Thresholds in Cerebral Ischemia — The Ischemic Penumbra

COMPLETE ARREST of the cerebral circulation leads within seconds to cessation of neuronal electrical activity and within a few minutes to deterioration of the energy state and ion homeostasis. Depletion of high energy phosphates, membrane ion pump failure, efflux of cellular potassium, influx of sodium, chloride and water, and membrane depolarization occur swiftly. If such chaos persists for longer than 5-10 minutes, irreversible cell damage is likely. Such is the inevitable sequence of events if blood flow to the brain is arrested. If, however, the ischemia is incomplete the outcome is more difficult to predict and is largely dependent on residual perfusion and oxygen availability. It is in large measure the outcome of incomplete cerebral ischemia, which is of particular interest in cerebrovascular disease. With occlusion of a cerebral vessel and signs of acute stroke, ischemia is hardly ever total. Some residual perfusion persists in the ischemic area dependent on collateral vessels and local perfusion pressures.

Recent evidence indicates that immediate failure of basic functions such as synaptic transmission, ion pumping and energy metabolism in the ischemic brain, is critically dependent on residual blood flow, and that these functions fail at certain critical flow thresholds. It appears, further, that the development of infarction is critically correlated to residual perfusion, and there is a lethal threshold of residual blood flow below which tissue infarction develops after a certain time. Such knowledge provides the theoretical background for application of the instrumentation now being developed for repeated non-invasive 3-dimensional imaging of residual flow in the ischemic brain. By these means one hopes it will become possible to conduct treatment and to evaluate prognosis in the acute stroke patient by reproducible repeatable measurement in man.

Flow Threshold for Failure of Neuronal Electrical Function

In man, flattening of the EEG occurs immediately if hemispheric flow falls below 0.16–0.17 ml·g⁻¹·min⁻¹ as evidenced by measurements of cerebral blood flow and EEG during clamping of one carotid artery in endarterectomy. The critical relationship between cerebral electrical activity and blood flow which such clinical observation suggested has been amply proven in experimental studies. Symon and Branston and co-workers demonstrated that the evoked somatosensory potential recorded in baboon cortex was abolished at local flows below about 0.15 ml·g⁻¹·min⁻¹. This flow level could be regarded as critical in the sense that electrical function in the cortex was abolished below but sustained above this level. It has, therefore, been referred to as the flow threshold of electrical failure in the cerebral cortex. The threshold seems rather fixed. Heiss and co-workers found cessation of spontaneous neuronal spike activity in the cerebral cortex of cats if local blood flow fell below 0.18 ml·g⁻¹·min⁻¹. Almost identical values were determined in the studies referred to above irrespective of species differences and varying modes of anesthesia.

Flow Threshold for Failure of Energy Metabolism and Ion Pumping

When the flow threshold of electrical failure was first described it was not clear how the energy state and hence the ion homeostasis were affected at these critical levels of flow. Since oxygen uptake at the electrical threshold supposedly was somewhat reduced, energy failure and pump failure with efflux of cellular potassium and membrane depolarization was naturally suspected as the cause of electrical failure. Subsequent studies in the baboon, however, in which this hypothesis was tested, clearly showed that the extracellular potassium concentration in the cortex remained normal or only slightly elevated at the threshold when electrical function ceased.

Increase in extracellular potassium concentration, indicative of "pump failure," did not occur unless local blood flow was further reduced. In these and in subsequent studies on the baboon with middle cerebral artery occlusion, it was possible to determine a critical ischemic flow threshold of about 0.10 ml·g⁻¹·min⁻¹ below which the extracellular potassium concentration increased massively due to efflux of potassium from the cells. Further studies in the rat with bicuculline-induced continuous generalized seizures have confirmed this observation. In these studies, progressive brain ischemia was induced by controlled hypotension, allowing a correlation between electrical events (EEG), extracellular potassium concentration, and cerebral energy metabolism. In this model, electrical failure appeared as cessation of seizure discharges while extracellular potassium concentration remained normal or only slightly elevated.
At the point of seizure interruption, the extracellular potassium concentration decreased, indicating that sufficient energy remained for ion pumping. This was verified by direct tissue analyses. Thus, although lactic acid concentrations were elevated and phosphocreatine decreased, the ATP concentration was close to normal.

Although cerebral energy stores are maintained close to normal at the threshold of electrical failure the rate of ion pumping is affected even earlier, as evidenced by a reduction in the rate of potassium clearance in the interictal periods. This may reflect failing oxygen supply and a declining rate of ATP production. Reductions in blood pressure below the threshold for electrical failure caused massive increase in extracellular potassium, indicating ion pump failure. Metabolic studies showed ATP depletion at this point. These studies did not allow measurements of blood flow, but the significant difference in the blood pressure levels separating the thresholds of electrical failure and of ion pump failure (46 and 32 mm Hg, respectively), suggest progressive ischemia and not merely a natural course of severe ischemia. Their close correspondence with the baboon experiment, as regards electrical failure and potassium homeostasis, further emphasize this view.

