Flow Thresholds of Functional and Morphological Damage of Brain Tissue

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THE FUNCTIONAL STATE of the central nervous system is dependent on adequate delivery of the main substrates. For the supply of sufficient amounts of glucose and oxygen cerebral blood flow (CBF) has to be kept above a critical level. However, when perfusion drops below a certain threshold, in consequence, cerebral function becomes impaired. While the increase of blood flow above this threshold restitutes full cerebral function, a further decrease of the flow below a critical limit for certain period of time leads to irreversible functional impairment and may initiate destruction of the structural integrity of the tissue. The upper level was termed as the flow threshold for failure of neuronal function, the lower level as the flow threshold of membrane failure; the condition of an ischemic brain region perfused within the range of the two thresholds was called "ischemic penumbra."

**Methods for Determination of Flow Thresholds**

In recent years various experimental and clinical approaches were chosen to determine the threshold of brain function and of ischemic damage.

Determination of functional impairment: While the development of neurological deficits cannot be followed in man, animal experiments with chronic preparations permit to relate certain flow values to partial or complete reversible or irreversible disturbances of function. More widely applicable are electrophysiological techniques as indicators of disturbed function related to flow changes. During carotid surgery EEG activity was used as indicator. More accurate determinations of the flow-function relationship were possible in animal experiments using evoked potentials, spontaneous activity of single cortical cells or cortical DC potentials. In most of these studies blood flow was measured with inert gas clearance techniques (133Xe in man, H$_2$ in animals).

Determination of morphological damage: When the development of gross cerebral infarction was studied in early experiments, complete ischemia or states with "minimal flow" were used and the maximal permissible duration of flow disturbances was determined without a clear definition of the residual flow. The tolerated durations of cerebral ischemia have been rather high but could not be confirmed in more recent studies in which blood flow was measured during ischemic periods, and ischemia was followed by a period of reperfusion. CBF was measured by recording the clearance of hydrogen gas with Pt-electrodes inserted into the brain or by autoradiographic methods; morphological damage was assessed as macroscopic cerebral infarctions, microscopic foci of infarctions, and selective cell necrosis.

Chemical indicators of reversible or irreversible damage: Several chemical indicators can be used to show ischemic tissue changes: Increase in extracellular potassium concentration is due to a net K$^+$ efflux from the cell and thereby indicates membrane depolarization and membrane failure, which is due to ATP depletion. The concentration of high energy phosphates (ATP and creatine phosphate), the energy charge of the brain, is a rather late indicator of irreversible energy failure. Changes in energy state and ion homeostasis are not factors conclusive for irreversible damage, since they both can be fully recovered even after prolonged periods of ischemia. Some abnormal chemical mechanisms might be initiated during the transient ischemia or even during the postischemic reperfusion period, which jeopardize still viable neurons and cause irreversible damage. Such processes may be indicated by disturbed calcium-ion homeostasis and raised concentrations of free fatty acids. Their influence on the development of ischemic damage is incompletely understood. However, disturbed energy metabolism and Na$^+$-K$^+$ transport can fully recover. This suggests that membrane failure may trigger or uncover the process causing irreversible structural damage, without being part of these processes. The flow threshold for membrane failure is therefore close to the flow threshold of infarction, but the development of infarction requires time.

**Functional Threshold**

Experiments in chronic animal preparations with implanted electrodes and occluding devices permit to establish the threshold for the function of the whole brain which resembles most closely a threshold of neurologic function in stroke victims. Jones et al. showed in monkeys that above a flow of 0.23 ml/g/min no deficits could be observed. Flow decreases below this value resulted in immediate weakness of limbs which deteriorated with further diminished perfusion. At values less than 0.09 to 0.08 ml/g/min hemiplegia was complete. This threshold for paralysis was independent of duration: Flow decreases below 0.23 ml/g/min immediately caused impaired tissue function which was reversible with elevation of flow above that value.

In electrophysiological studies thresholds for partial...
functions were investigated: EEG which gives some indication of the function of the cortex is decreased in amplitude when flow drops below 0.2 ml/g/min and becomes isoelectric at a value of 0.15-0.16 ml/g/min.\textsuperscript{6} Evoked potentials indicate the arrival of an impulse volley into the cortex via an afferent pathway and the excitation of the postsynaptic neuronal network in the cortex: they are decreased in amplitude at flows below 0.2 ml/g/min and abolished at 0.15 ml/g/min,\textsuperscript{6} the value which was termed threshold of synaptic transmission failure.\textsuperscript{2} However, the presynaptic component can be elicited down to values of 0.12 ml/g/min showing that fiber systems tolerate ischemia better than nerve cells.\textsuperscript{7} The flow at which individual nerve cells cease spontaneous activity was found to be around 0.18 ml/g/min,\textsuperscript{8} but a high interneuronal variability exists with some cells stopping discharge at 0.22 ml/g/min and others being spontaneously active at values as low as 0.064 ml/g/min.\textsuperscript{27} These values found in the cat fit well to the functional threshold for developing weakness to complete ischemia determined in chronic monkey experiments.

**Threshold for Morphological Integrit**

While function is impaired immediately when flow drops below a certain level, the development of morphological damage is time dependent. This fact was well realized in the early experiments when the maximal permissible duration of minimal flow — defined as complete ischemia or flow below 0.1 ml/g/min — was determined without leading to tissue damage. The rather long time period after MCA occlusion without tissue damage (4-6 hours, 10-12) might either be due to a residual flow which was higher than estimated, or be due to the lack of a recirculation period which might be necessary for maturation of tissue necrosis,\textsuperscript{29} or be due to the effect of anesthesia.

