Clinical review: Imaging in ischaemic stroke – implications for acute management

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Abstract

Imaging has become a cornerstone of stroke management, translating pathophysiological knowledge to everyday decision-making. Plain computed tomography is widely available and remains the standard for initial assessment: the technique rules out haemorrhage, visualizes the occluding thrombus and identifies early tissue hypodensity and swelling, which have different implications for thrombolysis. Based on evidence from positron emission tomography (PET), however, multimodal imaging is increasingly advocated. Computed tomography perfusion and angiography provide information on the occlusion site, on recanalization and on the extent of salvageable tissue. Magnetic resonance-based diffusion-weighted imaging (DWI) has exquisite sensitivity for acute ischaemia, however, and there is increasingly robust evidence that DWI combined with perfusion-weighted magnetic resonance imaging (PWI) and angiography improves functional outcome by selecting appropriate patients for thrombolysis (small DWI lesion but large PWI defect) and by ruling out those who would receive no benefit or might be harmed (very large DWI lesion, no PWI defect), especially beyond the 3-hour time window. Combined DWI–PWI also helps predict malignant oedema formation and therefore helps guide selection for early brain decompression. Finally, DWI–PWI is increasingly used for patient selection in therapeutic trials. Although further methodological developments are awaited, implementing the individual pathophysiologic diagnosis based on multimodal imaging is already refining indications for thrombolysis and offers new opportunities for management of acute stroke patients.

Introduction

In the present era of thrombolysis, of specialized acute stroke units and of endovascular and neurosurgical interventions, imaging has become a cornerstone of modern stroke management. Imaging of the ischaemic process has taken centre stage in four key areas: shaping the basic concepts of stroke pathophysiology; guiding therapeutic approaches that tackle these concepts; translating this knowledge to everyday clinical decision-making; and motivating new therapeutic developments in the field. The present review will briefly discuss these roles, focusing on recent advances in imaging that pertain to everyday practice.

Basic concepts

Following occlusion of a major intracranial artery, particularly the middle cerebral artery (MCA), a gradient of hypoperfusion emerges in the supplied basal ganglia, white matter and cortical mantle [1]. Regions suffering the most severe hypoperfusion (often in and around the sylvian fissure in proximal occlusion) rapidly progress to irreversible damage, representing the ‘ischaemic core’. This tissue exhibits very low cerebral blood flow (CBF), cerebral blood volume (CBV) and metabolic rates of oxygen and glucose [2]. The remaining hypoperfused tissue – with lost autoregulation – is pathophysiologically divided relative to a well-defined perfusion threshold into two compartments; namely, the ‘penumbra’ and the ‘oligemia’.

In the penumbra, oxygen metabolism is preserved relative to CBF, the oxygen extraction fraction is elevated and often reaches its theoretical maximum of 100% (severe ‘misery perfusion’), and the CBV is normal or elevated. Tissue within the penumbra is functionally impaired and contributes to the clinical deficit, yet is still viable and hence potentially salvageable by effective reperfusion. The extent of the penumbra, however, decreases over time by gradual recruitment into the core, and as such represents a key target for therapeutic intervention, albeit with a progressively shrinking temporal window of opportunity – hence the ‘time is brain’ rule [3]. This course of events varies from patient to patient, but up to one-third of patients still exhibit large volumes of penumbra 18 hours after stroke onset [4].

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ADC = apparent diffusion coefficient; ASPECTS = Alberta Stroke Programme Early CT Score; CBF = cerebral blood flow; CBV = cerebral blood volume; CT = computed tomography; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; MCA = middle cerebral artery; MR = magnetic resonance; MRI = magnetic resonance imaging; MTT = mean transit time; PET = positron emission tomography; PCT = perfusion computed tomography; PWI = perfusion-weighted imaging; rt-PA = recombinant tissue plasminogen activator; TTP = time to peak.
The oligaemic compartment, on the other hand, suffers a milder degree of hypoperfusion with normal oxygen consumption and with elevated CBV and oxygen extraction fraction, and is not normally at risk of infarction [4]. If the occlusion persists, however, secondary events such as systemic hypotension, intracranial hypertension or hyperglycaemia may topple this delicate balance and force the oligaemia into a penumbral state, and eventually recruitment into the necrotic core. Figure 1 illustrates these concepts.