**Ischemic “Penumbra”**

The condition of the ischemic brain with flow between the 2 thresholds — the upper threshold of electrical failure and the lower of energy failure and ion pump failure — can be described by electrical silence with normal or only slightly elevated extracellular potassium concentration. These areas can be identified geographically by microelectrode observation in baboon cortex. The residual perfusion supplies sufficient oxygen to maintain a close to normal tissue concentration of ATP. Since the concentrations of phosphocreatine and lactate are greatly reduced and increased, respectively, and since the concentrations of ADP and AMP are moderately increased, some degree of energy failure exists. Results obtained in hypoxia suggest that such moderate energy imbalance does not lead to neuronal damage. In focal ischemia the tissue in this condition forms a ring around the more densely ischemic center, in which energy failure and ion pump failure have developed. In analogy to the half-shaded zone around the center of a complete solar eclipse this part of the ischemic brain has been termed the “penumbra.” This term is descriptive only, and may equally well be applied in global ischemia. Although rather labile in the epileptic rat brain, the state of the “penumbra” seems stable for hours in focal ischemia and its identification may be valuable in experimental and even clinical conditions.

**A Possible Flow Threshold for Infarction?**

Is loss of electrical function in the ischemic penumbra a sacrifice which temporarily may save vital processes? May recovery without irreversible damage be obtained only if residual blood flow is maintained on the safe side of the threshold for energy failure and ion pump failure, so that we may speak of this threshold as a lethal threshold? In accordance with this view, Symon and Brierley found that in chronic ischemic infarction, the area in which infarction developed corresponded to the zones which, immediately following acute occlusion, had flow rates of less than 0.10 ml·min⁻¹. Correspondingly, Morawetz et al. found that recovery without histological signs of structural infarction, following a 2 to 3 hour period of focal ischemia in the monkey, could only be found at sites where local blood flow was sustained above 0.12 ml·g⁻¹·min⁻¹, i.e., presumably on the safe side of the flow threshold for energy failure and ion pump failure. The concept of a flow threshold for infarction and its possible relation to the threshold for ion pump failure needs evaluation. It is clear that energy state and ion homeostasis are not the factors per se indicating irreversible damage since they both can be fully recovered even after prolonged periods of normothermic ischemia from which recovery without histological signs of structural infarction, following a 2 to 3 hour period of focal ischemia in the monkey, could only be found at sites where local blood flow was sustained above 0.12 ml·g⁻¹·min⁻¹, i.e., presumably on the safe side of the flow threshold for energy failure and ion pump failure.

Circumstances that May Alter the Ischemic Flow Thresholds

Presumably, the critical parameter for tissue function is oxygen availability rather than blood flow. This has been confirmed by studies in the rat. If controlled hypotension was combined with hypoxia the critical levels of blood pressure at which electrical failure and ion pump failure occurred, were elevated (78 and 65 mm Hg in hypoxia compared to 46 and 32 mm Hg in normoxia). Similarly, flow thresholds could be expected to be elevated in anemia.

A more complex problem is the possible dependence of the ischemic flow thresholds on preconditioning conditions. The question can be posed: is the brain more vulnerable to ischemia in conditions of hypermetabolism, and is it less vulnerable in conditions of hypometabolism? The only condition of hypermetabolism so far studied is bicuculline-induced seizures in the rat. In this model the metabolic rate is increased almost threefold. At the point of the ischemic arrest of seizures the oxygen consumption was reduced to about half of the pre-ischemic value. This is still a rather high level of oxygen consumption and, correspondingly, the degree of hypotension required to induce electrical failure in the epileptic brain was so moderate that it could easily have been tolerated by non-epileptic animals. The only condition of hypometabolism so far studied is the chloralose anesthetized baboon with acute focal ischemia to which a large dose of methohexital or pentobarbital was given. Barbiturates in these circumstances had no effect either on the flow threshold for electrical failure nor on the threshold for ion pump failure. It is conceivable that other conditions of hypometabolism may lower the ischemic flow thresholds. Lowering of the threshold for energy failure and ion pump failure, possibly related to the development of infarction, has...
a clear bearing on the problem of clinical protection of the ischemic brain.

Clinical Implications

In the patient with acute stroke clinical examination cannot distinguish between areas of severe ischemia with energy failure, high extracellular potassium, and developing infarction, and areas with less severe ischemia in the penumbra with electrical failure but sustained energy metabolism and low extracellular potassium and with the possible potential for recovery. There is some evidence that clinical and electrical function may turn on and off in the penumbra. This is the background for the sometimes dramatic but often transient clinical improvement which can be induced e.g., by an increase in blood pressure or by theophylline. Presence of viable brain tissue in the penumbra also explains why the acute clinical presentation of stroke is a rather poor predictor of outcome. It should be emphasized that in terms of absolute flow units, the distance between the two ischemic flow thresholds is delicately small — only about 0.05 ml/g·min while, as indicated, the difference in terms of viability may be infinite. This may explain why application of a microsurgical anastomosis to a cortical artery may preserve viability although the absolute flow through the anastomosis may be very small. The “inverse-steal” phenomenon, which sometimes can be induced by hyperventilation or by careful non-hypotensive barbiturate sedation and which increases blood flow in the ischemic focus while decreasing it in the non-ischemic part of the brain, may improve the outcome in focal ischemia even if the amount of blood supplied by this mechanism is small. In this connection, we may also recall the importance of avoiding profound hypotension in the patient with acute stroke, since this will aggravate ischemia so that the residual perfusion in the penumbra may fall below the lethal threshold.

Measures that maintain or raise the residual perfusion in the area of acute focal ischemia are probably all-important determinants of the final outcome in stroke. At present, such therapeutic intervention is “blind” since the effect on hemodynamics in the ischemic area cannot be monitored. This problem is, however, being approached by the development of instrumentation for repeatable non-invasive 3-dimensional imaging of regional cerebral blood flow and metabolism.

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