Magnetic resonance imaging of the ischaemic penumbra

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Summary

Acute cerebral ischaemia should no longer be considered a tragic untreatable event but a medical emergency. To be able to start therapy, imaging is needed to assess the presence of a potential penumbra, i.e. an area of the brain which is hypoperfused but not yet definitively infarcted. With the development of diffusion and perfusion MR techniques, the concept of a penumbra model has been developed in which it corresponds to the acute mismatch between diffusion and perfusion volumes. This penumbra should constitute the target for potential therapies.

Key words: penumbra; ischaemia; stroke thrombolysis; magnetic resonance imaging; diffusion; perfusion

Introduction

Acute ischaemic stroke is increasingly considered a medical emergency. Treatment modalities such as intra-arterial or intravenous thrombolysis have proved of therapeutic value, with decreased mortality and morbidity if treatment is started early within the so-called “therapeutic window” [1–6]. It is therefore increasingly important to have methods available which make it possible to establish early diagnosis. The aim of early imaging should be to (1) rule out haemorrhage, (2) demonstrate signs of early ischaemia in order to start or stop thrombolysis, and (3) detect underlying vascular disease.

Computed tomography has traditionally been used to demonstrate intracerebral haemorrhage; it has also shown itself well suited to detecting early signs of acute ischaemia due to increased water content in the affected tissue. Magnetic resonance techniques have evolved with the development of fast imaging techniques, and diffusion-weighted [7–9] and perfusion MR imaging [10–18] have now been introduced clinically. Thus, MR imaging can now fully assess the brain in cases of acute stroke: conventional T1 and T2 images are able to visualize the anatomy and presence of any chronic lesions, MR angiography to demonstrate the underlying vascular pathology and DWI to detect an area of tissue damage due to hypoperfusion which will be further assessed by perfusion imaging. A full vascular imaging protocol is thus usually possible in less than 30 minutes. Diffusion-weighted MRI involves modification of a spin-echo sequence [19] where the image is rendered sensitive to the motion of water in the tissue examined: in the acute phase of stroke a redistribution of water occurs with vasogenic oedema causing a local decrease in diffusion which is seen as a high signal on diffusion images (DWI) but corresponds to a fall in the local apparent diffusion coefficient (ADC) [20]. Perfusion imaging is usually done with exogenous contrast, and in ischaemia a decrease in perfusion is observed in the affected region.
The ischaemic penumbra

The target of reperfusion therapy in acute stroke is ischaemic brain tissue which will not survive without reperfusion. Such tissue is functionally impaired but morphologically intact; it corresponds to the ischaemic penumbra, which is thought to be situated between the thresholds of electrophysiological dysfunction and of tissue damage [21–23]. Its exact definition has somewhat varied over time, initially relating to a physiological and functional entity, but now more to a haemodynamic one. Its volume and extent may also vary with time. A firm definition of brain tissue at risk from hypoperfusion is, therefore, hardly possible and must rely on functional tests such as measurement of cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT), and assessment of irreversible tissue injury. The chances of reperfusion therapy are greater if treatment is initiated early (time is brain) and the volume of irreversibly injured brain tissue is relatively small compared with that of functionally impaired tissue. Nevertheless, many attempts have been made via imaging to assess the tissue at risk from hypoperfusion. Traditionally the penumbra in humans has been studied by radionuclide techniques for brain perfusion imaging such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) [24], but recently magnetic resonance imaging (MRI) techniques have also provided insight into the mechanisms underlying ischaemia. Radionuclide cerebral blood flow imaging techniques such as PET and SPECT have been shown to correlate with clinical outcome [25, 26] and have been used with success in clinical trials [27]. On the basis of these cerebral blood flow studies, the ischaemic penumbra has traditionally been defined as tissue with flow within the thresholds of function maintenance and morphological integrity. Tissues with a relative cerebral blood flow below 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 may be associated with preserved or higher CMRO2, corresponding to the state of misery perfusion which in part represents the penumbra. The penumbra has recovery potential and therefore is the target for interventional therapy in acute ischaemic stroke. In cats PET has shown that the penumbra represents a dynamic state in which ischaemic changes may occur for up to 24 hours after onset, and some studies have even reported finding viable tissue for up to 48 hours within an ischaemic region. This, among other things, has led people to question the concept of a rigid therapeutic window in cerebral ischaemia [28]. The concept in use today is the diffusion-perfusion mismatch described on MR imaging [29–34]: there is an initial lesion seen on the diffusion image which is surrounded by an area of hypoperfusion: this area around the diffusion defect corresponds to the penumbra (Figure 1). Further new models based on CT have been proposed [35, 36].

Figure 1
Patient with signs of acute cerebral ischaemia. The CT shows a dense middle cerebral artery. MR imaging was performed which shows no signs of major infarction on T2-weighted MRI. The perfusion image shows a large area of hypoperfusion in the middle cerebral artery territory. The diffusion images show an area of smaller diffusion defects.

