Exploiting the full width of the therapeutic window to salvage the ischemic penumbra: imaging for cost-effective, personalized therapy

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Thirty years ago, Jens Astrup and colleagues described, in *Stroke*, a dual threshold in ischemia: a threshold for complete electrical failure and another threshold, clearly lower, for release of K+. On the basis of their findings they introduced the concept of a state in which the neurons remain structurally intact but functionally inactive. They also concluded that neurons can survive for some time in a state of lethargy, as shown by the observation that an increase in regional cerebral blood flow (rCBF), if sufficient, can restore evoked potentials and normalize extracellular K+ activity, as well as pH (1). They coined the term ischemic penumbra, a concept that they elaborated upon in a subsequent paper in which Astrup stated: "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" (2). Astrup was probably referring to the early seminal PET studies of Baron et al. (3,4), and Lenzi et al. (5).

The concepts outlined in these papers marked the start of a new era in our understanding of the pathophysiology of cerebral circulation and stroke, and were among the reasons for the development of 3D imaging techniques for the assessment of cerebral perfusion and metabolism, which, in turn, provided scope for a rational approach to the treatment of stroke.

Since these early studies the concept of the ischemic penumbra has become increasingly important, in parallel with the development of treatments for acute ischemic stroke. Notwithstanding the various definitions proposed for the ischemic penumbra, based on biochemical, electrophysiological, clinical and experimental observations, for a practical and patient-oriented approach it may acceptably be defined as the portion of ischemic territory that, with timely intervention, can potentially be salvaged. The ischemic penumbra is a dynamic and functional entity rather than a morphologically defined state. Thus, key questions are: How long does the ischemic penumbra persist? Which portion of the ischemic brain is in the penumbral state? How does the penumbra vary over time and with intervention? Does the penumbra undergo characteristic structural and functional changes during infarct development? Can it be assessed in a clinical environment? How does penumbra assessment impact on patient management and outcome?

In the proper treatment of acute stroke, the hypoperfused tissue should be differentiated (6-8) into: tissue that should survive, tissue that may either die or survive, and tissue that will inevitably die. In oligemia, a condition characterized by lower-than-normal cerebral blood flow (CBF), i.e. below 50 ml/100 g/min, but not lower than 20 ml/100 g/min, tissue function can be maintained for a very long time. Oligemia evolves into penumbra, a condition in which CBF is lower than 20 ml/100 g/min – and hence potentially into necrosis –, when CBF falls below 12 ml/100 g/min. PET studies have also shown that the penumbra is characterized by reduced CBF, an increased oxygen extraction fraction, and relatively preserved oxygen consumption ($CMRO_2$). In a series of PET studies performed 5-18 h after stroke onset, Baron et al. determined the threshold for penumbra to be around 20 ml/100 g/min, and documented that the extent of neurological recovery is proportional to the volume of penumbra that eventually escaped infarction. Within this time

This editorial derives from a literature search. It includes extensive portions of the texts of the examined articles as well as the opinions of the authors, who have contributed equally to the paper.

interval, the thresholds for irreversible damage were around 8 ml/100 g/min for CBF and around 0.9 ml/100 g/min for $CMRO_2$. A shorter duration since clinical onset may be associated with a lower threshold for irreversibility (9-11). In a strictly homogeneous sample of prospectively studied patients, Marchal et al. identified, up to 17 hours after stroke onset, substantial volumes of tissue with $CMRO_2$ well above the assumed threshold for viability that nevertheless spontaneously evolved toward necrosis. This tissue exhibiting penumbral ranges of both CBF and oxygen extraction fraction could represent the part of penumbra that, with appropriate and timely therapy, might be saved in some patients (12).

As summarized by Muir et al. (13), unless early reperfusion occurs, the penumbra is gradually recruited into the core, i.e., the volume of irreversibly damaged tissue grows and the amount of penumbra decreases. Tissue outcome depends on two factors: the severity of flow reduction and its duration. Thus, within the penumbra, the lower the CBF, the higher the risk of early infarction. Because both the core and the penumbra can contribute to neurological deficits, it is impossible to determine clinically their relative effects. A substantial penumbra is present in up to 90% of patients within 6h of onset; this falls to about 50% within 9h, but is still about 30% 18h after onset. Up to 52% of the ultimate infarct area still showed penumbra 16h after onset (12). Rescue of the penumbra, either by restoration of blood supply or by interruption of the adverse metabolic or neurochemical cascade, is the basis of acute stroke therapy: survival of the penumbra is the main determinant of clinical recovery (14,15), and probably underpins peri-infarct reorganization (16,17).