This understanding of the pathophysiology underlies the urgency of acute stroke management and is the rationale for approaches, established or still experimental, to rescue the penumbra, such as reperfusion therapy, neuroprotection, induced arterial hypertension and oxygen therapy. Besides being instrumental in this development, imaging in the acute setting brings these physiological concepts to the bedside and aims to identify the different tissue compartments amenable to therapy and to define the potential for recovery in the individual patient.

**Imaging techniques**

**Plain computed tomography**

Despite being surpassed by magnetic resonance imaging (MRI) in versatility and image quality, plain computed tomography (CT) remains the standard tool for initial assessment in most centres because it is widely available and because the large thrombolysis trials were all CT-based [5,6]. Apart from ruling out haemorrhage, early tissue ischaemic changes can be identified by CT within 3 hours of onset in up to 75% of patients with MCA stroke [7], yet with moderate interobserver agreement depending on experience [8]. These changes comprise: tissue hypodensity, which is associated with severe reductions in CBF and CBV on perfusion imaging [9] and whose extent can predict final infarction [10]; and cortical swelling without hypodensity, which on MRI is associated with increased CBV, moderate hypoperfusion and a normal or near-normal apparent diffusion coefficient (ADC), reflecting salvageable tissue [11].

Early ischaemic changes thus include elements of both the core and the penumbra. Large parenchymal hypodensity also statistically predicts the risk of thrombolysis-associated haemorrhage, hence the widespread notion of withholding this treatment if it exceeds one-third of the MCA territory [6]. The Alberta Stroke Programme Early CT Score (ASPECTS) [7] has better interrater reliability in assessing early ischaemic changes [12], yet this is not independently associated with poor clinical outcome [13]. Since the ASPECTS combines swelling and hypodensity, it may not distinguish irreversibly damaged tissue from viable tissue. A recent study comparing CT with MRI [14] has confirmed that focal brain swelling does not always represent infarcted tissue, supporting the removal of this criterion from the ASPECTS scoring system.

An additional early CT sign in ischaemic stroke is the direct visualization of the thrombus, seen as increased attenuation in the transverse M1 segment (hyperdense MCA sign) or in cross-section within the sylvian fissure (dot sign) [15]. The specificity of these signs is high, but their sensitivity is moderate (30–40%) [16], probably because CT cannot detect fresh fibrin-poor thrombi [17]. In a general stroke population, the hyperdense MCA sign is associated with poor prognosis and a risk of thrombolysis-associated haemorrhage [18], but its resolution is associated with a favourable outcome. In patients with acute MCA occlusion, however, this sign has no independent prognostic value [19]. Equivalent signs have recently been reported on MRI [20].

Plain CT is also very sensitive to intracranial haemorrhage and subarachnoid haemorrhage. Studies using gradient-recalled echo T2* MRI, however, have shown that intracranial haemorrhage can be equally detected with very high sensitivity even by inexperienced users [21,22], and that fluid-attenuated inversion recovery (FLAIR) MRI can also demonstrate subarachnoid haemorrhage equally well [23]. These findings may support the idea of omitting CT as the initial investigation in acute stroke and proceeding directly to MRI (see below).

**Computed tomography and magnetic resonance angiography**

In the acute setting, CT or magnetic resonance (MR) angiography can determine the site of occlusion, early recanalization and the presence of abnormalities in the proximal arterial tree such as stenosis, occlusion or dissection, pertaining to
the cause of the stroke [24]. These data can usefully inform the decision to use intravenous thrombolysis or to proceed to mechanical embolectomy, for example in 'T occlusion' of the carotid termination [25,26].

Unlike CT, time-of-flight MR angiography is noninvasive, utilizing the intrinsic properties of moving blood [27]. Although less accurate than contrast-enhanced MR angiography, this makes the technique particularly appealing when combined with perfusion-weighted imaging (PWI) as it avoids the repeated use of a contrast agent.

Source images from CT angiography can themselves be used to detect areas of very low CBV, which are comparable with MRI diffusion-weighted imaging (DWI) lesions [24,28] and are predictive of subsequent infarction within 6 hours [29]. The added value is attractive, yet the technique still needs to be fully validated.

