**Neuroimaging of the ischaemic penumbra**

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**Summary**


As ischaemic stroke is no longer considered a fatal or catastrophic disease with no or little therapeutic possibilities, it is indispensable to demonstrate the target for any intervention. This target is the ischaemic penumbra, which is considered to be tissue at risk of undergoing infarction if nothing is done acutely within the time window. This penumbra has varied in its definition over the last few decades but now an operational model based on new magnetic resonance imaging or computed tomography techniques has emerged. The proposed model is the diffusion-perfusion mismatch, where the central diffusion lesion represents the infarcted core which is surrounded by an area of diminished perfusion. This model shows progression of the DWI lesion into the periinfarct hypoperfusion and is reversed in case of successful intervention such as thrombolysis.

**Keywords:** stroke; penumbra; magnetic resonance imaging; diffusion; perfusion; cerebral blood flow

**Introduction**

Ischaemic stroke is now to be considered an emergency since thrombolysis at least when performed intravenously is now an accepted standard of care if a patient arrives at the hospital within the therapeutic window [1–4]. Also it is believed that intravenous thrombolysis might represent an even more powerful approach to patients with the acute onset of neurological symptoms due to cerebrovascular diseases. When considering the middle cerebral artery territory, the therapeutic window in the acute stage is of approximately 3 hours, whereas in the posterior vertebrobasilar circulation is somewhat longer, up to 9 to 12 hours.

The ischaemic penumbra corresponds to an ischaemic brain region in a state of diminished cerebral blood flow that has not yet led to complete infarction and is potentially salvageable: it has been believed to be situated between the thresholds for functional impairment and morphologic damage and it is considered to be a dynamic process [5]. While its exact definition has varied over the years, the ischaemic penumbra is accepted as being the therapeutical target.

Conventional imaging techniques were in the beginning unable to reliably demonstrate the penumbra. This was initially done with nuclear medicine tracer techniques.

The penumbra in humans has traditionally been studied by nuclear medicine brain perfusion techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) [6], but recently magnetic resonance imaging (MRI) techniques have also allowed us to gain insight into the mechanisms underlying ischaemia. Cerebral blood flow techniques such as PET and SPECT have been shown to correlate with clinical outcome [7, 8] and have been used with success for clinical trials [9]. Traditionally, based on those cerebral blood flow studies, the ischaemic penumbra has been defined as tissue with flow within the thresholds for maintenance of function and morphologic integrity. Tissues with a relative cerebral blood flow (CBF) of less than 12 mL/100 g/min were found to infarct, with zones having an rCBF between 12 and 22 mL/100 g/min being unstable and corresponding to the penumbral region. Reduced CBF can
be associated with preserved or higher CMRO\textsubscript{2}, corresponding to the state of misery perfusion which in part represents the penumbra [10]. The penumbra has recovery potential and is therefore the target for interventional therapy in acute ischaemic stroke. In cats, using PET, it was found that the penumbra represented a dynamic state in which ischaemic changes could occur for up to 24 hours after onset [11], and some studies even stipulated that viable tissue could be found up to 48 hours within an ischaemic region [12]. This among other things has brought people to question the concept of a rigid therapeutic window in cerebral ischaemia [13]. However, despite these data it seems important to know that apparently early flow disturbances leading to rapid cellular damage are the major contributor to infarction, meaning that therapy should be targeted to the initially hypoperfused regions [14]. More importantly it has been demonstrated that functional imaging could represent a correlator for functional recovery after stroke [15] or thrombolysis [16].

With drastic advances in both MR and CT technology it is now feasible to acutely image these patients.

**CT-based techniques**

Computed tomography had previously been used mainly to demonstrate cerebral haemorrhage, be it parenchymal or subarachnoid. However, due to an increase in its capacity to demonstrate small changes in tissue density, CT has evolved into a very powerful tool. While it has been used as the tool to demonstrate the absence of blood in the big thrombolysis trials, it has also been shown to be able to reliably demonstrate the presence of acute ischaemic changes in the human brain. Indeed, early signs corresponding to acute ischaemic signs can be demonstrated with great accuracy by experienced readers [17–23]. With new advancements in CT technology, CT perfusion is now also a reality [24, 25], with algorithms being developed that will allow to demonstrate the penumbra [26].

**MR-based techniques**

Conventional MR techniques, using T\textsubscript{2}-weighted images, were insufficient to demonstrate early ischaemic changes: these were only seen after 8 to 12 hours after onset of symptoms [27–30]. Also one main problem has been the controversy regarding its capacity to demonstrate haemorrhage, which now seems to be resolved with the advent of fast gradient-echo techniques [31–33]. Also the development of further techniques such as fast contrast-enhanced MR angiography now allows to completely investigate the vascular tree from the aortic arch to the circle of Willis [34]. All these advances have now permitted to develop stroke imaging protocols that allow imaging of pathology, pathophysiology and haemodynamics in less than 20 minutes [35, 36].

