Editorial

Mapping the ischaemic penumbra with PET: a new approach

After decades of nihilism, recent evidence indicates that neurological outcome after acute stroke can be improved through three types of measures (Brott and Bogousslavsky, 2000): (i) restoring perfusion in the ischaemic tissue with the thrombolytic agent recombinant tissue plasminogen activator (rt-PA) given intravenously within 3 h of clinical onset; (ii) preventing secondary deleterious events such as hyperglycaemia, pyrexia, hypoxia, systemic hypotension, stroke recurrence and pulmonary embolism, best achieved in specialized stroke units; and (iii) providing appropriate rehabilitation. The reperfusion strategy is based on experimental evidence in the nonhuman primate with middle cerebral artery (MCA) occlusion that, surrounding the profoundly ischaemic core of already irreversible damage, there exists an area of brain tissue (the ‘penumbra’) which, though severely ischaemic and functionally silent, can still escape infarction if perfusion is restored before a certain time has elapsed (Lassen, 1990); the penumbra has been documented in man (Baron, 1999; Heiss, 2000). Although beneficial when considering cohorts, i.v. rt-PA is hazardous in individual patients owing to the several-fold increased risk of symptomatic haemorrhagic transformation (Brott and Bogousslavsky, 2000). In addition, it is an expensive treatment which should only be used when necessary. Because of this, it would appear sensible to reserve rt-PA for those patients still having an area of critically ischaemic tissue at the time of assessment, i.e. excluding those with already completed irreversible damage due to rapid deterioration of the ischaemic tissue beyond reversibility or with already established spontaneous reperfusion (Baron et al., 1995). Interestingly, one trial (in need of replication) found that in patients selected for the presence of proximal MCA occlusion, the intra-arterial administration of another thrombolytic agent, pro-urokinase, resulted in significant and large clinical benefits even if given as late as 6 h after stroke (Furlan et al., 1999). This indicates that a proportion of the penumbra was still there long after the 3-h window in such patients, consistent with imaging studies (Marchal et al., 1996; Read et al., 2000). Clearly, if i.v. thrombolysis is to be tested beyond the 3-h time-point, the idea of selecting the appropriate patients becomes even more compelling.

One way to achieve this goal is through physiological imaging, the aim being to obtain maps of the following four tissue subtypes: (i) already irreversibly damaged (‘core’); (ii) at-risk (penumbra); (iii) mildly hypoperfused or simply autoregulated but normally not at-risk (‘oligemia’); and (iv) unaffected. To identify these tissue categories in an objective manner, however, one needs first to determine thresholds that reliably and efficiently separate them (Fig. 1). The threshold concept originates from classic experimental literature which clearly documented the existence of a penumbra threshold for cerebral blood flow (CBF) at about 22 ml/100 g/min, while the infarction threshold depended on time elapsed since arterial occlusion but tended towards the penumbra threshold for times longer than 3 h (Lassen, 1990). Hence, ever since physiological imaging applications to clinical stroke emerged, investigators have attempted to determine such thresholds (see Heiss, 2000). Recently, detailed PET studies in patients studied 5 to 18 h (mean 10 h) after onset reported a CBF penumbra threshold ~17–22 ml/100 g/min, and an infarction threshold ~7–8 ml/100 g/min and 0.87 mls/100 g/min for CBF and oxygen consumption, respectively (with no clear threshold found for other haemodynamic variables) (Furlan et al., 1996; Marchal et al., 1996, 1999). Problems with implementing this approach in the clinical realm are, however, that (i) the CBF thresholds for infarction must depend on time elapsed, but the exact relationship is unknown in man; (ii) the exact time of stroke onset can be difficult to ascertain in many patients; (iii) the CBF may be unreliable if studied alone if partial reperfusion has occurred; and (iv) although the oxygen consumption threshold is likely time-independent, this variable is presently obtainable only with PET. Although more accessible methods such as SPECT, xenon-CT and diffusion/perfusion MRI have been assessed for their ability to deliver clinically applicable penumbra and infarction thresholds, much more work is necessary to validate them (Heiss, 2000). There is thus the need to continue looking for more precise yet applicable ways to define these thresholds.

