Peer reviewed article

Magnetic resonance imaging of the ischaemic penumbra

Karl-Olof Lövblad[a], Marwan El-Koussy[a], Helmut Oswald[b], Alison E. Baird[c], Gerhard Schroth[a], Heinrich Mattle[d]

[a] Department of Neuroradiology, Inselspital, University of Bern, Switzerland
[b] T-Systems, Bern, Switzerland
[c] Department of Neurology, Inselspital, Bern, Switzerland
[d] Stroke Neuroscience Unit, NINDS, Bethesda, Maryland, USA

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 tissular 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.

This research is supported by a grant from the Swiss National Science Foundation (3100–66348.01).

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].

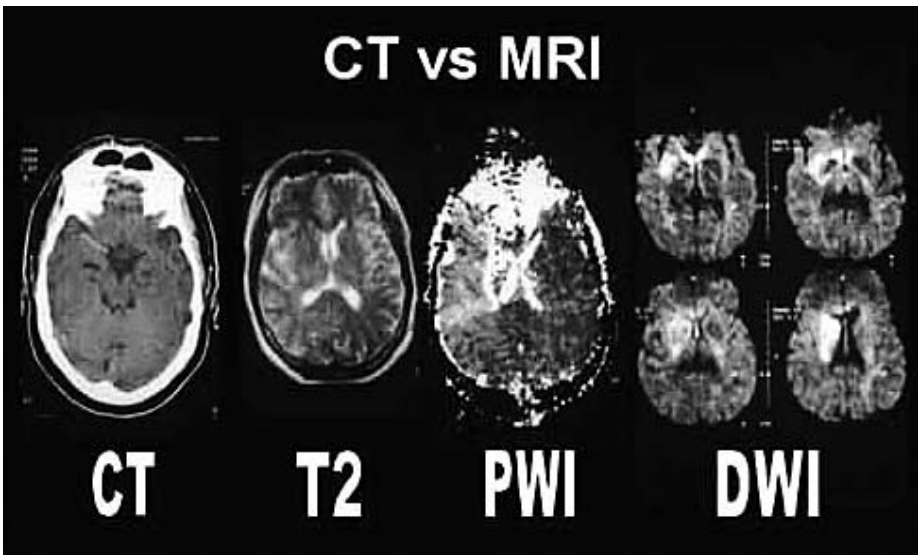


Figure 1

Patient with signs of acute cerebral ischaemia. The CT shows a dense middle cerebral artery. MR imaging was performed whch 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 l esions [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^{-1} × min^{-1} [98]. However, others have observed a decrease in the ADC as early as a CBF of 40 mL × 100 g^{-1} × min^{-1} 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-

