Neuroimaging of the ischaemic penumbra

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Summary

Lövblad K-O. Neuroimaging of the ischaemic penumbra. Schweiz Arch Neurol Psychiatr 2004; 155:309–14.

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 intra-arterial 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

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1 Karl-Olof Lövblad is supported by a grant from the Swiss National Science Foundation (Grant 3100-066348.01).

be associated with preserved or higher CMRO2, 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_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_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 T_2 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. echo-planar 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 penumbra 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

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

2 Gonner F, Remonda L, Mattle H, Sturzenegger M, Ozdoba C, Lövblad KO, et al. Local intra-arterial thrombolysis in acute ischemic 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 ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA 1999;282:2003–11.

4 Arnold M, Nedeltchev K, Sturzenegger M, Schroth G, Loher TJ, Stepper F, et al. Thrombolysis in patients with acute stroke caused by cervical artery dissection: analysis of 9 patients and review of the literature. Arch Neurol 2002;59:549–53.

5 Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia – the ischemic penumbra. Stroke 1981;12:723–5.

6 Heiss WD. Ischemic penumbra: evidence from functional imaging in man. J Cereb Blood Flow Metab 2000;20:1276–93.

7 Heiss WD, Emunds HG, Herholz K. Cerebral glucose metabolism as a predictor of rehabilitation after ischemic stroke. Stroke 1993;24:1784–8.

8 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;61:26–9.

9 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;18:1298–307.

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

11 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;14:892–902.

12 Heiss WD, Huber M, Fink GR, Herholz K, Pietrzyk U, Wagner R, et al. Progressive derangement of periinfarct viable tissue in ischemic stroke. J Cereb Blood Flow Metab 1992;12:193–203.

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

14 Heiss WD, Thiel A, Grond M, Graf R. Which targets are relevant for therapy of acute ischemic stroke? Stroke 2000;31:984–6.

15 Herholz K, Heiss WD. Functional imaging correlates of recovery after stroke in humans. J Cereb Blood Flow Metab 2000;20:1619–31.

16 Alexandrov AV, Grotta JC, Davis SM, Lassen NA. Brain SPECT and thrombolysis in acute ischemic stroke: time for a clinical trial. J Nucl Med 1996;37:1259–62.

17 von Kummer R, Bourquain H, Bastianello S, Bozzao L, Manelfe C, Meier D, et al. for the ECASS II Group. Early prediction of irreversible brain damage after ischemic stroke by computed tomography. Radiology 2001;219:95–100.

18 von Kummer R, Meyding-Lamadé U, Forsting M, Rosin L, Rieke K, Hacke W, et al. Sensitivity and prognostic value of early computed tomography in middle cerebral artery trunk occlusion. AJNR Am J Neuroradiol 1994;15:9–15.

19 Unger E, Littlefield J, Gado M. Water content and water structure in CT and MR signal changes: possible influence in detection of early stroke. AJNR Am J Neuroradiol 1988;9:687–91.

20 Rieth KG, Fujiwara K, Di Chiro G, Klatzo I, Brooks RA, Johnston GS, et al. Serial measurements of CT attenuation and specific gravity in experimental cerebral edema. Radiology 1980;135:343–8.

21 von Kummer R, Allen KL, Holle R, Bozzao L, Bastianello S, Manelfe C, et al. Acute stroke: usefulness of early CT findings before thrombolytic therapy. Radiology 1997;205:327–33.

22 von Kummer R, Holle R, Gizyska U, Hofmann E, Jansen O, Petersen D, et al. Interobserver agreement in assessing early CT signs of middle cerebral artery infarction. AJNR Am J Neuroradiol 1996;17:1743–8.

23 Marks MP, Holmgren EB, Fox AJ, Patel S, von Kummer R, Froehlich J. Evaluation of early computed tomographic findings in acute ischemic stroke. Stroke 1999;30:389–92.

24 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;51:417–32.

25 Wintermark M, Reichhart 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.

26 Meuli RA. Imaging viable brain tissue with CT scan during acute stroke. Cerebrovasc Dis 2004;17(Suppl 3):28–34.

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

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

29 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.

30 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.

31 Patel MR, Edelman RR, Warach S. Detection of hyperacute primary intraparenchymal hemorrhage by magnetic resonance imaging. Stroke 1996;27:2321–4.

