident infarction.[3,4] For CBF values between these limits, interruption of electrical function was reversible.[5] Subsequent work has not changed these limits substantially.[6,7]

Little effort has been directed at defining the metabolic state of the penumbra zone, probably because animal experiments do not easily permit several physiological variables to be determined simultaneously. However, Nedergaard and colleagues[8] showed increased glucose utilization in brain regions adjacent to an infarct, the increase persisting for only 6 hours after MCA occlusion.[8] This phenomenon was likely a consequence of the increase in extracellular K^+ noted in the penumbra region. Astrup et al[9] showed that the blood flow threshold for massive release of K^+ from cells was lower than the threshold for

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hypoxic hyperpolarization and loss of excitability ("electrical failure"), with rises of K^+ concentration to 10 mM being noted in the penumbra. Potassium concentration changes of this magnitude can induce calcium ion movements,[10] which may in the medium term contribute to irreversible damage of the penumbra zone.

The time limits within which the penumbra is functionally reversible have also been investigated. Marcoux et al[11] showed that selective necrosis of grey matter occurs if CBF does not rise above 5-15 ml/100g/min for 1-3 hours. Rosner and Heiss[12] showed that the duration of neuronal viability depended on the magnitude of perfusion within the CBF range that defines the penumbra. Thus, judged by electrophysiological criteria, neurons within a region perfused at 5 ml/100g/min remained viable for 30 minutes, and this viability increased to 50 minutes when cerebral perfusion was doubled. Using cats, Carter et al[13] showed that the direct cortical response (DCR) was attenuated at a CBF of 23.7 ml/100g/min and obliterated at 8.7 ml/100g/min. The duration of ischemia after which DCR was unlikely to recover was approximately 30 minutes for a CBF of 5 ml/100g/min, 60 minutes for a CBF of 10 ml/100g/min, 90 minutes for a CBF of 15 ml/100g/min and more than 2 hours for a CBF of 17 ml/100g/min. Thus, despite the attenuation of the electrical response and the presumably consequent clinical deficit, it is safe to conclude that the reversibility of function may be maintained for several hours when CBF is near the upper limit of the penumbra range.

Data Obtained From Positron Emission Tomography

Positron emission tomography (PET) studies have the advantage that they yield multiple physiological variables of the human brain non-invasively and practically simultaneously. Determinations of CBF and $CMRO_2$ in the entire brain can now be completed in one hour and have improved our understanding of the ischemic penumbra significantly.

A transient ischemic attack (TIA) is the clinical expression of reversible ischemia. Powers et al[14] studied 7 patients with TIA's and showed that minimal flow and energy requirements for ischemia that does not result in infarction were a CBF of 22 ml/100g/min and a $CMRO_2$ of 65 μmol/100g/min. An elevation of the fraction of oxygen extracted by the brain and an increase of cerebral blood volume was also noted, the latter likely due to dilatation of precapillary resistance vessels. This finding, associated with the increased cerebral glucose utilization already referred to, confirms Cremer's suggestion that localized regulatory links exist between blood flow, capillary surface area and glucose transport in response to metabolic demand.[15]

The alternative to the study of patients with TIA's is the investigation of cerebral infarction in the acute phase. At the Montreal Neurological Institute, we studied stroke patients twice, first within 24-48 hours, and again 7 days after the stroke. These studies (unpublished observations) allow us to show that a region with CBF values characteristic of penumbra on the first scan will lower its metabolic rate for oxygen during the following days, terminating with values indistinguishable from the severely ischemic zone. Thus, PET studies recognize an area consistent with penumbra whose function deteriorates over time but that may be the target of therapeutic intervention.

Additional Data Needed

If the penumbra concept is to be useful both to therapy and to our understanding of the ischemic process, then it must be examined on the basis of the following questions:

1) How predictable is the course of the metabolic and histological responses seen after a stroke, particularly in the penumbra zone? The metabolic and perfusion thresholds for infarction, both in terms of levels and duration, must be known more precisely, and the still active debate over the histological appearance of this region must be resolved.[16,17]

2) What role does hyperemia play in deciding the fate of the penumbra? We have shown by PET that cerebral infarcts which spontaneously reperfuse soon after a stroke are smaller,[18] but it is not clear whether this trend is mediated only through the influence of reperfusion on the course of the penumbra.

3) What events contribute to the metabolic "decline" of a penumbra zone towards infarction? If this is not only a consequence of depth and duration of ischemia, what role do calcium or other ions play in it? What is the role of H^+ ion homeostasis? The binding properties of the calcium channels are influenced by their physiological environment.[19,20] What is their role in determining the fate of the penumbra?

These questions are now being addressed by PET studies of the human brain and the data correlated with the clinical and radiographic consequences of stroke.

Therapeutic Possibilities Using the Concept of Penumbra

Over the past few years, we have learned from two expensive multicenter trials in ischemia (the EC-IC bypass study[21] and the trial of prostacyclin in stroke[22]) that therapeutic efforts intended solely to reperfuse ischemic cerebral regions are unlikely to succeed. Other agents that are presumed to attenuate the clinical responses to cerebral ischemia must be critically evaluated but, in my opinion, only after preliminary evaluation by PET has shown that they indeed yield the expected physiological responses. It is useful to remember that PET studies of the metabolic and perfusion effects of EC-IC bypass[23] and prostacyclin administration,[24] performed on far smaller patient populations, predicted the clinical findings. More logically, however, the PET evaluation should precede the enrollment of hundreds of patients into a trial. Presently available drugs with therapeutic potential that are undergoing PET-based trials include calcium channel blockers and N-methyl-D-aspartate receptor antagonists (MK-801). Others will likely be designed as our understanding of the ischemic penumbra improves.

In conclusion, the concept of an ischemic penumbra is an excellent defence against the nihilistic approach towards stroke therapy but its full potential will be realized only with an investment of time and funds in new research.

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