Imaging of acute stroke

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Thrombolytic therapy has led to a higher proportion of patients presenting to hospital early, and this, with parallel developments in imaging technology, has greatly improved the understanding of acute stroke pathophysiology. Additionally, MRI, including diffusion-weighted imaging (DWI) and gradient echo, or T2⁎, imaging is important in understanding basic structural information—such as distinguishing acute ischaemia from haemorrhage. It has also greatly increased sensitivity in the diagnosis of acute cerebral ischaemia. The pathophysiology of the ischaemic penumbra can now be assessed with CT or MRI-based perfusion imaging techniques, which are widely available and clinically applicable. Pathophysiological information from CT or MRI increasingly helps clinical trial design, may allow targeted therapy in individual patients, and may extend the time scale for reperfusion therapy.

Introduction

Recent developments in imaging have revolutionised our approach to acute stroke by allowing us to directly image the ischaemic process and giving us a better understanding of the pathophysiology. Translation of basic research concepts into clinical practice fuelled pivotal randomised controlled trials of intravenous thrombolysis, which now constitutes the basis of management. Imaging has documented substantial individual differences in both the time course of infarct growth and the occurrence of spontaneous recanalisation, supporting the idea that management decisions be based on the individual patient’s pathophysiological diagnosis.¹ Physiological imaging is now incorporated in the design of many randomised controlled trials, particularly at the dose-finding stage, and is the basis of the current shift towards small trials of highly homogeneous samples powered to address specific pathophysiological processes, with expected increases in trial efficiency.¹²

In this review we will focus on the imaging of acute ischaemic stroke (about 85% of all strokes), particularly, middle cerebral artery (MCA) territory stroke (about 50% of all ischaemic strokes).³ MCA stroke is the syndrome most studied in terms of pathophysiology and therapy. Posterior circulation and small vessel strokes will be discussed separately.

After a brief pathophysiological overview, we will look at the advances achieved with MRI, currently the most useful imaging technique to assess acute stroke; and the use of CT in combination with CT perfusion for decision-making in MCA stroke.

This review is not intended to be a guideline but aims to discuss how imaging can help in decision-making for therapy, from a neurological and pathophysiological, rather than a radiological, perspective. Levels of evidence have not been included, but where relevant systematic reviews have been done these will be mentioned in this review.

Pathophysiology

General concepts

The pathophysiological model developed from animal studies, particularly in primates, forms the basis for our understanding of the acute phase of MCA stroke.¹ Acute proximal MCA occlusion reduces distal cerebral perfusion pressure. Cerebral perfusion pressure reductions in the cortical MCA territory are most severe in its centre (perisylvian region) and least in the watershed areas; the lentiform nucleus and some of the white matter, which have far fewer anastomoses, are the most severely affected.³ Cerebral perfusion pressure reduction is, in most areas, severe enough to override cerebrovascular autoregulation, resulting in hypoperfusion according to a similar gradient. Lost autoregulation means that local perfusion is affected by systemic blood pressure, proximal carotid disease, and intracranial pressure. Ischaemia, when severe, can result in tissue infarction (ie, pannecrosis); when less severe or prolonged, however, ischaemia can induce selective neuronal death, an intermediate state reputed to be undetectable on CT.⁴

The key pathophysiological concept is the distinction of hypoperfused tissue into three operational compartments;⁷ tissue that will inevitably die (core), tissue that will in principle survive (oligaemia), and tissue that may either die or survive (the ischaemic penumbra; figure 1). Reduction of cerebral blood flow from its normal mean, around 50 mL/100 g per min, to less than 20 mL/100 g per min, results in impaired neural function⁶ but preserved tissue integrity; this defines the penumbra. Changes in water homoeostasis, including shrinkage of

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**Figure 1: A diagram showing the three hypoperfused tissue compartments in acute MCA stroke**

A further compartment with normal perfusion but partially exhausted vascular reserve, not illustrated here, may surround the oligaemic compartment (see text).