32 Linfante I, Llinas RH, Caplan LR, Warach S. MRI features of intracerebral hemorrhage within 2 hours from symptom onset. Stroke 1999;30:2263–7.

33 El-Koussy M, Guzman R, Bassetti C, Stepper F, Barth A, Lövblad KO, et al. CT and MRI in acute hemorrhagic stroke. Cerebrovasc Dis 2000;10:480–2.

34 Remonda L, Heid O, Schroth G. Carotid artery stenosis, occlusion, and pseudo-occlusion: first-pass, gadolinium-enhanced, three-dimensional MR angiography-preliminary study. Radiology 1998;209:95–102.

35 Schellinger PD, Jansen O, Fiebach JB, Hacke W, Sartor K. A standardized MRI stroke protocol: comparison with CT in hyperacute intracerebral hemorrhage. Stroke 1999;30:765–8.

36 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 ischemia. AJNR Am J Neuroradiol 2000;21:1184–9.

37 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.

38 Le Bihan D. Theoretical principles of perfusion imaging application to magnetic resonance imaging. Invest Radiol 1992;27:6–11.

39 Edelman RR, Wielopolski P, Schmitt F. Echo-planar MR imaging. Radiology 1994;192:600–12.

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

41 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;36:715–25.

42 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;36:726–36.

43 Kamada K, Saguer M, Moller M, Wicklow K, Katenhauser M, Kober H, et al. Functional and metabolic analysis of cerebral ischemia using magnetoencephalography and proton magnetic resonance spectroscopy. Ann Neurol 1997;42:554–63.

44 Moseley ME, Cohen Y, Mintorovitch J, Chileuitt L, Shimizu H, Kucharczyk J, et al. Early detection of regional cerebral ischemia in cats: comparison of diffusion- and T_2-weighted MRI and spectroscopy. Magn Reson Med 1990;14:330–46.

45 Dardzinski BJ, Sotak CH, Fisher M, Hasegawa Y, Li L, Minematsu K. Apparent diffusion coefficient mapping of experimental focal cerebral ischemia using diffusion-weighted echo-planar imaging. Magn Reson Med 1993;30:318–25.

46 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.

47 Hasegawa Y, Fisher M, Latour LL Dardzinski BJ, Sotak CH. MRI diffusion mapping of reversible and irreversible injury in focal brain ischemia. Neurology 1994;44:1484–90.

48 Takano K, Carano RAD, Tatlisumak T, Meiler M, Stoka CH, Kleinert HD, et al. Efficacy of intra-arterial and intravenous prourokinase in an embolic stroke model evaluated by diffusion-perfusion magnetic resonance imaging. Neurology 1998;50:870–5.

49 Warach S, Chien D, Li W, Ronthal M, Edelman RR. Fast magnetic resonance diffusion-weighted imaging of acute stroke. Neurology 1992;42:1717–23.

50 Chien D, Kwong KK, Gress DR, Buonanno FS, Buxton RB, Rosen BR. MR diffusion imaging of cerebral infarction in humans. AJNR Am J Neuroradiol 1992;13:1097–102.

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

52 Warach SJ, Dashe JF, Edelman RR. Clinical outcome in ischemic stroke predicted by early diffusion-weighted and perfusion magnetic resonance imaging: a preliminary analysis. J Cereb Blood Flow Metab 1996;16:53–9.

53 Sorensen AG, Buonano FS, Gonzalez RG, Schwamm LH, Lev MH, Huang-Hellinger FR, et al. Hyperacute stroke: evaluation with combined multisection diffusion-weighted and hemodynamically weighted echo-planar MR imaging. Radiology 1996;199:391–401.

54 Lutsep HL, Albers GW, DeCrespigny A, Kamat GN, Marks MP, Moseley ME. Clinical utility of diffusion-weighted magnetic resonance imaging in the assessment of ischemic stroke. Ann Neurol 1997;41:574–80.

55 Edelman RR, Siewert B, Darby DG, Thangaraj V, Nobre AC, Mesulam MM, et al. Qualitative mapping of cerebral blood flow and functional localization with echo-planar MR imaging and signal targeting with alternating radio frequency. Radiology 1994;192:513–20.

56 Sorensen AG, Copen WA, Ostergaard L, Buonanno FS, Gonzalez RG, Rordorf G, et al. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean tissue transit time. Radiology 1999;210:519–27.