Le Bihan et al. developed diffusion imaging, wherein a pair of diffusion sensitising gradients are placed in a spin-echo sequence [37, 38]. This renders the sequence and its subsequent images extremely sensitive to water. Initially these sequences were performed using traditional techniques and were thus inherently extremely sensitive to patient motion also. This, in addition to the acquisition length was a major problem rendering its implementation extremely difficult clinically. However, the development of clinically available echo-planar imaging has allowed to speed up imaging and to produce clinically useful images to be acquired in less than a second [39].

In addition to this, perfusion imaging of the brain was also allowed to develop along with the development of echo-planar MRI. Indeed the T\textsubscript{2}*-sequences that are needed require strong gradients and fast imaging in order to be performed many times over many repetitions in a relatively short time [40–42].

Further less well-explored methods are spectroscopy and magnetoencephalography [43].

Based on an abundant animal literature demonstrating the use of diffusion end perfusion techniques in acute stroke [44–48], DWI was applied with great success in the setting of human ischaemic stroke by Warach et al. [49–54]. At first they had done this with a turbo-STEAM technique [49], but they then went over to multi-slice whole-brain echo-planar diffusion imaging which enabled them to cover the whole brain in 30 seconds.

Perfusion imaging also allowed to reliably demonstrate surrounding areas of hypoperfused brain tissue [55, 56], especially when combined with DWI [57].

The combination of perfusion and diffusion images obtained during the same session enabled Warach et al. to report their findings on the penumbra in the acute human setting of ischaemic stroke [58, 59] and thus establishing the mismatch concept. They found acute hyperintensities on the DWI images with a maximal b value that represented the acute ischaemic lesion. These DWI lesions were found to correspond to a decrease in the apparent diffusion coefficient in the affected cerebral tissue [60]. While the DWI lesion itself is very suggestive
of a stroke, it is often insufficient to alone postulate viable tissue [61, 62] outside the central core. When they additionally applied perfusion imaging, they were able to determine the presence of a very often larger area of perfusion deficit surrounding the acute DWI lesion [63]. This area of peri-infarction hypoperfusion corresponds to their model of penumbral tissue. While it is true that the earlier imaging is performed, the more there is growth in absence of therapy of the DWI lesion, there is a strong correlation between the DWI lesion volume and clinical status and outcome as well as with the final lesion volume [64]. Therefore, despite there being some controversy as to what is exactly measured with the acute DWI lesion, it does correspond to what will constitute the late ischaemic lesion on follow-up T2 imaging (usually at 3 months). There is also a very strong correlation between variation in lesion size and variation in clinical status as Baird et al. were able to demonstrate [65]. This has been studied further [66–70]. Liu et al. demonstrated a strong correlation between the MR penumbra and the SPECT findings, strengthening the hypothesis with a well-established method of cerebral blood flow measurement [71]. Based on this model Wu et al. were able to predict local tissular outcome based on a model of DWI–PWI mismatch [72].

The question of lesion reversibility was raised early on and many observers had reported lesions that did not remain on follow-up images. Also, animal studies of stroke using DWI had demonstrated it to be associated with thresholds of reversibility [46–48]: indeed, the apparent diffusion coefficient (ADC), when it was below a certain threshold, corresponds to definitively infarcted tissue, whereas above it a tendency to reversal was to be found. Rings of onion-shaped ADC values seem to surround the central ischaemic lesion seen on DWI: therefore a better delimitation of the ischaemic core can be done by also taking the ADC maps into account in calculating the penumbra [73]. Also in animal models where ischaemia was successfully treated ADC decreases were found to normalise. In the human setting this has been observed albeit less often: indeed, after ultra-early thrombolysis we can observe that the acute DWI lesions will tend to reverse even completely [74–78]. Thrombolysis will reverse the hypoperfusion abnormality and even the central diffusion defect [79].

This can probably be improved by additionally performing measurements of the stroke with diffusion tensor imaging. Indeed, there is a change in anisotropy in the early stages of ischaemia [80]. It is very probable that DTI will allow us to demonstrate early changes in the penumbra that are less evident on the DWI maps or on the ADC maps [81–83].

Conclusions

Due to major technological advances, i.e. echoplanar imaging in MRI and multi-slice technology in CT, it is now possible to perform extremely fast perfusion imaging of the brain in patients with acute stroke.

When considering MR imaging, its advantages are the following: the acute diffusion image shows us the presence of a clearly visible lesion that lights up (the light bulb effect as described initially by Koroshetz and Gonzalez), along with the automatically generated ADC maps (on newer generation machines) that also allow us to assess the extent of ischaemic disease. Measuring the ADC allows us to get an idea about the depth of ischaemia in the penumbral tissue itself and to obtain data regarding tissue viability.

CT technology, however, is showing to be of great promise due to its ability to deliver reliable perfusion maps acutely. Nevertheless, the occasional lack of a clearly visible lesion on the unenhanced CT that would rival the light bulb effect of diffusion imaging is a major drawback. The capacity of MRI to quantify the extent of the lesion or the depth of ischaemia with DWI is also unrivalled by CT techniques at the moment.

References