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Hypoperfusion <20 mL/100 g per min
Salvage of this tissue is correlated with better clinical recovery

Uncertain fate

Physiological and/or biochemical characteristics consistent with cellular dysfunction but not death

Panels: Currently accepted operational criteria defining the penumbra

**Hyopoperfusion <20 mL/100 g per min**

Abnormal neuronal function documented by a correlation with acute clinical deficit

Physiological and/or biochemical characteristics consistent with cellular dysfunction but not death

Uncertain fate

Salvage of this tissue is correlated with better clinical recovery

the extracellular space and net uptake of water from plasma, also take place in the penumbra. Unless early reperfusion occurs, the penumbra is gradually recruited into the core—ie, the volume of irreversibly damaged tissue grows and the amount of penumbra decreases. Tissue outcome depends on two factors: the severity of flow reduction and its duration—ie, the cerebral blood flow threshold that defines the core increases with time until it reaches the penumbra threshold, at which point all the penumbra has been recruited. Thus, within the penumbra, the lower the cerebral blood flow, the higher the risk of early infarction. Because both the core and the penumbra can contribute to neurological deficits, it is impossible to clinically determine their relative effects.

Rescue of the penumbra, either by restoration of blood supply or by interruption of the adverse metabolic or neurochemical cascade, is the basis of acute stroke therapy. Imaging studies, with various techniques, have established the clinical importance of penumbral salvage, showing a clear association between the volume of penumbra not progressing to infarction and the improvement in neurological scores. To be accepted as penumbra, the affected tissue must fulfil several well-defined operational criteria (panel).

Tissue with small reductions in cerebral blood flow—20–50 mL/100 g per min, defined as oligaemia, probably maintains its function for a very long time and is unlikely to proceed to infarction. However, the oligaemia may be pushed into penumbral state—and hence potentially into the core—by secondary events that reduce the cerebral perfusion pressure, such as vasogenic oedema and systemic hypotension, or by factors that aggravate the flow–metabolism mismatch such as hyperglycaemia and pyrexia. This may explain the benefits from avoiding physiological complications and maintaining blood pressure early after MCA stroke.

**Insights from PET**

PET shaped the concepts underlying modern acute stroke imaging and remains the gold standard. Based on validated thresholds, affected tissue can be classified as core, penumbra, oligaemia, and hyperperfused. In early proximal MCA occlusion, the core typically involves the striatocapsular area, whereas the penumbra typically involves the cortical mantle. However, occasionally the core extends widely into cortical areas as early as 4 h after onset, probably due to inadequate pial collaterals or a carotid occlusion. The volume of core is associated with both admission clinical scores and final infarct volume.

Substantial penumbra is present in up to 90% of patients within 6 h of onset; this falls to about 50% within 9 h but is still about 30% 18 h after onset. Up to 52% of the ultimate infarct still shows penumbra 16 h after onset, suggesting delayed therapeutic opportunities in some patients. The penumbra progresses to, or escapes, infarction partly or in all, depending on subsequent events such as reperfusion. Survival of the penumbra is the main determinant of clinical recovery and probably underpins peri-infarct reorganisation. Thus, although mapping the core provides a marker of the inevitable damage, mapping the penumbra shows the potential for recovery.

Oligaemia displays mild misery perfusion—ie, a moderately reduced cerebral blood flow (above the penumbra threshold) and a high oxygen extraction fraction. A high oxygen extraction fraction in itself does not equate with penumbra as this fraction rises as soon as the cerebral blood flow decreases. The high oxygen extraction fraction area represents exclusively the penumbra in patients but virtually only the oligaemia in others.

Early spontaneous hyperperfusion, present in about a third of patients within 18 h, almost invariably predicts preserved cerebral oxygen metabolism (CMRO2) and tissue integrity, suggesting this as a marker of prior recanalisation that salvaged the penumbra. After thrombolysis, however, hyperperfusion may signal poor tissue outcome, possibly because pressure is forced into a damaged vascular tree.

An extensive core invariably predicts poor clinical outcome and malignant infarction, whereas extensive spontaneous hyperperfusion invariably predicts excellent outcome, independently of admission clinical scores. By contrast, when there is extensive penumbra, the clinical course is unpredictable. The occurrence of these three main patterns of changes highlights the substantial pathophysiological heterogeneity underlying acute MCA stroke.

**Overview of imaging techniques**

Following major technological advances over the past 15 years, imaging can now characterise brain structure and the pathological status of established lesions, brain perfusion, intracranial and extracranial vascular pathology (including direct visualisation of the clot), tissue viability, and metabolic state, bringing complex physiological concepts into everyday clinical practice.