The failure of the intactness of the cell membrane must precede the development of structural destruction of the cell. The ischemic flow threshold of membrane failure indicated by ATP depletion and increase of extracellular concentration of potassium ion\textsuperscript{17,30} was found to be at 0.06 to 0.08 ml/g/min. This flow threshold is closely associated with the development of structural cell damage,\textsuperscript{2} but histological necrosis and macroscopical infarction can develop at markedly higher flow values persisting for certain time periods, and cells can survive lower perfusion for a limited duration. During MCA occlusion residual flows below 0.12 ml/g/min for 2-3 hours led to infarction in gray and white matter, while lower flows were tolerated for shorter duration (e.g. 0.06-0.08 ml/g/min for 1 hour) without evidence of tissue damage.\textsuperscript{13} These values necessary for development of moderate to large infarction (i.e. 0.12 ml/g/min for 2 hours) were repeatedly confirmed,\textsuperscript{3, 27} but a residual flow of 0.17 to 0.18 ml/g/min during permanent MCA occlusion led also to large infarctions.\textsuperscript{3} However, microscopic foci of infarction were found already after 15-30 min of MCA occlusion in the monkey.\textsuperscript{3} Selective cell necrosis appeared after 10 min complete ischemia in the rat\textsuperscript{16} and irreversible neuronal changes limited to the neocortex were occasionally seen after 5-8 min complete ischemia in the cat.\textsuperscript{31}

That the threshold for cellular damage is not a peculiar flow value but a function of residual flow and duration of ischemia was stressed in a study of survival of cortical neurons as indicated by recovery of spontaneous activity after onset of ischemia of varying severity and duration:\textsuperscript{27} Neurons did not recover their spontaneous activity when they had been subjected to a reduction of flow below 0.05 ml/g/min for 20 min, or below 0.08 ml/g/min for more than 30 min, or to higher flow levels for progressively longer periods of time (e.g. 0.12 ml/g/min for 50 min, 0.15 ml/g/min for 80 min). From these data a discriminant curve was estimated representing the worst possible constellation of residual blood flow and duration of ischemia allowing survival without permanent loss of neuronal activity. This curve tended towards infinity at a flow of 0.18 ml/g/min indicating that this value is the threshold for morphological damage when maintained permanently. These results on functional aspects of cell activity agree well with the morphological data.

**Selective Ischemic Vulnerability**

The concept of selective vulnerability\textsuperscript{22, 31} is usually applied by morphologists to the different sensitivity of various parts of the central nervous system, of various cell types in a certain area, or even of neurons of the same kind to ischemic or hypoxic damage. This selective cell necrosis as a sign of permanent morphological damage was found occasionally within minutes of complete cerebral hypoxia and ischemia in the cat\textsuperscript{11} and in the rat,\textsuperscript{16, 34} and occurred after ischemia of 0.05-0.15 ml/g/min for 1-3 hours in the monkey.\textsuperscript{1} Selective ischemic vulnerability is also clearly documented in the results on single cortical neurons\textsuperscript{27} which showed a broad overlap of the groups of devitalized and viable cells with respect to severity and duration of ischemia.

The concept of selective vulnerability is also applicable to the physiologic function of the nervous tissue and of individual nerve cells: More complex functions are impaired at higher flow values, and the less the residual flow after MCA occlusion the worse the neurologic deficits become.\textsuperscript{3} In close agreement to these findings some cells discontinue their spontaneous activity at 0.22 ml/g/min, while others keep firing down to values as low as 0.064 ml/g/min.\textsuperscript{27} This gradual disappearance of the function of individual cortical cells with decrease of residual flow during ischemia is in good agreement to the gradual development of neurologic deficits as observed in awake monkeys.\textsuperscript{3} Which properties of a cell — size, location with respect to supplying vessel, or others — affect its tolerance against ischemia remains a field for speculation.

**Clinical Implications**

The concept of the "ischemic penumbra,"\textsuperscript{1} of ischemia at a residual flow below the functional threshold but above the threshold for morphological integrity, is of utmost importance for the development of
therapeutic regimens in stroke victims. After focal ischemic attacks symptoms may recover completely or partially either shortly after the occurrence of the deficits or more rarely with long intervals after the onset, and such improvements may occur spontaneously, or after surgical revascularization, perfused at a value insufficient for functional activity but adequate for structural integrity. Slight flow increases restore function in viable cells. The concept of the ischemic penumbra is complicated by two facts: the duration of ischemia on cell damage, which itself is dependent on the absolute value of residual flow; and the high variability of ischemic vulnerability among different neurons. It has to be kept in mind that the destruction of the most sensitive neurons is important for the irreversibility of the neurological defect. Therefore, the ischemic cell damage of the most vulnerable part must be prevented. In principle, this can be done by improving the flow to the critical area by a small amount (0.1–0.2 ml/g/min) within the tolerable time limits. As long as clinical neurology is still far from being able to fulfill this requirement, helpful therapeutic regimens could be initiated by studies of regional cerebral blood flow and metabolism in stroke victims to select cases with still viable but functionally inactive tissue.

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