DWI remains by far the most sensitive method of detecting acute ischaemia [30,31] and can be positive a few minutes from onset [32], allowing accurate localization and subtyping of stroke. The DWI signal reflects restriction of the random motion of water in tissue and the decline of its ADC – although the exact biological correlates are not completely understood, this probably involves energy failure and subsequent cytotoxic oedema [33,34]. In combination with perfusion imaging, DWI can also be used, albeit cautiously, to define the ischaemic core and the penumbra [35] (see below).

Multimodal stroke imaging

Largely based on seminal positron emission tomography (PET) observations [3,4,36], most authorities nowadays consider that the heterogeneity and complexity of acute ischaemic stroke necessitates a multimodal approach to imaging that provides not only structural but also functional and haemodynamic information to aid the decision-making process [37]. For CT this approach currently includes plain CT, CT angiography and perfusion computed tomography (PCT) [28,38], while in MRI the approach includes a combination of conventional sequences (such as T1W, T2W and fluid-attenuated inversion recovery) and T2*W, time-of-flight MR angiography, DWI and PWI [39].

Perfusion computed tomography

PCT images are acquired in the cine mode after intravenous injection of an iodinated contrast agent, generating maps of CBF, CBV as well as mean transit time (MTT) and time to peak (TTP) [40]. The maps are reproducible, especially when relative perfusion parameters are used [41], and reportedly have >90% sensitivity and specificity for detecting large hemispheric stroke [42]. Anatomical coverage, however, is typically restricted to 20 mm (two to four slices), reducing sensitivity to stroke not caused by proximal major artery occlusion [43].

Recent studies on PCT in acute stroke demonstrated that tissue with CBV <2 ml/100 g represents the core, while a relative MTT above 145% of the normal hemisphere best outlines all at-risk tissue [44]. The penumbra can thus be estimated as the tissue existing between those two thresholds. Using this methodology, PCT parameters correlate very well with MR DWI–PWI and are a good predictor of the final infarct volume and clinical recovery [38,41,45,46]. PCT is also potentially useful in decision-making when the time of onset is unknown, such as with awakening stroke [47]. In combination with CT angiography, PCT has comparable utility with that of MR in selecting patients for thrombolysis [38].

Magnetic resonance diffusion-perfusion imaging

The commonly used dynamic susceptibility-weighted contrast PWI technique is similar in principle to PCT, and measures changes in the magnetic field induced by passage of gadolinium-based contrast in cerebral tissue – but with lesser accuracy, particularly for CBF. Arterial spin labelling PWI is a newer technique that avoids the use of a contrast agent through magnetically labelling the arterial blood entering the skull and then tracking its motion through the tissue [48]. The latter technique, however, is less widely available and still requires further validation in stroke.

Among the generated MRI perfusion maps, TTP and MTT are preferred for identifying hypoperfused tissue because they correlate best with tissue fate [49,50]. Comparison of the perfusion deficit depicted on these maps with the DWI lesion (assumed to denote the core) yields either a mismatch pattern (PWI > DWI), a matched lesion pattern (PWI = DWI) or a reperfusion pattern (DWI > PWI). The mismatch pattern is taken to indicate the existence of salvageable at-risk tissue and is found in about 70% of all patients with anterior-circulation stroke within 6 hours of onset [51]. The pattern’s presence is strongly associated with proximal MCA occlusion [51] and its resolution on reperfusion is associated with neurological recovery [52-54]. Moreover, successful reperfusion prevents further expansion of the DWI lesion into the area of mismatch [55].

The DWI–PWI mismatch can be used to select patients who are most likely to benefit from thrombolytic therapy [56], and the mismatch is incorporated into several ongoing thrombolysis trials (see below). It has also been used to show how variables such as hyperglycaemia [57], haematocrit [58] and age [59] influence outcome through altering the fate of the penumbra. DWI has also shown utility in providing a physiologic endpoint for new therapies such as normobaric high-flow oxygen [60].

The clinical implications of a matched DWI–PWI pattern are less clear. In the presence of a large DWI lesion and proximal MCA occlusion, this pattern appears to accurately predict the development of a malignant MCA syndrome [61,62]. For other scenarios where a matched pattern is found, the evidence is lacking with regard to outcome and with regard
to whether there is any benefit from instituting thrombolysis or another specific therapy. The third pattern of normal (or increased) perfusion with a variable size DWI lesion indicates recanalization [63], and effectively does not appear to benefit from thrombolysis (see below).