Structural imaging with either CT or conventional MRI sequences has only limited sensitivity to acute ischaemic changes (40–70% in the first 6 h across all subtypes), depending notably on anatomical location, background abnormalities, scan quality, and reader experience. Although CT remains the best method for detection of intracerebral haemorrhage, MRI, with appropriate sequences, can be equally sensitive.

Non-invasive time-of-flight (ie, non-contrast) magnetic resonance angiography and slightly more invasive CT angiography or contrast-enhanced magnetic resonance angiography (with intravenous contrast administration) now allow routine vascular imaging. Extracranial vascular imaging or ultrasound can identify individuals at high risk of repeated stroke, or those who may benefit from specific interventions. Real-time monitoring of MCA flow is possible with transcranial doppler, which in addition can promote early recanalisation after alteplase therapy.34

Plain CT
Contrary to previous dogma, plain CT can be abnormal within 3 h of onset in 75% of patients with MCA stroke.35 Early ischaemic changes include hypoattenuation or focal tissue swelling (figure 2), which differ in pathophysiological basis. Tissue density declines with time from vessel occlusion in the core and indicates increased water content.36,37 Net uptake of water can, however, also take place in the penumbra.38 Hypodensity is associated with the most severe reductions in cerebral blood flow and volume on perfusion imaging,39 and the anatomical extent of early hypodensity within 3–6 h of stroke onset predicts final infarction, with few exceptions.39 However, brain swelling, without hypoattenuation, indicates increased cerebral blood volume,40 associated with normal apparent diffusion coefficient, moderate hypoperfusion, and increased mean transit time—ie, viable tissue.41 Thus, conventionally defined early ischaemic changes include elements of both core and penumbra.

Interobserver agreement for early ischaemic changes is moderate41–44 but this depends on the individual's experience. Systematic review of CT using the Alberta stroke programme early CT score (ASPECTS),45 particularly with some clinical information, has better inter-rater reliability, indicates (severity×duration) preceding hypoperfusion,45 is predictive of response to thrombolysis, and can be done in real time.46,47 Because current ASPECTS scoring combines swelling and hypodensity, it may not be the best method to distinguish irreversibly damaged tissue from viable tissue. Review of data from both the National Institute of Neurological Disorders and Stroke (NINDS) and ECASS-II trials with alteplase suggest that early ischaemic changes (assessed by ASPECTS) are not independently associated with poor clinical outcome, but a very poor ASPECTS score (≤2) was associated with increased risk of intracerebral haemorrhage in the ECASS-II cohort, and poor outcome in the NINDS cohort.48,49 The presence and extent of early ischaemic changes probably indicate stroke severity and their prevalence does not vary substantially over time.39 The recognition that the anatomical extent of parenchymal hypodensity in patients treated with alteplase predicts the risk of intracerebral haemorrhage has led to the introduction of the "one-third MCA territory" rule (ie, do not thrombolyse) for randomised controlled trials.50 More studies are needed to clarify the respective predictive value of hypodensity and swelling for different time windows.

Increased attenuation of an arterial segment, the "hyperdense MCA sign" (figure 2), is highly specific for occlusion by a thrombus51 but has limited sensitivity (27–34% in large series).52–54 Because radiograph attenuation of clots depends on haematocrit,55 a possible explanation is that white, fibrin-poor thrombi are not identified on CT, explaining its poor sensitivity.51 In a general stroke population, the hyperdense MCA sign is associated with poor prognosis and risk of thrombolysis-associated intracerebral haemorrhage56–58 and its resolution with thrombolytic therapy is associated with favourable outcome. In patients with acute MCA occlusion, however, the hyperdense MCA sign has no independent prognostic value and is not predictive of responsiveness to intravenous alteplase given within 3 h.59 The presence of distal occlusion of the MCA can be...
identified by the sylvian dot sign (figure 2), which has reasonable specificity (38–46%).

CT and magnetic resonance angiography
Although complete coverage from the aortic arch to the circle of Willis is possible with CT angiography, it is still rarely implemented. Acute CT angiography improves localisation and syndromic classification compared with clinical features alone, and the source images from CT angiography are more sensitive than plain CT. Intracranial CT angiography can identify the presence and site of occlusion, which has substantial implications for management of patients. For instance, the potential for intravenous alteplase to effect recanalisation is reduced for sites such as terminal carotid occlusions, therefore influencing the therapeutic approach—eg, with intra-arterial thrombolysis or mechanical clot retrieval. However, the value of these alternative approaches has yet to be established in prospective trials. By visualising the extracranial vasculature, CT angiography of neck vessels is important for management. Carotid dissection or complex atherosclerotic plaque might prompt alternative early treatments (eg, aggressive antiplatelet therapy, high-dose statins, anticoagulants, or even stenting).