In this issue of Brain, Heiss et al. (2001) for the first time used the PET combination of 15O-water, a perfusion tracer, and 11C-labelled flumazenil (FMZ), a neuronal benzodiazepine/GABA A receptor ligand known to be a potential
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Fig. 1 Diagram illustrating the four categories of brain tissue important to distinguish with physiological imaging in acute ischaemic stroke, and the concept of absolute thresholds separating them for the variables studied (CBF = cerebral blood flow; CBV = cerebral blood volume; MTT = mean circulatory transit time; CMRO₂ = cerebral metabolic rate of oxygen; FMZ = [¹¹C]flumazenil tissue uptake). See text for details. The cursor on the right of the sliding scale indicates that unless some favourable event such as reperfusion occurs, more and more tissue will fall under the category of irreversible damage with elapsing time until all the penumbra, and potentially part of the oligaemia as well, become incorporated into the core.

marker of neuronal integrity (Sette et al., 1993). Despite the daunting complexities involved in delivering this in an emergent basis, they were able to study 10 patients within 2–12 h of onset (mean 6 h). By means of late T₂-weighted MRI, the acute-stage abnormalities in CBF and FMZ uptake were mapped against the ultimate outcome of the tissue, i.e. infarction or integrity. Using a sophisticated statistical approach based on histogram analysis, they then determined probabilistic penumbra and infarction thresholds for each one of these two parameters, and in turn, the tissue compartments referred to above. Specifically, the analysis disclosed that the penumbra threshold was best defined by CBF, and the infarction threshold by FMZ uptake. There are some limitations in this study: (i) tissue outcome may have been altered by therapy in three rt-PA treated patients included; (ii) only the cortical rim was assessable by FMZ, leaving the basal ganglia and white matter unexplored; (iii) the low unaffected-hemisphere cortical flow reported suggests that the CBF may have been underestimated, explaining the rather low penumbra CBF threshold obtained relative to previous reports; and (iv) the thresholds were derived from region-of-interest analysis, which may make them unsuitable for clinical application at the voxel level. Regardless, this study is important in that it documents that not only CBF and oxygen consumption, but also a neuronal marker such as FMZ, can be used to objectively map the tissue’s status in acute stroke.

Although only a proof-of-principle study since PET will not be clinically applicable in acute stroke in the foreseeable future, it paves the way for the other imaging methods referred to above and highlights the potential for application of SPECT radioligands.

Based on their calculations of the size of the tissue compartments, Heiss and colleagues go on to make pathophysiological interpretations that have far-reaching therapeutic implications, yet which could be contested (Heiss et al., 2001). Firstly, they consider that because only ~20% of the final infarct was penumbral at the time of assessment, only that much would be salvageable by reperfusion. However, the penumbra is likely to be much larger earlier on—which would explain the benefits from rt-PA within 3 h—and furthermore, the penumbra was as large as 55.9% individually with, in addition, the three larger fractions being observed in patients studied in the 6–11 h range (their Table 1), similar to previous findings (Marchal et al., 1996). Secondly, they consider that the small size of the subcompartment with both CBF above the penumbra threshold and FMZ above the infarction threshold that went on to infarction (median 12.9%) may explain the failure of neuroprotection trials thus far. However, this compartment was ≥45% in three patients (their Table 1), which would mean that proper case selection might reveal benefits even for neuroprotection and, furthermore, it remains to be proven that only this subcompartment would be targeted by neuroprotection alone. The demise of the oligaemic compartment might also result from secondary events such as hyperglycaemia, pyrexia, vasogenic oedema or systemic hypotension, which would explain the benefits from avoiding such complications. In addition, this tissue was defined by a
CBF higher than the penumbra threshold, but, as said above, the latter was on the low side and its accuracy will need to be tested by replicating this study. Finally, it could be argued that this hypoperfused and ultimately infarcted tissue should be embraced within the penumbra, if defined as all that tissue that has the potential of being saved from infarction. Indeed, consistent with earlier reports, this study suggests that up to 12 h after onset, on average 45% and in individual cases up to 85% of the final infarct appears still viable and therefore amenable to therapy.

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References