A number of uncertainties have recently arisen regarding the pathophysiologic accuracy of the DWI–PWI mismatch concept. Studies in animals and in humans have documented the reversibility of DWI lesions and normalization of the ADC, thus arguing against equivalence of the DWI lesion to the ‘core’ [64,65]. Predictors of such normalization are thrombolytic therapy and recanalization, particularly within the 3-hour time window [66]. This suggests that the DWI lesion may include penumbral tissue, as echoed recently using PET [67,68]. Corresponding uncertainties also exist regarding PWI, particularly in the selection of parameters for defining the tissue at risk and in the choice of arterial input function [49,69]. The DWI–PWI mismatch may thus overestimate the penumbra by including oligemic tissue or even normally perfused but autoregulated tissue that is not at risk [70]. These questions become particularly relevant when defining the management of matched DWI–PWI lesions, since response to recanalization depends on whether or not there still is penumbral tissue. Nevertheless, the DWI–PWI concept remains a clinically and experimentally useful tool provided these shortcomings are recognized.

**Implications of imaging for thrombolysis**

**The 3-hour window**

Patients treated with intravenous thrombolysis within the first 3 hours after stroke are at least 30% more likely to have little or no disability at 3 months (number needed to treat = 8) [5,71]. This is essentially based on selecting patients who have stroke symptoms that are not rapidly resolving or minor (NIH stroke scale < 3) with the absence of haemorrhage on plain CT. Nonetheless, despite the use of clinical exclusion criteria [72], the treatment carries a risk of around 6–7% of thrombolysis-associated symptomatic haemorrhage; therefore, the emerging role of imaging in this acute setting, beyond exclusion of intracranial haemorrhage and subarachnoid haemorrhage, is to identify and exclude that subgroup of patients who are unlikely to benefit and may be harmed by recombinant tissue plasminogen activator (rt-PA), in turn reducing the number needed to treat. As already mentioned, early hypodensity on plain CT >1/3 MCA territory is associated with thrombolysis-associated haemorrhage. Nonetheless, this fact is still debated since analysis of the 0–3 hour group in the NINDS cohort does not support this exclusion on the basis of the extent of early ischaemic changes alone (that is, including swelling) [73].

Similarly, MR-based studies show that severely reduced ADC, CBF and CBV are associated with subsequent haemorrhagic transformation within the infarction [74,75]. These studies, however, do not distinguish symptomatic and asymptomatic grades of haemorrhagic transformation, and thus their relevance to clinical outcome is unclear. Another proposed MRI marker of haemorrhagic transformation is delayed gadolinium enhancement of cerebrospinal fluid space on FLAIR [76]. This marker appears only after reperfusion has been achieved and thus its clinical usefulness is uncertain. Thomalla and colleagues [77] make the distinction between haemorrhagic transformation and parenchymal haemorrhage, arguing that the former is a clinically irrelevant epiphenomenon whereas the latter is a direct effect of rt-PA therapy and deserves further investigation. Finally, T2* MRI can identify microbleeds, which may also arguably pose a risk of parenchymal haemorrhage after thrombolysis, yet the evidence for or against this view is still scarce [78,79].

The constraint of the 3-hour window makes it necessary that imaging is performed in as short a time as possible. Because CT provides relatively limited information in early stroke, multimodal MRI is increasingly being advocated as the imaging investigation of choice [80]. The main concern, however, is the possible delay in treatment – up to 20 minutes in experienced centres [81] – but this may be balanced by the gain in diagnostic accuracy. Furthermore, shorter door-to-needle times can probably be achieved through omitting CT, increasing the familiarity of staff with MRI [82] and tailoring MRI protocols to suit hyperacute stroke patients [39]. Recent data thus indeed suggest that MR-based protocols are of clinical benefit even within the 3-hour window (see below).

**Expanding the time window for thrombolysis**

For several reasons, including poor public knowledge about stroke, ineffective delivery of patients to capable centres and lack of preparedness in many community hospitals, only about 20% of stroke patients arrive at emergency departments within the 3-hour window and only 3–8% of eligible patients currently receive rt-PA therapy, except in a few regional referral centres [83]. Being able to extend this time window beyond 3 hours will therefore be extremely important. A recent meta-analysis of several rt-PA studies has suggested a potential for a favourable outcome if treatment is given beyond 3 hours [84], and this motivates ongoing thrombolysis trials such as IST3 and ECASS3. Indeed, the pathophysiological model outlined earlier suggests that reperfusion can be beneficial beyond 3 hours through salvage of the penumbra in appropriate patients. Efforts are thus currently directed at adopting acute MR to select suitable patients beyond the 3-hour window.