Time-of-flight magnetic resonance angiography is the preferred method when combined with DWI/PWI (diffusion weighted imaging/perfusion weighted imaging) because it avoids the repeated administration of contrast (required for PWI), and reliably detects proximal MCA occlusion (figures 3 and 4), although there can be difficulty in distinguishing MCA occlusion from stenosis. This type of angiography can be used to image the neck vessels with the newest scanners. However, contrast magnetic resonance angiography, when available, has higher quality and accuracy than time-of-flight magnetic resonance angiography. The sensitivity and specificity of CT and magnetic resonance angiography have been assessed against conventional angiography in extracranial carotid disease, but not in acute stroke.

Physiological brain imaging
In this review we will focus on the most widely used imaging techniques, MRI and CT. The main physiological imaging techniques are summarised in table 1; however several imaging techniques are used less commonly. Combining DWI with PWI and time-of-flight magnetic resonance angiography in acute stroke has successfully widened the opportunities to apply pathophysiological insights to clinical management.

The DWI lesion
DWI has revolutionised the diagnostic sensitivity of imaging ischaemia. DWI can indicate the degree of free diffusion of water molecules—apparent diffusion coefficient. If the cerebral blood flow goes below the penumbra threshold this causes failure of energy-dependent processes, resulting in intracellular (cytotoxic) oedema, shrinkage of the extracellular compartment, and consequently reduced apparent diffusion coefficient. The latter translates into a high DWI signal, resulting in even very small ischaemic lesions being conspicuous. Furthermore, DWI is abnormal within minutes of stroke onset. Apparent diffusion coefficient values gradually return to normal in 5–10 days and then increase in
chronic lesions.76–78 This gradual increase may indicate the development of vasogenic oedema and cellular necrosis.79 However, the DWI lesion persists for another week or so because it also detects prolonged T2 signal ("T2 shine-through"). Proper interpretation of DWI—eg, to distinguish acute recurrence—must therefore consider the apparent diffusion coefficient map.

DWI is more sensitive to acute ischaemia than plain CT or T2-weighted MRI, which show only tissue changes caused by severe and prolonged ischaemia, usually sufficient to cause infarction.80–82 Interobserver agreement in stroke more than 6 h after onset is substantially better with DWI than with plain CT.83,84 Within 6 h of stroke onset, DWI has reported sensitivity of 95% and specificity of nearly 100%.83

**Figure 4: Main patterns of DWI and PWI changes in acute MCA stroke**

Top: fuzzy DWI lesion in left MCA territory matching an area of diminished time to peak, indicating local hyperperfusion and suggesting spontaneous recanalisation had occurred prior to imaging at 3 h after onset (note the prolonged time to peak at the posterior edge of the DWI lesion, suggesting distal branch occlusion). Middle: the next day, perfusion has essentially normalised as well as the DWI lesion, save for a narrow posterior streak, suggesting the spontaneous recanalisation saved the at-risk tissue from progressing to infarction. Bottom: At day 7, there has been no return of the DWI lesion, indicating the tissue was effectively salvaged, without even minimal damage.

**DWI–PWI mismatch**

Unless there is early reperfusion, DWI lesions expand over a period up to 24 h,85 largely from recruitment of part or all of the surrounding hypoperfused tissue. DWI lesion expansion occurs almost exclusively in those patients who initially have a perfusion defect larger than the DWI lesion, DWI–PWI mismatch.85,86 Factors that may hasten or amplify the growth of DWI lesions include hyperglycaemia,87 high haematocrit,88 old age,89 and systemic hypoxia.90 The DWI–PWI mismatch pattern is present in about 70% of all patients with anterior-circulation stroke scanned within 6 h of onset,91 is strongly associated with proximal MCA occlusion,91 and resolves on reperfusion.85,86 Resolution of hypoperfusion from early sustained revascularisation prevents DWI lesion expansion86,89 and a
large mismatch volume increases the chance of a spectacular shrinking deficit on early reperfusion. Finally, the volume of tissue salvaged is associated with neurological recovery and functional outcome. Thus, combined DWI and PWI might define the core (the DWI lesion) and the penumbra—tissue that has low perfusion and normal DWI or apparent diffusion coefficient but that can be recruited into the DWI lesion. Table 2 summarises the evidence base for the DWI–PWI mismatch hypothesis.