Biochemical and imaging parameters have been used to try to characterize the ischemic tissue that defines the existence of ischemic penumbra. Both approaches can be applied in experimental stroke models, but imaging is currently the only available practical approach for identifying the ischemic penumbra in stroke patients and it continues to have a huge impact on the understanding of the ischemic penumbra and the management of acute stroke. It is also proving invaluable in clinical decision making in acute stroke, especially in relation to reperfusion therapies in the 3- to 6-hour window (17). Thus, identification of the penumbra in the hyperacute period is crucial because tolerance to perfusional disturbances is related to its duration, which can determine the progression of the ischemia from the core into the oligemic penumbral region. While the penumbra remains viable for some time, it is also true that the infarct core gradually expands into the ischemic penumbra (18).

Furthermore, the penumbra may rapidly become necrotic when cerebral perfusion pressure is aggravated because of conditions such as vasogenic edema and systemic hypotension, or because of factors that aggravate the flow-metabolism mismatch such as hyperglycemia and pyrexia, or stroke recurrence and pulmonary embolism.

Baron and co-workers found evidence of penumbra in about one third of cases studied between 5 and 18h after onset, and as late as 16h after symptom onset in occasional patients, suggesting that the therapeutic window may be extended in a fraction of cases at least. PET studies performed within 3h of stroke onset suggest that early thrombolysis indeed saves tissue with a CBF below a critical threshold of 12 ml/100 g/min (19).

According to Muir et al. (13), currently accepted operational criteria for defining the penumbra are: hypoperfusion <20 ml/100 g per min; abnormal neuronal function documented by a correlation with acute clinical deficit; physiological and/or biochemical characteristics consistent with cellular dysfunction but not death; uncertain fate; salvage of this tissue correlated with better clinical recovery.

Thus, mapping the penumbra in the individual patient should make it possible to design a rational stroke patient management programme. This goal could indeed be achieved by restoring perfusion in the ischemic tissue with recombinant tissue plasminogen activator (rt-PA) and by preventing secondary events, including hyperglycemia, pyrexia, hypoxia, systemic hypotension, stroke recurrence and pulmonary embolism.

Imaging studies, using various techniques, have established the clinical importance of penumbral salvage, showing a clear association between the volume of the penumbra not progressing to infarction and the improvement in neurological scores (14,20-23).

Following major technological advances over the past 15 years, imaging can now characterize brain structure and the pathological status of established lesions, brain perfusion, intracranial and extracranial vascular pathology (including direct visualization of the clot), tissue viability, and metabolic state, thereby bringing complex physiological concepts into everyday clinical practice (24).

Identifying and quantifying the ischemic penumbra with MRI, x-ray-CT and PET is a fast-developing area with broad implications for the future of acute stroke care, because it is widely agreed that acute stroke therapies should target this potentially salvageable tissue. PET and diffusion/perfusion MRI (DWI, PWI) were correlated to determine the accuracy of the DWI/PWI mismatch in identifying the penumbra. Not surprisingly, it was observed that the mismatch overestimated the extent of penumbral tissue; accordingly it should be seen only as an approximation of the ischemic penumbra (25).

Several studies have compared DWI/PWI to quantitative PET imaging of flow and oxygen consumption, which "shaped the concept underlying modern acute stroke imaging and remains the gold standard" (13), in order to validate the DWI/PWI mismatch pattern as a surrogate for the PET-based discrimination of irreversibly damaged, penumbral and hypoperfused tissue; in short, testing this notion not at patient level, where studies are showing general agreement, but on a voxel-by-voxel basis, where biological and individual heterogeneity is more identifiable. The notion that the DWI lesion contains the ultimately infarcted tissue with false-positive prediction of up to 25% (26,27) and that the mismatch overestimates the penumbra as defined by increased oxygen extraction fraction, extending into considerable areas with non-critical oligemia (28), was supported by further investigations (29).

In particular, advanced MRI techniques have the potential to identify patients who are optimal candidates for reperfusion therapies in longer time windows (21,30-37).

A PWI/DWI mismatch has been proposed as a surrogate for the ischemic penumbra, and patients with a mismatch

are hypothesized to be more likely to benefit from early reperfusion than patients with other MRI patterns (22,31,33-35,37).

Recently, in the DEFUSE study, Albers and colleagues looked at whether previously established MRI profiles can identify stroke patients who show a robust clinical response after early reperfusion (treated 3 to 6 hours after symptom onset). They concluded that in stroke patients treated 3 to 6 hours after onset, baseline MRI findings can identify subgroups likely to benefit from reperfusion therapies and can potentially identify subgroups that are unlikely to benefit or that may be harmed (38).

Between 20 and 30% of patients who are denied thrombolysis on the basis of mild or rapidly improving stroke symptoms have a poor outcome (39-41).

These patients present a therapeutic dilemma because current guidelines do not recognize them as candidates for thrombolysis (36,37,42,43). This underlines the importance of a case-based as opposed to a symptom-based approach when selecting patients with persistent cerebral hypoperfusion for thrombolysis treatment (13) to prevent stroke progression. A marked neurological deficit is an important criterion for thrombolysis in the presence of cerebral infarction, to avoid intracerebral hemorrhage. However, the absence of structural brain lesions reduces the risk of bleeding and may even allow an extension of the 3h therapeutic window for thrombolysis. Clinical trials are needed to address these issues (43).