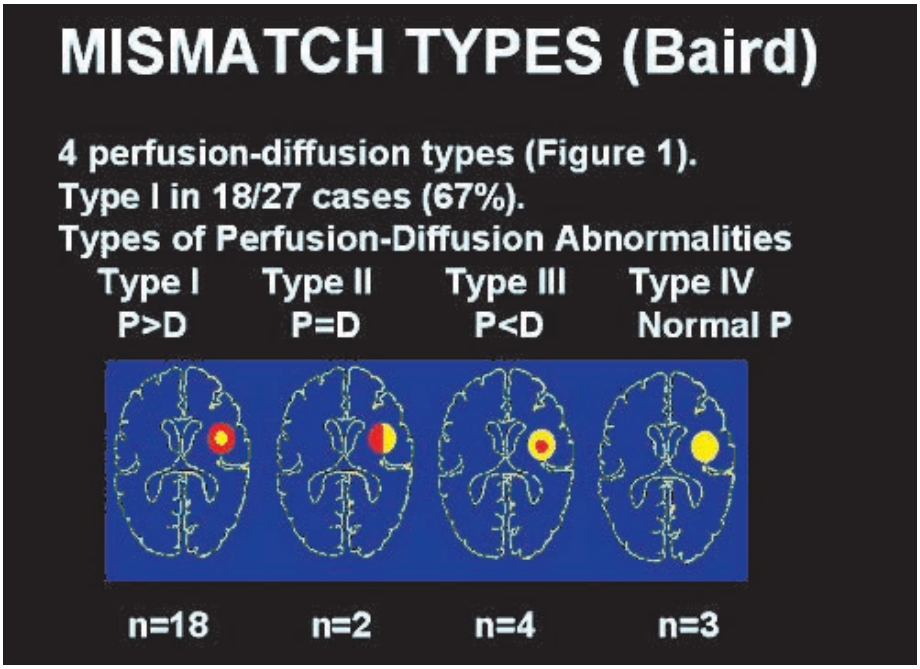


Figure 2

Mismatch types as defined by diffusion and perfusion MR imaging in a series of patients studied by Baird et al. There are mainly four possible types, the most frequent being where the central ischaemic core is the diffusion defect which is surrounded by a larger area of hypoperfusion.

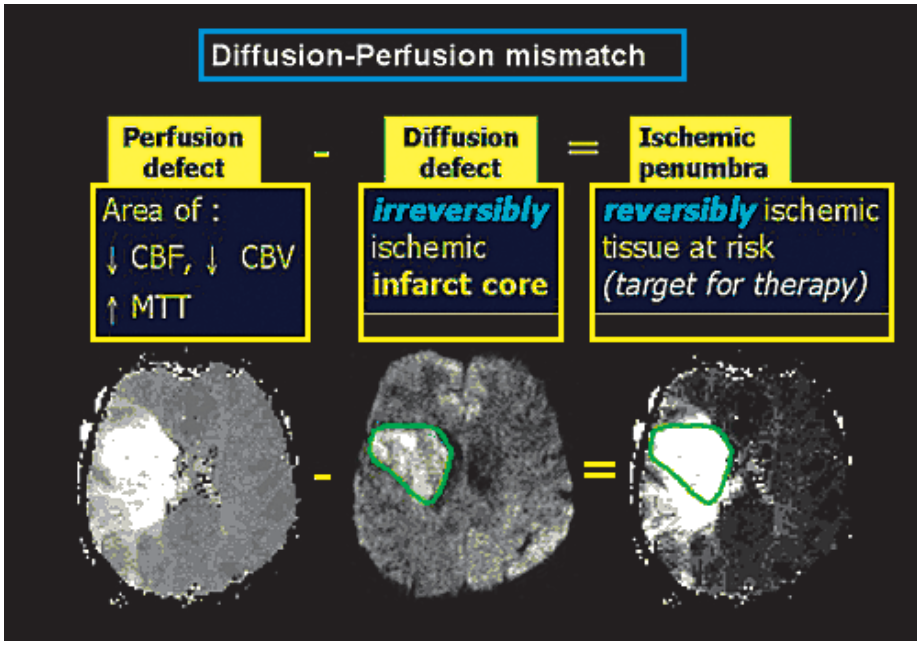


Figure 3

The mismatch concept. The central diffusion area is subtracted from the hypoperfused area's volume; the periphery corresponds to the potential penumbra.