Although this concept seems appealing, it is challenged by the possibility of DWI lesions reversible. Normalisation of the apparent diffusion coefficient decline on reperfusion is reported in animal studies and in as many as 20% of patients in the 6 h time window. Predictors of apparent diffusion coefficient normalisation include thrombolytic therapy, particularly within the 3 h time window, recanalisation, and peripheral branch occlusion. The severity of hypoperfusion is probably the best predictor of the risk of infarction rather than the apparent diffusion coefficient value. However, delayed DWI lesion reappearance on later imaging (first reported in animal models) has been reported in man. This lesion reappearance occurs in regions of intermediate ischaemia (as judged by apparent diffusion coefficient values) and causal hypotheses include cell death (which can be selective) due to various factors.

There are also uncertainties regarding MRI-based bolus-tracking perfusion imaging. Definition of the optimum perfusion variable is not uniform across studies. The different variables (typically time to peak, mean transit time, cerebral blood volume and flow) differ in their predictive value for defining final infarction. Lesion volumes depend partly on the selection of the arterial input function. Interpretation of studies that describe the correlation of initial PWI lesion volume with later infarct volume is further complicated by the varied natural course of recanalisation and reperfusion. Some studies suggest optimum variables and thresholds.

The hypothesis that mismatch is associated with penumbra has also been challenged by combined PET and MRI studies showing that the DWI lesion contains core but also penumbra, whereas the mismatch contains penumbra but also oligaemia. However, a mean transit time delay of more than 4 s adequately approximates the natural course of recanalisation and reperfusion. Some studies suggest optimum variables and thresholds.

**Other DWI–PWI patterns**

Apart from the mismatch pattern, acute patients with anterior circulation stroke can have matched DWI–PWI

### Table 1: Main physiological imaging techniques, with the parameters they map, the criteria they use to identify the penumbra, and their main advantages and limitations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Definition of penumbra</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfusion</td>
<td>CBF, CBV, MT, TTP</td>
<td>Relative CBF &lt;66%* CBF &gt;2.5 mL/100g CBV &gt;20 mL/100g per min</td>
<td>Combined with plain CT; available; fast</td>
</tr>
<tr>
<td>Xe</td>
<td>CBF</td>
<td>CBF &gt;20 mL/100g per min</td>
<td>Quantitative, combined with plain CT</td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI–PWI</td>
<td>CBF, CBV, MT, TTP, ADC</td>
<td>Relative TTP (or MT) delay &gt;4s and normal DWI</td>
<td>Fast; best sensitivity; no radiation involved, directly visualises core</td>
</tr>
<tr>
<td>Arterial spin labelling</td>
<td>CBF</td>
<td>Relative binding &gt;3.4 and CBF &lt; 14 mL/100g per min</td>
<td>Produces a direct positive image of viable hypoxic tissue</td>
</tr>
<tr>
<td>MRI-based OEF (and PWI)</td>
<td>CBF, OEF, CMRO₂</td>
<td>Not validated</td>
<td>No contrast needed</td>
</tr>
<tr>
<td>Spectroscopy</td>
<td>NAA, lactate</td>
<td>Elevated lactate and normal NAA</td>
<td>Biochemically characterises tissue</td>
</tr>
<tr>
<td>PET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-tracer ³¹O</td>
<td>CBF, CBV, MT, CMRO₂, OEF</td>
<td>Relative CBF &lt;22 mL/100g per min and OEF &gt;0.70</td>
<td>Quantitative, validated</td>
</tr>
<tr>
<td>¹³C-FMZ (+¹¹C-H₂O)</td>
<td>Tracer binding</td>
<td>Relative binding &gt;3.4 and CBF &lt; 14 mL/100g per min</td>
<td>Based on physiological neuronal integrity</td>
</tr>
<tr>
<td>¹⁵F-FMISO</td>
<td>Tracer uptake</td>
<td>Uptake ratio &gt;1.3 in CBF</td>
<td>Produces a direct positive image of viable hypoxic tissue</td>
</tr>
<tr>
<td>SPECT</td>
<td></td>
<td></td>
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<tr>
<td>⁹⁹mTc-labelled HMPAO or ECD</td>
<td>CBF</td>
<td>Relative CBF &gt;65%*</td>
<td>Cheap and relatively available</td>
</tr>
</tbody>
</table>