A more precise identification of the ischemic penumbra will likely encompass quantification of absolute diffusion and perfusion values that will then be related to ultimate tissue outcome after therapy. Hopefully, in the near future, imaging identification of ischemic penumbra will guide acute stroke therapy, targeting the patients most likely to respond to treatment.

Last but not least, it should be remarked that several trials have been conducted to visualize neuron-specific injury in cerebrovascular disease, using ^{11}C flumazenil for PET and ^{123}I-iomazenil for SPECT. These tracers bind selectively to the central benzodiazepine receptor which is purely neuronal. The accumulation of these ligands in ischemic areas is indicative of tissue viability, whereas a reduction of uptake indicates the existence of neuron-specific injury (44-46). It has been shown that in patients with acute ischaemic stroke (47) irreversibly damaged cortex can be reliably detected in the first hours after onset of symptoms by a sharp decrease in the binding of the ^{11}C-labeled flumazenil. Heiss et al. (48) have reported that the findings of FMZ binding combined with measures of perfusion can be used to identify various cortical subcompartments in acutely ischemic tissue, which may or may not benefit from active treatment. Furthermore, Heiss et al. (49) compared MRI DWI and flumazenil–PET and found that they are comparable in predicting the probability of ischemic cortical infarction, whereas FMZ–PET carries a lower probability of false-positive prediction.

Two conclusions can be drawn. First, the number of patients who are appropriately treated for acute ischemic stroke is startlingly low (only 3-5% of patients with stroke) and effective treatments are having only a minor impact on this major public health problem; against that, modern, and now widely available, imaging techniques, including MR, CT, SPECT and PET, could (detecting an ischemic penumbra) identify a large proportion of patients as suitable for therapy well beyond the traditional therapeutic windows.

Second, the identification of a penumbra offers the possibility to exploit a series of therapeutic interventions. Weinberger summarizes a series of observations and concepts: thrombolytic therapy does not interfere with the ischemic cascade directly, but changes the cellular and molecular environment that induces it (50). New therapies based on an understanding of the complex interactions of the ischemic cascade may eventually extend the therapeutic window in which the penumbra can be salvaged and provide direct neuroprotection.

After years of limited success, the results of recent studies have revived interest in the perspectives of neuroprotective stroke therapy. Schabitz and Fisher recently outlined in a review how a neuroprotective candidate drug should be developed, beginning with a thorough preclinical evaluation according to the STAIR (Stroke Therapy Academic Industry Roundtable) criteria (51).

As seen in the treatment of other CNS diseases, particularly multiple sclerosis, stroke therapy is moving towards the “cocktail treatment” strategy, the aim being to address the different pathophysiological aspects of the neuronal damage related to the penumbra.

In practice, numerous experimental treatments are being tested for safety and efficacy. Systemic thrombolysis does not always result in complete recanalization, with rates varying between 20 and 66%. Even if recanalization is achieved with rt-PA, reocclusion with neurological deterioration can occur in more than 30% of treated patients. New agents should be employed as adjuncts to thrombolytic therapy. Combination treatment with a thrombolytic therapy and neuroprotective drugs might improve stroke outcomes. One might envisage a prophylactic treatment for patients at risk of ischemic stroke, either to extend the window for thrombolytic efficacy or to reduce the damaged area. In particular the prevention of oxidative damage with free radical trapping agents may be effective. A combination treatment could reduce the damage due to ischemia, as well as the reperfusion injury, which may be caused by the deleterious effects of oxygen radical species following reperfusion. The STAIR-V conference, held to discuss relevant issues relating to acute stroke drug development and regulatory approval (52), concluded that while the development and approval of additional pharmacological therapies for acute ischemic stroke remain complex and challenging areas, efforts to develop additional stroke treatments will require adaptation and improvement of the design and implementation of clinical trials, greater cooperation among the parties involved, and greater awareness of regulatory requirements and changes in the regulatory process. The traditional approach to acute stroke clinical trial design has presented problems at a number of levels. Research questions must now be prioritized. New approaches to trial design are needed. The stroke research community must address the problems of slow recruitment into clinical trials and multiple competing trials. Surrogate markers, especially imaging, must be validated and combination therapies developed.

Finally, licensing agencies must work with the stroke community and recognize the unique challenges presented by acute stroke trial design, which may warrant a different regulatory approach from other disease processes. The requirements of device trials are now impacting on trial methodology and will be the topic of a future STAIR conference. Finally, there is a need to move from the concept that "time is brain" to the concept that "physiology is brain" (53), and the penumbra is the part of the brain we should be most concerned with. In the meantime, as pointed out by Ehlers and colleagues, while a high-quality thrombolysis treatment with 24-hour in-house neurology coverage and MRI might not be cost-effective in the short term compared with conservative treatment, in the long term it could result in large-scale reductions in health spending (54).

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