The ischaemic brain in magnetic resonance imaging

Diffusion imaging with MRI
Conventional magnetic resonance imaging using standard sequences (T1-, T2-weighted imaging) is unreliable in the first hours after onset of symptoms, i.e. within the therapeutic time window [37–40], but the development of diffusion-weighted imaging has changed this [41–43]: new reports appear to show this to be a new
method allowing detection of early ischaemic lesions [8, 9].

On the basis of animal experiments it was initially accepted that the high signal on diffusion-weighted imaging (DWI) corresponded to a decrease in the local ADC [41–44]. However, further studies in humans have shown inconsistent results after initial reports on the acute decrease in ADC values [45, 46].

It is generally accepted that signal changes appear on T2-weighted imaging relatively late after focal ischaemia and represent irreversible damage. The increase in signal on T2-weighted spin echo sequences and the corresponding decrease on T1-weighted sequences mainly represent tissue water uptake and may indicate ischaemic oedema or – later – ischaemic necrosis. These signal changes appear hours after stroke onset and are, therefore, irrelevant for acute stroke treatment. MR images, however, that have been specifically sensitized to the translational diffusion of water (DWI images) may reveal tissue contrast based on properties essentially very different from those demonstrated by standard sequences.

Within a few minutes of onset of focal ischaemia the ADC decreases by 30–50%, while T2- and T1-weighted MR images remain normal [47, 48]. DWI remains unchanged until CBF is reduced to 15–20 mL/100 g/min [98]. However, others have observed a decrease in the ADC as early as a CBF of 40 mL/100 g/min and lower [49]. In the experimental animal the signal intensity ratio (DWI intensity in the affected region divided by the contralateral brain region) on DWI increases gradually about 2.5 minutes after the onset of severe global cerebral ischaemia and recovers following 60 minutes of ischaemia when reperfusion had been initiated [48]. This time-course is consistent with the complete loss of tissue adenosine triphosphate, breakdown of the sodium and potassium membrane pump, and consequent cellular oedema in severely ischaemic brain tissue [50]. It has been shown that the area with increased signal on DWI precisely indicates the area with depletion of ATP [51], and that the induction of cellular oedema by other means than focal ischaemia will also cause a fall in the ADC [52]. It is clear from these observations in experimental animals that DWI is a highly sensitive means of detecting brain areas with ATP depletion and consequently at high risk of irreversible injury.

In stroke patients, brain tissue with a high signal on DWI and/or with a low ADC represents tissue that is either going to die [53] or brain tissue that may recover with reperfusion [54]. A direct comparison between ADC and the histopathology of ischaemic brain tissue shows that DWI is the best predictor of ischaemic damage among different MRI techniques and that a severely decreased ADC is associated with most severe tissue damage.

Measurements of the ADC in animals have shown that ADC values may correspond to thresholds above which tissue is still not irreversibly damaged [54]. While some reports have found that the ADC corresponds to reperfusion after thrombolysis [54], some newer studies appear partly to challenge this [55–57].

While the changes we see early on may not have been fully elucidated, it has been proved that early changes observed in patients do tend to evolve towards ischaemic lesions, and that the early lesions correlate well with the late T2-weighted infarcts [58], even though there may be initial lesion growth [59].

Also, evidence has recently emerged that not all the high signal observed on DWI may correspond to irreversibly damaged tissue, and that the penumbra may acutely be inside a high DWI signal [54, 60] and not only outside this region in the mismatch. Further advances, such as diffusion ten-
sor imaging, may provide a better definition of the penumbra [61, 62], since it has been shown that in early ischaemia anisotropy changes [63].

**MR perfusion imaging**

Bolus passage of paramagnetic contrast material allows rapid imaging of the related magnetic field disturbances; with the passage of contrast, a decrease in signal is observed on the primary $T2^*$ images. MR perfusion rests on the measurement of changes in the local magnetic field induced by paramagnetic effects of contrast materials [10]. Its application to cerebral perfusion is now well established [11]. However, T2 methods are usually used in routine practice, while T1 imaging may be of greater advantage since there is no extreme signal drop as the in $T2^*$-weighted imaging [12]: the higher contrast on $T2^*$ imaging is preferable for acute clinical evaluation, where a strong contrast is necessary, but T1 would provide more accurate assessment of perfusion changes, especially in the penumbra. The deconvolution method should allow accurate measurements, but is at the moment far too dependent on the choice and placement of the area for the input function to be repeated [13, 14]: indeed, there is no consensus on where to place the region of interest corresponding to the input function. Perfusion imaging then makes it possible to acquire maps of mean transit time (MTT), relative cerebral blood volume ($rCBV$) and relative cerebral blood flow ($rCBF$). A comparison with SPECT in volunteers has yielded favourable results [15]. Consequently, the use of qualitative perfusion MRI in cerebral ischaemia is well established both in animal models [16] and in the human situation [17, 18]. The presence and capacity of collaterals is a critical point in the appraisal of patients with acute stroke. Perfusion techniques may demonstrate the presence of residual flow due to collateralisation over the circle of Willis. The presence and capacity of superficial pial collaterals may not be assessed completely because of the very low blood flow velocity.