The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study used MRI to evaluate treatment with alteplase 3–6 hours from stroke onset, and demonstrated a better clinical response among patients with small DWI and the presence of mismatch on MR than in other subgroups, including the ‘matched’ DWI–PWI and the small DWI and PWI lesion subgroups.
and at 24 hours, and smaller MR diffusion lesions were seen. Oxygen-treated patients improved clinically during therapy and at 24 hours, and smaller MR diffusion lesions were seen. Studies comparing MRI-based alteplase treatment within 3–6 hours with conventional CT-based treatment within 3 hours have demonstrated similar recanalization rates and functional outcomes [87,88]. Furthermore, MRI-based treatment in the timeframe of 0–6 hours also shows similar or superior safety and efficacy to CT-based treatment within 3 hours, when compared directly [89] or with data from a meta-analysis [90]. Preliminary findings from pooling of results of 1,210 patients confirm and amplify these conclusions [91].

MR-based selection has also been used in two studies testing the new thrombolytic agent desmoteplase. In the Desmoteplase in Acute Ischemic Stroke trial [92], the presence of a MR DWI–PWI mismatch of 20% or higher was used to select patients for thrombolysis in the window of 3–9 hours. A more favourable clinical outcome was demonstrated in patients who experienced reperfusion than in those who did not (52.5% versus 24.6%), and the treatment effect was independent of the duration from onset to treatment. Similar criteria were also used in the follow-up dose-finding study [93], with good clinical outcome. Results of the Desmoteplase in Acute Ischemic Stroke II study are still awaited. The mismatch concept is also being employed for selecting suitable candidates in ongoing trials of mechanical clot retrieval, such as MERCI.

Finally, MRI is also being employed for selecting suitable candidates in trials of mechanical clot retrieval in posterior circulation stroke [94] where CT is often unhelpful and the evidence is much more limited on the use of thrombolysis.

Implications of imaging for other specific therapies

Neuroprotection

When tested in humans, neuroprotectant agents designed to delay or prevent the demise of at-risk tissue and thus extend the therapeutic time window have consistently failed to produce the effects observed in animal studies. This failure may be attributed in part to the very limited use of physiologic imaging in such trials [95], in addition to potential flaws in trial design, inadequate preclinical data or even the choice of ineffective compounds.

Despite earlier failures, interest has recently been revived in normobaric oxygen therapy in acute stroke. In a pilot study [60], the MRI DWI–PWI mismatch was used to select acute stroke patients (<12 hours from onset) to receive either 100% oxygen or room air for 8 hours via a face mask. Oxygen-treated patients improved clinically during therapy and at 24 hours, and smaller MR diffusion lesions were seen in this group than in control subjects at early time points. Moreover, oxygen therapy was associated with an increase in relative CBF and CBV within the perfusion (MTT) abnormality, consistent with earlier observations of a vasodilatory response to hyperoxia in ischaemic brain tissue rather than the vasoconstriction induced in normal brain tissue [96]. Larger trials using a similar methodology may eventually establish the usefulness of this simple and widely available approach to neuroprotection.

Surgical brain decompression

Space-occupying malignant MCA infarctions carry a very poor prognosis under standard therapy, with a case-fatality rate approaching 80%. Decompressive surgery, in the form of wide hemicraniectomy and duraplasty, performed as early as possible (within 48 hours of stroke onset), has been shown in pooled randomized trials to not only significantly reduce mortality by an absolute 50% but also to improve functional outcome in the survivors, although less impressively [97]. Early decompression probably works not only by preventing life-threatening herniation and subsequent brainstem compression, but also by reducing the detrimental effects of raised intracranial pressure on tissue perfusion pressure, which can precipitate the penumbra, the oligaemia and even perhaps the simply autoregulated tissue into irreversible damage (see Figure 1).