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

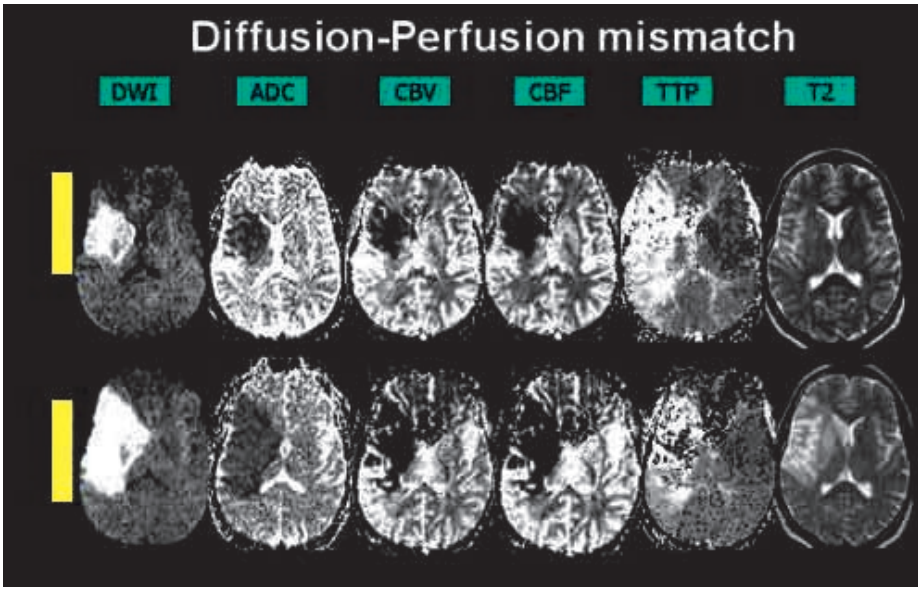


Figure 4

49-year old male with left-sided weakness. The diffusion image shows an area of hyperintensity in the MCA territory on the right side, surrounded by a larger area of hypoperfusion. The next MRI shows lesion growth into the surrounding area: the penumbra has demonstrated progredient ischaemia.

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-

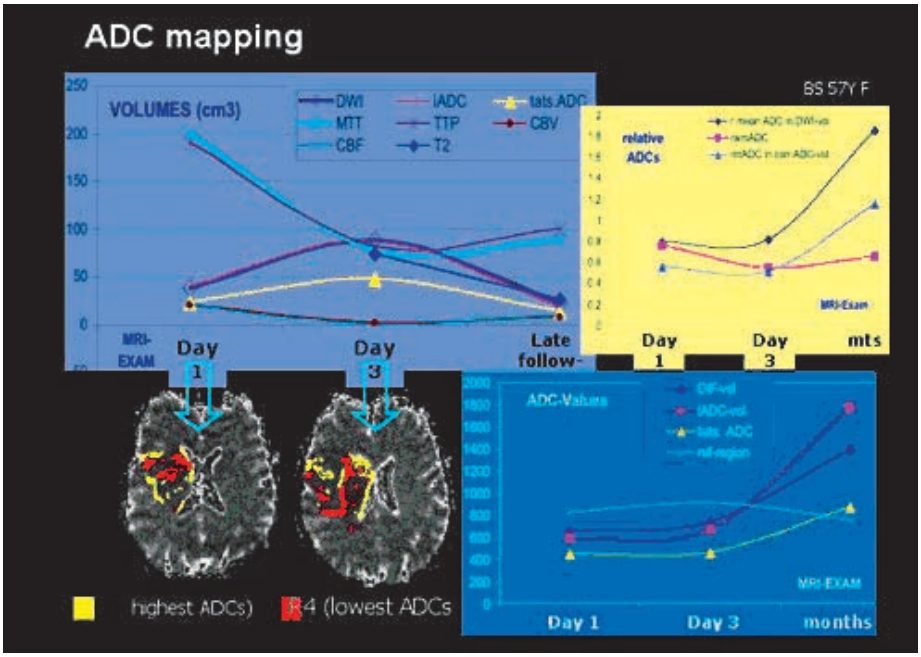


Figure 5

ADC mapping of the penumbra: in the penumbra there are onion-shaped areas of different ADC values with increasing values from the centre of the lesion towards the periphery.