**MRI of the penumbra**

Diffusion-weighted MRI initially demonstrates what is believed to constitute the initial central ischaemic core, and this central area of diffusion abnormality is often surrounded by a larger area of hypoperfused brain tissue; it is thought that parts at least of the DWI lesion correspond to irreversibly infarcted brain tissue, whereas the penumbra is situated in the area surrounding it (the so-called diffusion-perfusion mismatch) [29]. It has been demonstrated that without treatment infarcts tend to grow in this area of potential penumbra [18, 30, 31], and the subsequently infarcted tissue defines the definitive penumbra: follow-up imaging remains a necessity in order to study these conditions [32]. This was determined by Karonen et al., who performed a confirmatory study by comparing DWI/PWI studies with SPECT data from a collective of patients with stroke: as expected, they found that combined DWI and PWI could predict infarct enlargement in acute stroke, and that PWI can detect hypoperfused brain tissue in good agreement with SPECT in acute stroke [33, 34].

It has been shown that there is a progressive increase in ADC values when moving from the center of the DWI lesion core to its periphery, meaning that there is a dynamic transition in acute stroke thresholds. This can be seen as the presence of concentric onion-shaped regions of differing level of ischaemia [64].

In previous animal studies it has been shown that acute ischaemia, characterised by a fall in the ADC and high intensity on DWI images, may reverse under therapy. In the setting of human stroke, Marks and colleagues have found that DWI
revealed early reperfusion in 5/6 patients who had undergone iv tPA therapy [65]. Kidwell et al. confirmed these findings by demonstrating a decrease in infarct size, as determined by DWI, when comparing lesions before and after intra-arterial thrombolysis [60]. Lansberg et al. reported a case in which recanalisation led to normal DWI values in reperfused areas [66]. Schellinger was able to demonstrate that early recanalisation achieved by thrombolysis can save tissue at risk, if present, and may result in significantly smaller infarcts and a significantly better outcome [67, 68].

Results of the Bern group

Having previously determined that DWI was a sensitive tool for the detection of acute ischaemia [9] and that the mismatch was of clinical importance in acute evaluation of these patients [58, 59], we decided to embark on further investigation of the penumbral state with DWI, postulating that information regarding the state of cerebral perfusion could be obtained within the acutely obtained ADC maps.

We had indeed recently studied a series of 19 patients out of 107 treated acutely with intra-arterial thrombolysis in 1998 (n = 48) and 1999 (n = 59) in our Stroke Unit (11 men, 8 women; ages 35 to 85 years with symptoms compatible with supratentorial middle cerebral artery territory ischaemic stroke and who were treated within 6 hours of onset of symptoms) [62]. Clinically they were assessed in the acute stage by the Scandina-
vian Stroke Scale Score (SSSS) and the outcome was determined by the Barthel index. Local intra-arterial thrombolysis (LIF) was performed by the transfemoral approach: one million units of urokinase were delivered over one hour close to or in the thrombus itself. Selective internal carotid biplane digital subtraction angiography was performed both before and after LIF in order to compare the result of the therapy and to establish vessel patency. DWI was performed and ADC values were subsequently calculated from pixel-by-pixel ADC maps. We found no haemorrhagic complications due to intra-arterial thrombolysis. It was noted that there were two groups of patients according to angiographic criteria: those with angiographic recanalisation of more than 50% (n = 9) and those with less than 50% recanalisation. All patients with more than 50% angiographic recanalisation (9 cases) were found to have a clinical outcome defined by a Barthel score of 80 or more.

In the group of patients with less than 50% recanalisation (10 cases) there were two groups, the majority (8 cases) of whom had a Barthel score of 50 or lower and in two cases in which we found less than 50% recanalisation there was a better outcome with Barthel scores of 100 each and recanalisation of more than 50% with a higher rADC value. For both angiographic groups there is an initial decrease in the ADC with values of 429–1305 mm²/sec (within 12 hours: 429–610 mm²/sec) for the recanalisation group and 373–1120 mm²/sec (within 12 hours: 397–502 mm²/sec) for the less recanalised group. Accordingly, for both angiographic groups there is an initial decrease in the relative ADC with values of 0.45–1.37 (within 12 hours: 0.45–0.64) for the recanalisation group and 0.39–1.17 (within 12 hours: 0.42–0.53) for the less recanalised group. It can thus be seen that DWI demonstrates areas of reperfusion [54].