ADC=apparent diffusion coefficient; CBF=cerebral blood flow; CBV=cerebral blood volume; CMRO₂=cerebral metabolic rate of oxygen; OEF=oxygen extraction fraction; DWI=diffusion-weighted imaging; FMISO=fluoromisonidazole; FMZ=flumazenil; HMPAO=hexamethylpropyleneamine oxime; ECD=ethyl-cysteinate dimer; MTT=mean transit time; NAA=N-acetylaspartate; PWI=perfusion weighted imaging; SPECT=single photon emission CT; TTP=time to peak. *Relative to mean contralateral hemisphere. †Relative to contralateral healthy white matter. ‡The DWI lesion may not be associated with the core.
lesions or a DWI lesion without hypoperfusion (figures 3 and 4). These magnetic resonance patterns are consistent with the above described PET patterns.

In the absence of data from prospective randomised controlled trials, the matched DWI–PWI lesion pattern causes a management dilemma because it is unclear if the entire DWI lesion is already irreversibly damaged or whether it still contains a sizeable penumbra. There may therefore be an argument for reperfusion therapy, but the size of both the DWI and the PWI lesions, the magnetic resonance angiography findings, and the clinical presentation can affect decisions. For instance, a matched pattern with a large DWI lesion, a severe neurological deficit, and a proximal vessel occlusion predicts the development of a malignant MCA infarction. The third pattern of normal (or increased) perfusion with a variable size DWI lesion is indicative of spontaneous recanalisation and hence is inappropriate for thrombolysis.

**Use of acute stroke MRI in clinical trials**

Several DWI-based paradigms have been incorporated into randomised controlled trials. Several neuroprotectant trials included an MRI substudy with DWI-lesion expansion as a surrogate marker. The citocholine trials included more than 100 patients and supported the ability of DWI lesion to act as a surrogate. The hypothesis that mismatch is associated with at-risk tissue is supported by two trials of the thrombolytic drug desmoteplase. The drug was given 3–9 h after stroke onset (only to patients with a DWI–PWI mismatch ≥20%) and was shown to be potentially effective in improving clinical outcomes. The RESCUE study uses acute stroke MRI to select patients into a mechanical thrombectomy versus standard therapy trial. The ongoing EPITHET trial randomised all patients into a mechanical thrombectomy versus standard therapy. The RESCUE study uses acute stroke MRI to select patients into a mechanical thrombectomy versus standard therapy trial. The ongoing EPITHET trial randomised all patients into a mechanical thrombectomy versus standard therapy.

**Direct thrombus visualisation**

Analogous to hyperdensity on CT, signal change due to thrombotic occlusion of a vessel can be seen on FLAIR or gradient-echo MRI. These changes are of diagnostic value but are of no independent prognostic significance. However, recent evidence suggests this sign is predictive of fibrin-rich embolii, as opposed to platelet-rich, and is independently predictive of subsequent recanalisation.

**CT perfusion**

**Technical features**

Bolus-tracking CT perfusion also generates maps of cerebral blood flow and volume and time to peak or mean transit time. Most multidetector scanners restrict anatomical coverage typically to 20 mm (2–4 slices), reducing sensitivity to stroke not caused by large artery occlusion and preventing the full extent of perfusion changes to be imaged in MCA occlusion. The lack of direct visualisation of the tissue with acute cellular injury is another serious drawback of CT perfusion as compared with MRI. The technique is similar in execution and analysis to MRI-based PWI but it provides more robust physiological values.

**Mapping the penumbra and core**

CT-perfusion lesion maps have been assessed for prediction of later infarct and clinical outcome (figure 5). Relative cerebral blood flow volume thresholds (compared with the contralateral hemisphere) in hypoperfused tissue, destined to infarct or to survive, are similar to those described for single photon emission CT or PET and therefore might allow definition of the penumbra. The extent of deficits on cerebral blood flow or volume lesion maps has poorer interobserver agreement than mean transit time. Mean-transit-time and time-to-peak maps are more sensitive to ischaemia than plain CT or cerebral blood flow or volume maps. Mean transit time and time-to-peak lesion volumes are closely associated with final infarct volume in patients who do not recanalise, or who reperfuse. Time-to-peak and mean-transit-time lesions are larger.
Wintermark and colleagues hypothesised, based on PET data and animal studies, that if cerebral blood volume is below a threshold of 2.5 mL/100 mg this signified the ischaemic core and a reduced relative cerebral blood flow below 64% would define tissue at risk; the difference between these two lesions therefore represents penumbra. Additional studies have confirmed good correlations of cerebral blood flow values on CT-perfusion maps compared with PET or xenon CT, although quantitative perfusion measurements remain problematic.
**CT angiography of source images**