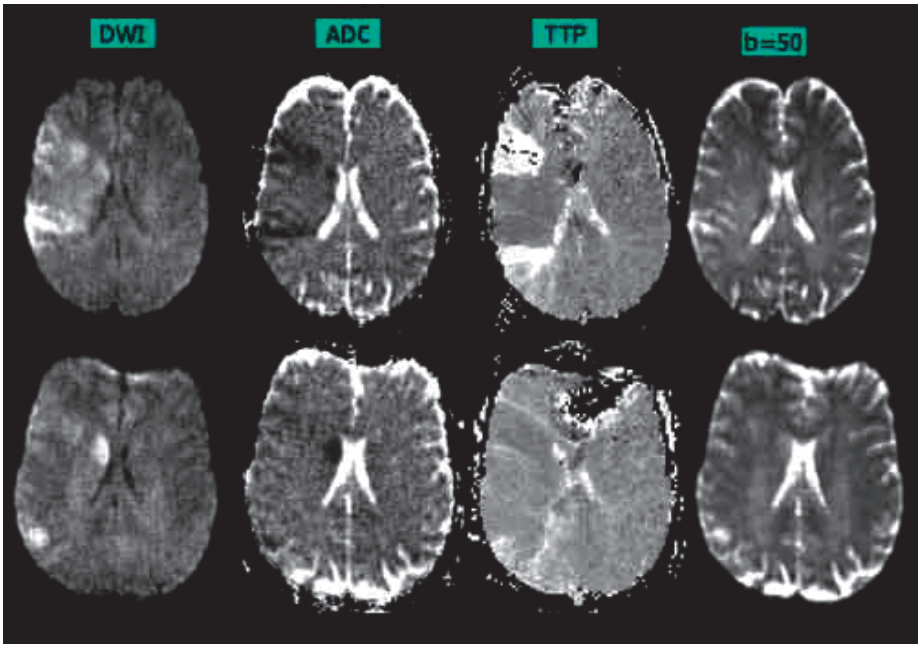


Figure 6

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.

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 thombolysis. 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 mm^2/sec (within 12 hours: 429–610 mm^2/sec) for the recanalisation group and 373–1120 mm^2/sec (within 12 hours: 397–502 mm^2/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

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 unsettling 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.

Correspondence:
PD Dr med Karl-Olof Lövblad
Neuroradiologie
Radiodiagnostic et radiologie interventionnelle
Hôpital Cantonal Universitaire HUG
24 rue Micheli-du-Crest
CH-1211 Genève 14
E-Mail: Karl-Olof.Lovblad@hcuge.ch

References

1 The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischaemic stroke. N Engl J Med 1995;333:1581–7.

2 Gonner F, Remonda L, Mattle H, Sturzenegger M, Ozdoba C, Lovblad KO, et al. Local intra-arterial thrombolysis in acute ischaemic stroke. Stroke 1998;29:1894–900.

3 Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischaemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA 1999;282:2003–11.

4 Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA 1995; 274:1017–25.

5 Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, Diez-Tejedor E, Trouillas P. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352(9136):1245–51.

6 Baron JC, von Kummer R, del Zoppo GJ. Treatment of acute ischaemic stroke: Challenging the concept of a rigid and universal time-window. Stroke 1995;26: 2219–21.

7 Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. Radiology 1986;161: 401–7.

8 Warach S, Gaa J, Siewert B, Wielopolski P, Edelman R. Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. Ann Neurol 1995;37: 231–41.

9 Lövblad K, Laubach H, Baird A, Curtin F, Schlaug G, Edelman R, Warach S. Clinical experience with diffusion-weighted MR in patients with acute stroke. AJNR Am J Neuroradiol 1998;19: 1061–6.

10 Rosen BR, Belliveau JW, Vevea JM, Brady TJ. Perfusion imaging with NMR contrast agents. Magn Reson Med 1990;14(2): 249–65.

11 Rosen BR, Belliveau JW, Chien D. Perfusion imaging by nuclear magnetic resonance. Magn Reson Q 5(4):263–81.

12 Kwong KK, Chesler DA, Weisskoff RM, Donahue KM, Davis TL, Ostergaard L, Campbell TA, Rosen BR. MR perfusion studies with T1-weighted echo planar imaging. Magn Reson Med 1995;34(6):878–87.

13 Ostergaard L, Weisskoff RM, Chesler DA, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part I: Mathematical approach and statistical analysis. Magn Reson Med 1996;36(5): 715–25.

14 Ostergaard L, Sorensen AG, Kwong KK, Weisskoff RM, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part II: Experimental comparison and preliminary results. Magn Reson Med 1996;36(5):726–36.