**Discussion**

With new MR techniques such as DWI and perfusion imaging we can now investigate acute cerebral human ischaemia. This is of major importance not only for scientific reasons but to equip us adequately to take the necessary measures if a stroke is suspected. The methods are sensitive for the detection of ischaemic changes which can be shown to be partly reversible both inside and outside the diffusion defect. While this haemodynamic model of the penumbra is somewhat different from the classical metabolic penumbra first described, the new model applies to the clinical situation. Also, the two models certainly overlap: in the first, classical model we have neurons situated between electrical silence and cell death, whereas in the MR imaging-based model we have neurons situated outside (but partly inside the core defined by DWI) and in an area of surrounding hypoperfusion. What has been common to both definitions is that there seem to be thresholds in the acutely ischaemic tissue and that these can be defined by many new parameters. With imaging methods we only indirectly reflect the classically defined electrophysiological changes, but we are able to define, at least in part, the central core (with diffusion imaging) and the hypoperfused area around it. Moreover, CT-perfusion imaging is able to extrapolate a penumbra by applying perfusion parameters to

**Figure 6**

Reversible lesion after intra-arterial thrombolysis. MRI performed acutely shows (upper row) the presence of a hyperintensity on DWI (left image) corresponding to a decrease in ADC and changes in the time to peak values. After successful intra-arterial thrombolysis (lower row) the DWI changes tend to diminish whereas the perfusion deficit is absent.
the affected area. Depending on the size, time interval and the type of diffusion-perfusion mismatch, it seems that we can now more successfully determine which patients are good candidates for thrombolytic treatment. Indeed, whenever imaging is performed early on it appears that the acute mismatch is greater and therefore the potential therapeutic gain more marked. Also, if we see an area of perfusion equivalent to or smaller that the diffusion defect, we may think that reperfusion has at least partly occurred and that these patients may not benefit as much from therapy. What we can tell from ADC mapping is that the state of ischaemia is not absolute but a progressive ongoing one in which various levels of ischaemia are present both inside and outside the central core. Thus, probably both inside and outside the DWI defect, we can find tissue which is doomed and tissue which can be saved.

This once more raises the problem of ischaemic thresholds: indeed, it seems that brain tissue, while very sensitive to ischaemia, is able to tolerate it to some degree for a short time: with DWI, and especially ADC mapping, it is now possible to determine the degree of ischaemia and to establish whether the tissue in question has reached the point of no return. This seems to occur at ADC levels of 70% and below. Indeed, we have seen – as others have also done – that DWI and especially ADC maps do indirectly or directly reflect the status of perfusion in the brain. Because the first DWI images are much less able to differentiate reversible from irreversible lesions based on imaging criteria alone, it is always necessary to study the ADC maps and also to further refine the potential technological arsenal we possess.

To better evaluate these changes we can now perform additional new studies, such as MR spectroscopy or diffusion tensor imaging, to assess the metabolic state or the anisotropy inside the ischaemic lesion.

This should enable us to define more precisely the area at risk of undergoing further infarction and to study the dynamics of the penumbra.

One central problem when confronted with acute MR imaging is its feasibility on a regular basis in the emergency situation. While MR techniques such as DWI and PWI are fairly firmly established in the literature as equivalent or superior to CT [70, 71], few studies have attempted to assess their real feasibility [71]. While most studies are favourable, the situation in the real world is often somewhat less simple. Indeed, these studies have very often been performed in well-equipped university centres by highly motivated young academic stroke specialists, who have personally performed the investigations for the purpose of gathering this new data. Also, conducting studies on a 24-hour service basis can be extremely difficult: the patient population affected by acute cerebral ischaemia very often has many co-morbidities such as myocardial disease, and may frequently have cardiac pacemakers rendering MR imaging impossible. The MR environment itself can be very unsettled since it may induce claustrophobia: this could however be avoided by the use of open magnets with lower fields [72] (possible since diffusion-weighted imaging is done irrespective of field strength). Also, very often, there is no technical staff on call or, when there is, it can be difficult to perform the whole protocol. However, with newer and faster sequences and with more patient- and technician-friendly MR systems being developed, it is today possible to perform a total MR stroke protocol in less than 20 minutes, comprising T1, T2, gradient echo images (to exclude haemorrhage), MR angiography as well as DWI and PWI sets. These sequences can be performed nowadays simply by pushing a button.Computed tomography, since no extra precautions are needed by staff because of the high magnetic fields, still offers the advantage that the gantry can be very easily and promptly accessed by staff and medical teams (anaesthesiology, neurology, neuroradiology). However, we believe that with increased awareness of stroke as an acute medical emergency the problems outlined above will be overcome.

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