An alternative approach uses the source images of CT angiography to produce whole brain perfused cerebral blood volume-weighted images. Relative cerebral blood volume values obtained by this method can predict subsequent infarction within 6 h. This method is attractive because it only requires a single contrast bolus for both perfusion and CT angiography; however, full validation of this technique is lacking.

**Implementation of acute stroke imaging**

Assuming equal access to DWI–PWI and CT perfusion and expertise in their interpretation, decisions on optimum imaging use can be dictated by time elapsed since onset of stroke and severity of symptoms.

**The 0–3 h interval**

Within 3 h of onset, the most important decision is the eligibility for intravenous alteplase. All randomised controlled trials of patients being treated with alteplase use plain CT and this remains the typical method of acute MCA stroke decision-making in most centres. Based on earlier studies that associated anatomically extensive hypodensity with poor outcome, the concept that hypodensity greater than one-third of MCA territory should exclude patients from alteplase therapy as it represents extensive core or inaccurate time of onset has been used as a selection criterion in some randomised controlled trials (ECASS I and II). However, results from the 0–3 h group in the NINDS cohort do not support this exclusion from intravenous alteplase on the basis of the extent of early ischaemic changes alone; this issue is still the subject of debate. Although MRI offers equivalent detection of acute intracerebral haemorrhage, superior diagnostic confirmation of ischaemia, and sensitive detection of old haemorrhage, there are more restrictions regarding its application safety to acutely ill patients. It remains unclear if the risk of remote parenchymal haemorrhage after intravenous thrombolysis is associated with microbleeds (detectable on gradient-echo MRI). Screening for eligibility for intravenous thrombolysis within 3 h of stroke with MRI was feasible in an experienced centre, but at the expense of about a 20 min delay in treatment. If we believe that “time is brain”, then plain CT might be the preferred method. However, proponents of MRI argue that time lost may be compensated by improved exclusion of patients who may be harmed by treatment, a concept that is supported by lower haemorrhagic rates in MRI-selected series using a 0–6 h window, although not yet formally in a prospective randomised controlled trial. Furthermore, if it is confirmed that plain CT can be omitted, this delay may be reduced in the future, while current advances in MRI deliver a complete study within 10 min. Other studies report the safety and feasibility of MRI screening in acute stroke, and that shorter door-to-treatment times are achievable by increasing the familiarity of emergency physicians with its use.

**The 3–6 h interval**

In the 3–6 h period after onset of stroke, treatment by revascularisation is supported by more limited evidence: randomised controlled trials of intravenous alteplase have not confirmed effectiveness, although a meta-analysis suggests substantial benefit until 4·5 h, which forms the basis of the ECASS III trial. A single intra-arterial trial (of prourokinase) used catheter angiography to select patients with MCA occlusion and reported positive results. Analysis of the CT images of these patients showed the usefulness of reperfusion in patients who had a high ASPECTS score (<7) and little in the way of developed injury, whereas there was no benefit if the injury had already developed. Therefore there is support showing the value of reperfusion in the 3–6 h window based on appropriate selection of patients. Although ideally, patients in this time window should be offered randomisation into a randomised controlled trial, not all centres are involved in trials; in this situation, physiological imaging may assist in treatment decisions. The body of evidence for MRI variables, particularly DWI–PWI mismatch, is greater than for CT-perfusion maps at present. Two studies compared treatment with intravenous alteplase (within 3–6 h) based on the presence of DWI–PWI mismatch with standard alteplase treatment in the first 3 h with conventional plain CT criteria. In both studies, functional outcome was similar in the two groups; Ribo and colleagues also reported similar recanalisation rates and neurological improvement. Thomalla and colleagues, comparing their results with prior meta-analysis, found more favourable outcome and reduced rates of symptomatic intracerebral haemorrhage in their cohort of MRI-selected patients within 6 h. Further supporting the idea that MRI can effectively select patients that will probably benefit up to 6 h after onset is a strong association between clinical improvement and the salvage of mismatch tissue. Because CT is not as sensitive as DWI for detection of lacunar or posterior fossa stroke, MRI has clear advantages over CT perfusion unless time is a constraint or the diagnosis of MCA stroke is clinically definite. CT perfusion can be used instead if the patient is unsuitable for MRI, and in future may be preferred if the penumbra defined by CT perfusion is validated in larger series.