15 Wirestam R, Ryding E, Lindgren A, Geijer B, Ostergaard L, Andersson L, Holtas S, Stahlberg F. Regional cerebral blood flow distributions in normal volunteers: dynamic susceptibility contrast MRI compared with 99mTc-HMPAO SPECT. J Comput Assist Tomogr 2000;24(4):526–30.

16 Rohl L, Sakoh M, Simonsen CZ, Vestergaard-Poulsen P, Sangill R, Sorensen JC, et al. Time evolution of cerebral perfusion and apparent diffusion coefficient measured by magnetic resonance imaging in a porcine stroke model. J Magn Reson Imaging 2002;15(2):123–9.

17 Karonen JO, Ostergaard L, Vainio P, Partanen K, Vanninen R, Vanninen E, et al. Diffusion and perfusion MR imaging in acute ischaemic stroke: a comparison to SPECT. Comput Methods Programs Biomed 2001;66(1):125–8.

18 Sorensen AG, Copen WA, Ostergaard L, Buonanno FS, Gonzalez RG, Rordorf G, Rosen BR, Schwamm LH, Weisskoff RM, Koroshetz WJ. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean tissue transit time. Radiology 1999;210(2):519–27.

19 Stejskal EO, Tanner JE. Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. J Chem Phys 1965;242:288 .

20 Weber J, Mattle HP, Heid O, Remonda L, Schroth G. Diffusion-weighted imaging in ischaemic stroke: a follow-up study. Neuroradiology 2000;42(3):184–91.

21 Heiss WD. Ischaemic penumbra: evidence from functional imaging in man. J Cereb Blood Flow Metab 2000;20(9):1276–93.

22 Heiss WD, Emunds HG, Herholz K.Cerebral glucose metabolism as a predictor of rehabilitation after ischaemic stroke. Stroke 1993;24(12):1784–8.

23 Baird AE, Austin MC, McKay WJ, Donnan GA. Changes in cerebral tissue perfusion during the first 48 hours of ischaemic stroke: relation to clinical outcome.J Neurol Neurosurg Psychiatry 1996;61(1):26–9.

24 Heiss WD, Grond M, Thiel A, von Stockhausen HM, Rudolf J, Ghaemi M, et al. Tissue at risk of infarction rescued by early reperfusion: a positron emission tomography study in systemic recombinant tissue plasminogen activator thrombolysis of acute stroke. J Cereb Blood Flow Metab 1998;18(12):1298–307.

25 Baron JC, Bousser MG, Rey A, Guillard A, Comar D, Castaigne P. Reversal of focal "misery-perfusion syndrome" by extra-intracranial arterial bypass in haemodynamic cerebral ischaemia. A case study with 15O positron emission tomography. Stroke 1981;12(4):454–9.

26 Heiss WD, Graf R, Wienhard K, Lottgen J, Saito R, Fujita T, et al. Dynamic penumbra demonstrated by sequential multitracer PET after middle cerebral artery occlusion in cats. J Cereb Blood Flow Metab 1994;14(6):892–902.

27 Heiss WD, Huber M, Fink GR, Herholz K, Pietrzyk U, Wagner R, Wienhard K.Progressive derangement of periinfarct viable tissue in ischaemic stroke. J Cereb Blood Flow Metab 1992; 12(2):193–203.

28 Baron JC, von Kummer R, del Zoppo GJ. Treatment of acute ischaemic stroke. Challenging the concept of a rigid and universal time window. Stroke 1995;26(12):2219–21.

29 Warach S, Wielopolski P, Edelman RR. Identification and characterization of the ischaemic penumbra of acute human stroke using echo planar diffusion and perfusion imaging. In: Proceedings of the 12th annual meeting of the Society of Magnetic Resonance in Medicine, Berkeley, Ca, 1993: 263.

30 Schlaug G, Benfield A, Baird A, Siewert B, Lövblad K, Parker R, et al. The ischaemic penumbra of human stroke: using functional MRI parameters to define tissue at risk for infarct progression. Neurology 1999;53:1528 –37.