57 Ostergaard L, Sorensen AG, Chesler DA, Weisskoff RM, Koroshetz WJ, Wu O, et al. Combined diffusion-weighted and perfusion-weighted flow heterogeneity magnetic resonance imaging in acute stroke. Stroke 2000;31:1097–103.

58 Warach S, Wielopolski P, Edelman RR. Identification and characterization of the ischemic 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. p. 263.

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

60 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.

61 Lövblad KO, Laubach HJ, Baird AE, Curtin F, Schlaug G, Edelman RR, et al. Clinical experience with diffusion weighted MR in patients with acute stroke. AJNR Am J Neuroradiol 1998;19:1061–6.

62 Lövblad KO, Jakob PM, Baird AE, Laubach HJ, Straub LJ, Weber J, et al. Imagerie fonctionelle de diffusion par résonance magnétique nucléaire dans l'accident vasculaire cérébral aigu. Schweiz Arch Neurol Psychiatr 1997;148:143–51.

63 Baird AE, Benfield A, Schlaug G, Siewert B, Lövblad KO, Edelman RR, et al. Enlargement of human cerebral ischemic lesion volumes measured by diffusion-weighted magnetic resonance imaging. Ann Neurol 1997;41:581–9.

64 Lövblad KO, Baird AE, Schlaug G, Benfield A, Siewert B, Voetsch B, et al. Ischemic lesion volumes in acute stroke by diffusion-weighted magnetic resonance imaging correlate with clinical outcome. Ann Neurol 1997;42:164–70.

65 Baird AE, Lövblad KO, Dashe JF, Connor A, Burzynski C, Schlaug G, et al. Clinical correlations of diffusion and perfusion lesion volumes in acute ischemic stroke. Cerebrovasc Dis 2000;10:441–8.

66 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 hemodynamic-weighted magnetic resonance imaging. Stroke 1998;29:2268–76.

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

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

69 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 ischemic stroke. Ischemic penumbra predicts infarct growth. Stroke 1999;30:1583–90.

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

71 Liu Y, Karonen JO, Vanninen RL, Ostergaard L, Roivainen R, Nuutinen J, et al. Cerebral hemodynamics in human acute ischemic stroke: a study with diffusion- and perfusion-weighted magnetic resonance imaging and SPECT.
J Cereb Blood Flow Metab 2000;20:910–20.

72 Wu O, Koroshetz WJ, Ostergaard L, Buonanno FS, Copen WA, Gonzalez RG, et al. Predicting tissue outcome in acute human cerebral ischemia using combined diffusion- and perfusion-weighted MR imaging.
Stroke 2001;32:933–42.

73 El-Koussy M, Lövblad KO, Kiefer C, Zeller O, Arnold M, Wels T, et al. Apparent diffusion coefficient mapping of infarcted tissue and the ischaemic penumbra in acute stroke.
Neuroradiology 2002;44:812–8.

74 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.

75 Kidwell CS, Saver JL, Mattiello J, Starkman S, Vinuela F, Duckwiler G, et al. Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging.
Ann Neurol 2000;47:462–9.

76 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.

77 Schellinger PD, Jansen O, Fiebach JB, Heiland S, Steiner T, Schwab S, et al. Monitoring intravenous recombinant plasminogen activator thrombolysis for acute ischemic stroke with diffusion and perfusion MRI.
Stroke 2000;31:1318–28.

78 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;353:2036–7.

79 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 ischemic stroke confirmed by cerebral angiography.
Neuroradiology 2001;43:591–4.

80 Sorensen AG, Wu O, Copen WA, Davis TL, Gonzalez RG, Koroshetz WJ, et al. Human acute cerebral ischemia: detection of changes in water diffusion anisotropy by using MR imaging. Radiology 1999;212:785–92.

81 Lövblad KO, El-Koussy M, Oswald H, Baird AE, Schroth G, Mattle H. Magnetic resonance imaging of the ischaemic penumbra. Swiss Med Wkly 2003;133:551–9.

82 Lövblad KO, Kiefer C, Oswald H, Arnold M, Nedeltchev K, Mattle H, et al. Imaging the ischemic penumbra.
Rivista di Neuroradiologia 2003;16:833–8.

83 Lövblad KO, Federspiel A, Oswald H, Kiefer C, Schroth G, Mattle H. Diffusionstensorbildgebung der ischämischen Penumbra. Schweiz Med Forum 2002;2:982–5.