**Other scenarios**

For stroke presenting more than 6 h after onset or minor symptoms, the sensitivity and specificity of DWI supports this as the optimum imaging modality. Imaging can also be of particular value in “awakening stroke” which represents about 25% of ischaemic strokes. These patients are usually excluded from clinical trials, yet if current thinking is correct, many occur shortly before waking and are therefore potentially within the time window for thrombolytic therapy. A recent report of two patients with unknown time of onset in whom decision to administer alteplase was guided by CT perfusion would support this idea.
Massive MCA infarction (ie, malignant MCA stroke), carries a high risk of brain herniation and a mortality hazard as high as 80%153. Decompressive craniectomy is commonly considered because early surgical intervention is associated with better outcome to deferred intervention in young patients.154 There are no good clinical predictors of progression to coma and death, but imaging seems very promising. Both PET29 and ethyl-cysteinate dimer SPECT155 accurately predict the advent of malignant MCA stroke. Significant DWI–PWI predictors include large apparent diffusion coefficient lesion (>82 mL), large time to peak delay (more than 4 s) volume (>162 mL), small mismatch, and National Institutes of Health Stroke Scale >19.114 A multicentre study is currently underway in Germany that is prospectively assessing these parameters. Recently, the “rate of expansion” of the DWI lesion (ie, the lesion volume divided by the time since stroke onset) was reported to have almost 100% accuracy in a preliminary report.156

Figure 6 shows a possible imaging-based reference framework for acute anterior circulation stroke within 6 h of symptom onset.

Lacunar stroke syndromes and posterior circulation strokes

Lacunar stroke syndromes

Although the clinical diagnosis of lacunar stroke within the first 6 h is unreliable,160 it is improved if DWI shows a congruent deep small lesion suggestive of single perforator occlusion. Conversely, when several DWI lesions and a clinical source of emboli are present, the chance that the lacunar syndrome represents embolic stroke is high.161 A diagnosis of lacunar infarction in the acute stage has undecided implications for management. The NINDS study found no difference in benefit from intravenous alteplase in lacunar versus other stroke subtypes within 3 h of onset; however this was only based on clinical syndromes and CT. Because spontaneous recovery from lacunar infarcts is generally good,4 and the risk of intracerebral haemorrhage can increase due to associated small vessel disease,163 definitive confirmation of lacunar infarction may change the risk:benefit ratio. This hypothesis remains to be tested.

Posterior circulation strokes

Sensitivity of DWI is better than CT in brainstem and cerebellar (and lacunar) strokes. Studies using physiological imaging have been limited in this scenario. Using multimodal MRI, Ostrem and colleagues164 studied five patients with acute basilar artery occlusion and found substantial volumes of diffusion–perfusion mismatch, consistent with the apparent benefit of intravenous alteplase in posterior circulation stroke up to 7 h after onset.165,166 CT perfusion is probably unhelpful in posterior circulation stroke due to bony artifacts. Vascular imaging by CT angiography or magnetic resonance angiography and fat-suppressed T1-weighted neck views are valuable in identifying, for example, basilar occlusion, large-vessel atherosclerotic disease or extracranial arterial dissection, which may alter management.

Conclusions

Structural, vascular, and physiological imaging of acute stroke increasingly informs both clinical trial design and individual patient management. It is likely that both CT and MRI-based techniques will be more widely applied in future, and the relative strengths and weaknesses of each imaging modality should be regarded as complementary rather than competing. Effectively, an ideal situation would be to have access to
both imaging modalities to adjust to the various clinical situations and contraindications that present in the real world.

Contributors
KM contributed to layout, literature search, wrote the first draft, and contributed figures. AB and RV contributed to the writing of the third draft and final version. J R contributed to the writing of third draft and final version and contributed figures. J CB coordinated the project, drafted the layout, did the literature search, contributed to the writing of the first and second drafts, contributed figures, edited the third draft and final version.

Conflict of interest
We have no conflicts of interest.

References