31 Rordorf G, Koroshetz WJ, Copen WA, Cramer SC, Schaefer PW, Budzik RF Jr, et al.Time course of lesion development in patients with acute stroke: serial diffusion- and haemodynamic-weighted magnetic resonance imaging. Stroke 1998;29(11): 2268–76.

32 Schwamm LH, Koroshetz WJ, Sorensen AG, Wang B, Copen WA, Budzik R, et al. Regional ischaemia and ischaemic injury in patients with acute middle cerebral artery stroke as defined by early diffusion-weighted and perfusion-weighted MRI. Stroke 1998;29(5):939–43.

33 Karonen JO, Liu Y, Vanninen RL, Ostergaard L, Kaarina Partanen PL, Vainio PA, et al. Combined perfusion- and diffusion-weighted MR imaging in acute ischaemic stroke during the 1st week: a longitudinal study. Radiology 2000;217(3):886–94.

34 Karonen JO, Vanninen RL, Liu Y, Ostergaard L, Kuikka JT, Nuutinen J, et al. Combined diffusion and perfusion MRI with correlation to single-photon emission CT in acute ischaemic stroke. Ischaemic penumbra predicts infarct growth. Stroke 1999;30(8):1583–90.

35 Wintermark M, Reichhard M, Cuisenaire O, Maeder P, Thiran JP, Schnyder P, et al. Comparison of admission perfusion computed tomography and qualitative diffusion and perfusion-weighted magnetic resonance imaging in acute stroke patients. Stroke 2002;33:2025–31.

36 Wintermark M, Reichhart M, Thiran JP, Maeder P, Chalaron M, Schnyder P, et al. Prognostic accuracy of cerebral blood flow measurement by perfusion computed tomography, at the time of emergency room admission, in acute stroke patients. Ann Neurol 2002;51(4):417–32.

37 Yuh W, Crain M, Loes D, Greene G, Ryals T, Sato Y. MR imaging of cerebral ischaemia: Findings in the first 24 hours. AJNR Am J Neuroradiol 1991;12:621–9.

38 Kertesz A, Black S, Nicholson L, Carr T. The sensitivity and specificity of MRI in stroke. Neurology 1987;37:1580–5.

39 Bryan N, Levy L, Whitlow W, Killian J, Preziosi T, Rosario J. Diagnosis of acute cerebral infarction: Comparison of CT and MR Imaging. AJNR Am J Neuroradiol 1991;12: 611–20.