Predicting the development of malignant MCA infarctions as early as possible, particularly from imaging parameters, is thus important to allow surgery to be undertaken in time. Imaging-based predictors such as occlusion of the proximal MCA, carotid T occlusion, involvement of both the superficial and deep MCA territories, an inadequate circle of Willis, and involvement of other vascular territories have modest but useful value [62,98]. DWI–PWI MR, however, appears of considerable potential. In one study, a DWI lesion volume above 145 ml within 14 hours of onset was reported to predict this fate with 100% sensitivity and 94% specificity [62]. In another study, a smaller ADC lesion volume (82 ml) was advocated if imaging was performed within 6 hours [61]. Furthermore, a ratio of the time to peak to ADC lesion volume < 2.4 and/or an ADC value within the core < 300 mm²/s were also proposed as predictors of malignant MCA infarctions in the same study. In the DEFUSE study [85], a DWI or PWI lesion volume > 100 ml also accurately predicted malignant MCA infarctions. There is also some evidence that other factors such as blood–brain barrier breakdown may be instrumental in the development of malignant infarction [99].

Hypothermia

Induction of moderate hypothermia (around 33°C) has also been considered in the treatment of malignant MCA infarctions, and some small open studies showed a beneficial effect on clinical outcome [100,101], although with attendant risks of pneumonia and a rebound increase in intracranial pressure on rewarming. The current trend in ongoing trials is...
to go for less dramatic hypothermia (around 35°C), and use intravenous infusion of cooling fluid, which seems less problematic. The Cooling for Acute Ischaemic Brain Damage study used MRI to show a decrease of infarct growth with hypothermia and pointed to its possible effectiveness, yet the small number of patients precluded statistically significant results [102]. Interestingly, marked resolution of the DWI lesion has recently been anecdotally reported after hypothermic treatment [103], thus challenging the inevitable grim outlook of malignant MCA infarctions and suggesting that imaging can be used to select potential responders to such treatment and to monitor treatment effects.

Implications of imaging for general management

Demonstration of a high oxygen extraction fraction or DWI–PWI mismatch in the setting of acute stroke implies that autoregulation of CBF is impaired in the affected territory. Any lowering of the systemic arterial pressure is therefore likely to further reduce the cerebral perfusion pressure and in turn the CBF in the affected tissue, which can be harmful not only for the penumbra – which may precipitate into necrosis – but also for the oligemia, which may become penumbral (Figure 1). Accordingly, reductions in systemic arterial pressure in acute ischaemic stroke have frequently been associated with worse outcome [104]. This issue is especially important in view of the frequent occurrence of reactive hypertension in this setting, and is reflected in recommendations for management of blood pressure in acute stroke [71]. Conversely, observing hyperfusion, particularly if early oedema is demonstrated by CT or MRI, may provide a rationale for treating arterial hypertension since some experimental studies suggest that hyperfusion in necrotic tissue may promote the development of malignant brain swelling.

Conclusions

Physiologic imaging in the acute stroke setting allows the clinician to visualize each patient’s pathophysiological situation before aggressive therapy is considered [36]. Based on the evidence reviewed above, three main patterns of changes, each with different management implications, can be encountered. If an early extensive core is documented, outcome is invariably poor with considerable risk of malignant MCA infarction, and surgical brain decompression should be considered. Secondly, when early recanalization (without an already extensive core) is documented, spontaneous outcome is invariably good so no aggressive therapy should be considered. Finally, if substantial penumbra (again without extensive core) is documented, management should aim at saving as much penumbra as possible – this pattern includes the best candidates for thrombolysis, although the risk of haemorrhagic transformation should be balanced with the expected benefit. This practical framework is based on current evidence but remains to be formally supported by randomized prospective trials.

Imaging has become an integral part of acute stroke care and the future holds more promise. Considerable evidence is already accumulating that multimodal CT or MRI, as compared with plain CT, provides information that is both useful in clinical trials and in the individual patient, even within the current 3-hour window. In the future, practical implementation of PCT with whole-brain coverage, estimation of CBF by noncontrast arterial spin labelling [48] and of oxygen extraction fraction based on the principles of blood-oxygen-level-dependent (BOLD) imaging [105], and, possibly, MR-based pH imaging [106] may add more dimensions to imaging of ischaemic stroke. Future advances in physiologic imaging, such as a readily available means of imaging selective neuronal loss, translating the knowledge from PET and single-photon emission CT studies [107,108], would also further refine our understanding of acute stroke pathophysiology and treatment.

Competing interests

The authors declare that they have no competing interests.

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