40 Mohr J, Biller J, Hilal S, Yuh W, Tatemichi T, Hedges S, et al. Magnetic resonance versus computed tomographic imaging in acute stroke. Stroke 1995;26:807–12.
41 Dardzinski BJ, Sotak CH, Fisher M, Hasegawa Y, Li L, Minematsu K. Apparent diffusion coefficient mapping of experimental focal cerebral ischaemia using diffusion-weighted echo-planar imaging. Magn Reson Med 1993:318–25.
42 Minematsu K, Fisher M, Li L, Davis MA, Knapp AG, Cotter RE, et al. Effects of a novel NMDA antagonist on experimental stroke rapidly and quantitatively assessed by diffusion-weighted MRI. Neurology 1993;43:397–403.
43 Hasegawa Y, Fisher M, Latour LL, Dardzinski BJ, Sotak CH. MRI diffusion mapping of reversible and irreversible injury in focal brain ischaemia. Neurology 1994;44:1484–90.
44 Takano K, Carano RAD, Tatlisumak T, Meiler M, Stoka CH, Kleinert HD, Fisher M. Efficacy of intra-arterial and intravenous prourokinase in an embolic stroke model evaluated by diffusion-perfusion magnetic resonance imaging. Neurology 1998;50: 870–5.
45 Schlaug G, Siewert B, Benfield A, Edelman RR, Warach S. Time course of the apparent diffusion coefficient (ADC) abnormality in human stroke. Neurology 1997;49:113–9.
46 Weber J, Mattle HP, Heid O, Remonda L, Schroth G. Diffusion-weighted imaging in ischaemic stroke: a follow-up study. Neuroradiology 2000;42:184–91.
47 Kuroiwa T, Nagaoka T, Ueki M, Yamada I, Miyasaki N, Akimoto H. Different apparent diffusion coefficient. Water content correlations of gray and white matter during early ischaemia. Stroke 1998;29:859–65.
48 Busza A, Allen K, King M, van Bruggen N, Williams S, Gadian D. Diffusion-weighted imaging studies of cerebral ischaemia in gerbils. Potential relevance to energy failure. Stroke 1992;23: 1602–12.
49 Wang Y, Hu W, Perez-Trepichio A, Ng T, Furlan A, Majors A, Jones S. Brain tissue sodium is a ticking clock telling time after arterial occlusion in rat focal cerebral ischaemia. Stroke 2000; 31:1386–92.
50 Mintorovitch J, Yang G, Shimizu H, Kucharczyk J, Chan P, Weinstein P. Diffusion-weighted magnetic resonance imaging of acute focal cerebral ischaemia: Comparison of signal intensity with changes in brain water and Na^+, K^+-ATPase activity. J Cereb Blood Flow Metab 1994;14:332–6.
51 Back T, Hoehn-Berlage M, Kohno K, Hossmann K. Diffusion NMR imgaging in experimental stroke: Correlation with cerebral metabolites. Stroke 1994;25:494–500.
52 Benveniste H, Hedlund L, Johnson G. Mechanism of detection of acute cerebral ischaemia in rats by diffusion-weighted magnetic resonance microscopy. Stroke 1992;23:746–54.
53 Oppenheim C, Samson Y, Manai R, Lalam T, Vandamme X, Crozier S, et al. Prediction of malignant middle cerebral artery infarction by diffusion-weighted imaging. Stroke 2000;31: 2175–81.
54 Taleb M, Lövblad KO, El-Koussy M, Guzman R, Bassetti C, Oswald H, et al. Reperfusion demonstrated by ADC mapping after intra-arterial thrombolysis for human ischaemic stroke confirmed by cerebral angiography. Neuroradiology 2001;43: 591–4.
55 Oppenheim C, Grandin C, Samson Y, Smith , Duprez T, Marsault C, Cosnard G. Is There an Apparent Diffusion Coefficient Threshold in Predicting Tissue Viability in Hyperacute Stroke? Stroke 2001;32:2486.
56 Ringer TM, Neumann-Haefelin T, Sobel RA, Moseley ME, Yenari MA. Reversal of early diffusion-weighted magnetic resonance imaging abnormalities does not necessarily reflect tissue salvage in experimental cerebral ischaemia. Stroke 2001; 32(10):2362–9.
57 Grant PE, He J, Halpern EF, Wu O, Schaefer PW, Schwamm LH, et al. Frequency and clinical context of decreased apparent diffusion coefficient reversal in the human brain. Radiology 2001;221(1):43–50.
58 Lovblad KO, Baird AE, Schlaug G, Benfield A, Siewert B, Voetsch B, et al. Ischaemic lesion volumes in acute stroke by diffusion-weighted magnetic resonance imaging correlate with clinical outcome. Ann Neurol 1997;42(2):164–70.
59 Baird AE, Benfield A, Schlaug G, Siewert B, Lovblad KO, Edelman RR, Warach S. Enlargement of human cerebral ischaemic lesion volumes measured by diffusion-weighted magnetic resonance imaging. Ann Neurol 1997:41(5):581–9.
60 Kidwell CS, Saver JL, Mattiello J Starkman S, Vinuela F, Duckwiler G, et al. Thrombolytic reversal of acute human cerebral ischaemic injury shown by diffusion/perfusion magnetic resonance imaging. Ann Neurol 2000:47:462–9.
61 Lovblad KO: DTI in neuropsychiatric disorders. Eur Psychiatry 2002;17;1:48.
62 Lövblad KO, Federspiel A, Oswald H, Kiefer C, Schroth G, Mattle H. Diffusionstensorbildgebung der ischämichen Penumbra. Schweiz Med Forum 2002;41:982–5.
63 Sorensen AG, Wu O, Copen WA, Davis TL, Gonzalez RG, Koroshetz WJ, et al. Human acute cerebral ischaemia: detection of changes in water diffusion anisotropy by using MR imaging. Radiology 1999;212(3):785–92.
64 El-Koussy M, Lövblad KO, Kiefer C, Arnold M, Wels T, Zeller O, et al. Apparent diffusion coefficient mapping of infarcted tissue and the penumbra in acute stroke Neuroradiology 2002;44:812–8.
65 Marks MP, Tong DC, Beaulieu C, Albers GW, de Crespigny A, Moseley ME. Evaluation of early reperfusion and IV tPA therapy using diffusion- and perfusion-weighted MRI. Neurology 1999;52:1792–8.
66 Lansberg MG, Tong DC, Norbash AM, Yenari MA, Moseley ME. Intra-arterial rtPA treatment of stroke assessed by diffusion- and perfusion-weighted MRI. Stroke 1999;30;678–80.
67 Schellinger PD, Jansen O, Fiebach JB, Heiland S, Steiner T, Schwab S, et al. Monitoring intravenous recombinant plasminogen activator thrombolysis for acute ischaemic stroke with diffusion and perfusion MRI. Stroke 2000;31:1318–28.
68 Jansen O, Schellinger P, Fiebach J, Hacke W, Sartor K. Early recanalisation in acute ischaemic stroke saves tissue at risk defined by MRI. Lancet 1999;12;353(9169):2036–7.
69 Schellinger PD, Fiebach JB, Jansen O, Ringleb PA, Mohr A, Steiner T, et al. Stroke magnetic resonance imaging within 6 hours after onset of hyperacute cerebral ischaemia. Ann Neurol 2001;49(4):460–9.
70 Schellinger PD, Jansen O, Fiebach JB, Hacke W, Sartor K. A standardized MRI stroke protocol: comparison with CT in hyperacute intracerebral haemorrhage. Stroke 1999;30(4):765–8.
71 Schellinger PD, Jansen O, Fiebach JB, Pohlers O, Ryssel H, Heiland S, et al. Feasibility and practicality of MR imaging of stroke in the management of hyperacute cerebral ischaemia. AJNR Am J Neuroradiol 2000;21(7):1184–9.
72 Mehdizade A, Somon T, Wetzel S, Kelekis A, Martin JB, Scheidegger JR, et al. Diffusion weighted MR imaging on a low-field open magnet.J Neuroradiol 2003;30(1):25–30.

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

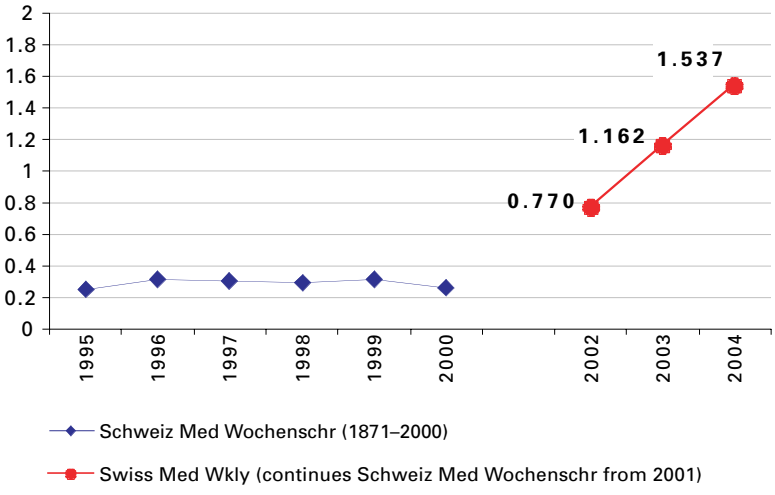
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch