REVIEW ARTICLE

Radiological imaging in acute ischaemic stroke

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Patients who suffer acute ischaemic stroke can be treated with thrombolysis if therapy is initiated early. Radiological evaluation of the intracranial tissue before such therapy can be given is mandatory. In this review current radiological diagnostic strategies are discussed for this patient group. Beyond non-enhanced computed tomography (CT), the standard imaging method for many years, more sophisticated CT stroke protocols including CT angiography and CT perfusion have been developed, and additionally an increasing number of patients are examined with magnetic resonance imaging as the first imaging method used. Advantages and challenges of the different methods are discussed.

Introduction

Acute ischaemic stroke (AIS) can be treatable if therapy is given early. In general intravenous thrombolytic therapy should be initiated within 4.5 h of symptom onset and expeditious revascularization is associated with better clinical outcome [1]. Ongoing trials regarding patient selection mostly include radiological imaging criteria. The main goals of imaging in patients with symptoms of AIS are to exclude contraindications for thrombolytic and/or reperfusion therapy and to rule out any differential diagnoses visible on imaging. It is also important to detect therapeutically relevant arterial stenoses and/or occlusions and to evaluate infarction core and penumbra. At present there is no consensus on a preferred imaging modality in patients presenting with AIS. The European Stroke Organization guidelines recommend brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) in all suspected stroke or transient ischaemic attack (TIA) patients [2]. Current radiological diagnostic strategies for this patient group are discussed in this review.

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Computed tomography

Non-enhanced computed tomography

Non-enhanced computed tomography (NECT) has the advantages of being fast, widely available and without contraindications. In general intravenous thrombolytic therapy can be administered after the exclusion of contraindications on NECT. The main contraindications visible on NECT are acute intracranial haemorrhage, hypodense acute ischaemic changes in more than one-third of the middle cerebral artery (MCA) territory, and intracranial tumours [3]. Early signs of ischaemia include loss of distinction between grey and white matter, subtle hypodensities in the brain parenchyma, sulcal effacement and obscured delineation of the basal ganglia and the insular ribbon (Figs 1 and 2) [4,5]. The hyperdense artery sign can be seen in the presence of a thrombus in a large artery; this has a high specificity but a low sensitivity

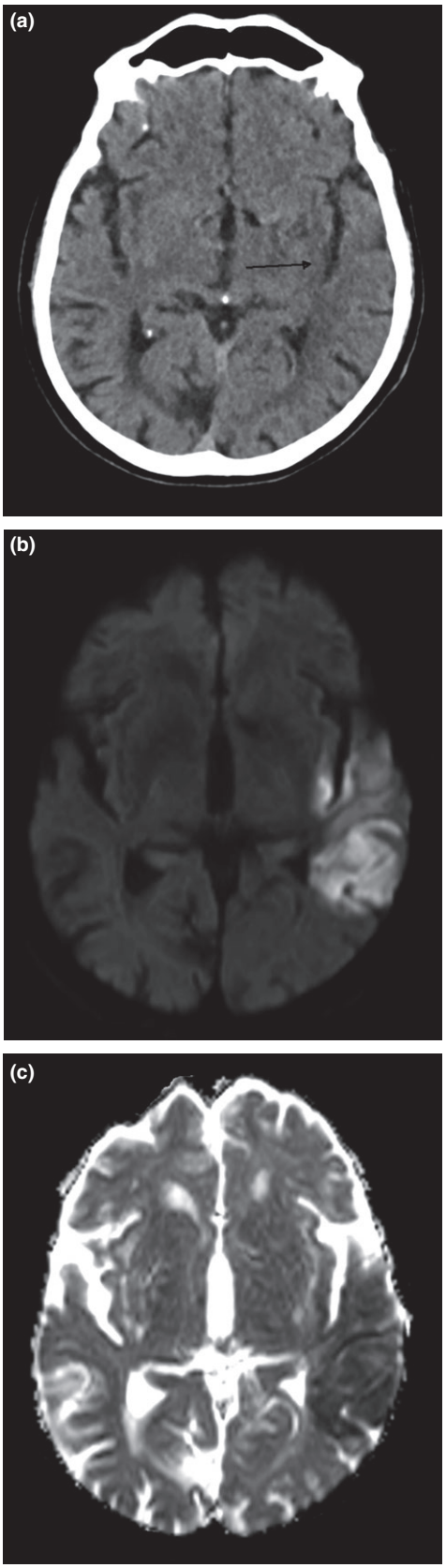


Figure 1 An 82-year-old male patient with acute aphasia and confusion. (a) Non-enhanced computed tomography performed 4 h after symptom onset shows early signs of ischaemia in the left hemisphere. This is most evident in the posterior insular cortex and posterior part of the temporal lobe with loss of grey–white differentiation (arrow). (b) Diffusion-weighted imaging with corresponding (c) apparent diffusion coefficient map 2 days later show the infarcted area in the posterior insular cortex and posterior parts of the left temporal lobe.

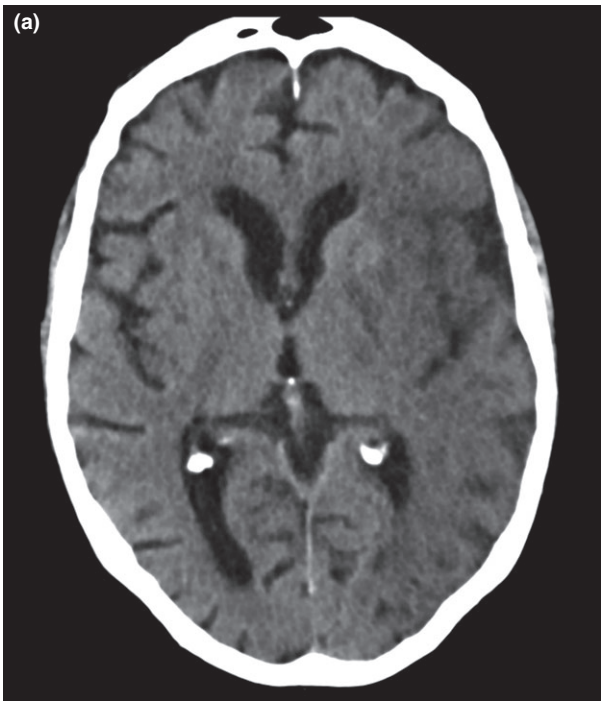
in MCA occlusions (30%–40%) [6]. A dense MCA sign longer than 8 mm predicts poor recanalization after intravenous thrombolysis [7]. An important sign of acute cerebral stroke seen in around 3% of patients, and which is frequently overlooked, is calcified cerebral embolism. The patients are at significant risk for recurrent embolic infarcts, often experienced within the first year after the initial stroke. The method of choice to detect calcified cerebral embolism is CT [8,9].

Early signs of ischaemia are often subtle on NECT, also having a high intra- and inter-observer variability. Additionally it can be challenging to identify early ischaemic changes within chronic white matter hypodensities. The NECT signs of ischaemia during the first 3 h of symptom onset have a sensitivity of 26%–60% and a specificity of 85%; the positive and negative predictive values are 96% and 27%, respectively [10,11]. In the setting of lacunar infarcts and hypodense changes in the posterior circulation, NECT has a lower sensitivity [12].

If the area of hypodense acute ischaemic change is larger than one-third of the MCA territory, reperfusion therapy is contraindicated. Other quantification methods, such as the Alberta Stroke Program Early CT Score (ASPECTS), can also be helpful in identifying patients not suitable for revascularization [13]. The MCA territory in each hemisphere is then divided into 10 regions. For each region where hypodense acute ischaemic changes are detected, one point is subtracted from 10. In general, patients with an ASPECTS below 7 are less likely to benefit from thrombolysis [13]. The posterior circulation ASPECTS is a predictive scale for quantifying posterior acute hypodense ischaemic changes [14].

Computed tomography angiography

In CT angiography (CTA) iodinated contrast is administered intravenously. The scanning typically starts from the aortic arch up to a level above the circle of Willis when the contrast medium is in the arterial phase. Stenoses and occlusions can be detected with high diagnostic accuracy in both pre-cranial and intracranial arteries thus revealing the origin of the



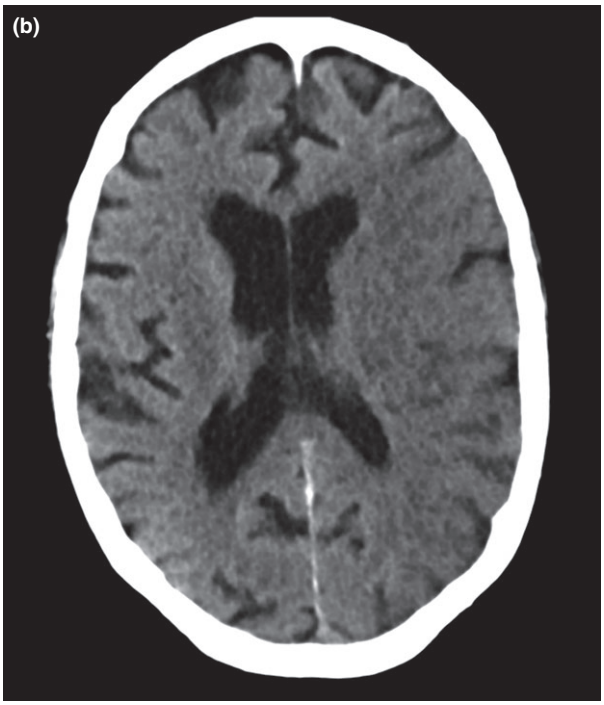


Figure 2 A 91-year-old male patient with acute right-sided hemiparesis, aphasia and reduced consciousness. (a), (b) On non-enhanced computed tomography performed 5 h after symptom onset hypodense areas with loss of differentiation between grey and white matter in large areas of the left hemisphere are visible due to acute ischaemic stroke. Most of the left middle cerebral artery territory is affected, including parts of the lentiform nucleus.

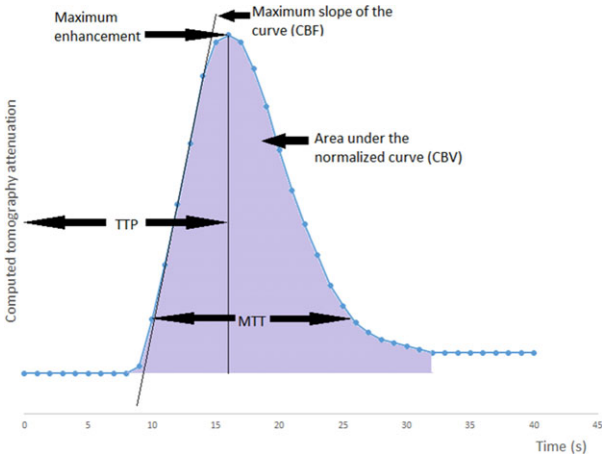


Figure 3 Time–density curve on computed tomography perfusion. Time to peak (TTP) is the time to the apex of the curve. Mean transit time (MTT) is the time from wash in to wash out of contrast agent. The area under the curve refers to the volume of blood (CBV) present at a given moment in a distinct brain area. Cerebral blood flow (CBF) is calculated from the gradient of the wash in of the time–density curve.

AIS (Fig. 3) [15]. CTA is essential in planning mechanical thrombectomy; and anatomical variations, arterial loops and angulated origins of arteries can be identified [16]. Other different therapeutic options such as early carotid thromboendarterectomy and appropriate medical therapy can be discussed [12,17]. The new generation of CT scanners can reconstruct a CT digital subtraction angiography where bone and soft tissue are subtracted, visualizing only the vasculature. In contrast to digital subtraction angiography, CTA lacks information about the flow of contrast from the arteries via capillaries to the veins. Despite this, CTA can provide a relevant overview of collateral flow, including leptomeningial collaterals around the ischaemic area. This information may be valuable in predicting the probability of salvaging brain tissue [17–19].

If no contrast is visible in the smaller arteries surrounding a large ischaemic area, there is a low probability that tissue in the penumbra zone can be rescued [20,21]. Studies performed on newer multislice CT scanners may lead to an overestimation of the infarct core volume shown on CTA source image analysis compared to diffusion-weighted imaging (DWI) on MRI [22].

Computed tomography perfusion

CT perfusion (CTP) is a technique where the same area of the brain is repeatedly scanned during the passage of the contrast medium from the arteries through the

capillaries to the veins and then into the venous sinuses [11]. Thereby density curves can be drawn for each pixel in the image and different colour coded parametric maps are derived from these curves (Fig. 3). A simplified explanation of the different parameters is as follows. Time to peak (TTP) shows the time to the apex of the time–density curve. It reflects the time it takes until the contrast bolus reaches the tissue and is the most sensitive marker for cerebral ischaemia. In an ischaemic area, TTP will be increased, as it takes a longer time for the contrast medium to reach an ischaemic area compared to normally perfused tissue. Alternatively, mean transit time (MTT) or time to maximum (T_{max}) can be calculated. MTT is the time from wash in to wash out of the contrast medium; this is also prolonged in an ischaemic area. T_{max} is the flow-scaled residue function in the tissue and is prolonged in an ischaemic lesion. Even if this parameter is widely used, its physiological meaning is not well understood. It is found to reflect delay, dispersion and to a lesser degree also MTT [23,24]. Cerebral blood volume (CBV) refers to the volume of blood present at a given moment in a distinct brain area and is calculated from the area under the time–density curve. Cerebral blood flow (CBF) is the blood supply to the brain in a given time and is derived from the gradient of the wash in of the time–density curve (Fig. 3). The relation between the parameters is described in the equation MTT = CBV/CBF [24].

The goal of CTP is to assess the ratio of infarct core (irreversibly damaged brain tissue) to penumbra, thus identifying the 'tissue at risk' [25]. The penumbra is the critically hypoperfused, infarct core adjacent tissue, which is still viable if reperfusion is achieved. It is of great interest to differentiate the penumbra from benign oligoaemia. Outside the penumbra, there is an area of benign oligoaemia which is hypoperfused to a lesser degree; it remains viable even if reperfusion fails [5].

There are different approaches for estimating the penumbra on CTP. The most common one is to presume that areas with significantly low CBV represent the ischaemic core, whereas areas with solely reduced CBF and/or TTP are considered to show the penumbra. Thus the visible mismatch comparing CBV and CBF represents roughly the penumbral area. However, other studies indicate that the most reliable predictor of infarct core is the reduction of the CBF to 30%–50% relative to the mean CBF in the contralateral hemisphere (Fig. 4) [25,26].

There are ongoing debates about the necessity of CTP in therapeutic decision making, and it is important to understand that the penumbra in the brain is a dynamic region, whereas perfusion maps are derived from a scan time of 1 min [25,27]. Results from some studies suggest that the use of CTP in patient selection for reperfusion therapy can potentially identify treatment responders. However, these trials show diverging results and the value of penumbra imaging is not yet fully understood [27–29]. Additionally, some regions of the brain are more resistant to permanent tissue damage due to ischaemia: white matter is more resistant to ischaemia than grey matter. Especially vulnerable areas of the brain include the caudate body, putamen, insular ribbon, middle frontal gyrus, precentral gyrus, paracentral lobule and the subcortical white matter [30–33]. The larger studies do not extract perfusion maps on selected areas of the brain.

It is important to emphasize that the rule of hypodensities in one-third of the MCA territory as a contraindication for reperfusion therapy on NECT should not be confused with the areas of change on colour coded perfusion maps.

Magnetic resonance imaging

A dedicated MRI protocol for AIS patients should be short and effective aiming to show acute ischaemic areas, exclude haemorrhage, and provide an overview of the anatomy to exclude tumours or other differential diagnoses to ischaemic stroke whilst visualizing the intracranial arteries [13].

Diffusion-weighted imaging

A transversal diffusion-weighted series is appreciated in the evaluation of restricted water diffusion in brain tissue as a sign of cytotoxic oedema. DWI has a superior sensitivity in the detection of acute ischaemia compared to CT [34,35] and shows areas of cytotoxic oedema as soon as 3–11 min after onset of AIS [36]. It is possible to visualize very small ischaemic areas even in the posterior fossa [13]. As the appearance of an acute stroke is characteristic and more detailed on MRI, MRI is superior to CT in the detection of stroke mimics [37]. The negative predictive value in the case of a negative initial DWI is reported to be 0.96. However, there are numerous reports of DWI-negative strokes, especially if the initial clinical evaluation is indicative of a TIA or in patients with minor neurological deficits [38–40]. The former clinical diagnosis TIA is now defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia without signs of acute infarction on neuroimaging [41].

In patients with cytotoxic oedema on DWI series, the area with diffusion restriction is defined as the ischaemic core [5]. Yet, there are reports of DWI lesions being reversible especially after mechanical thrombec-

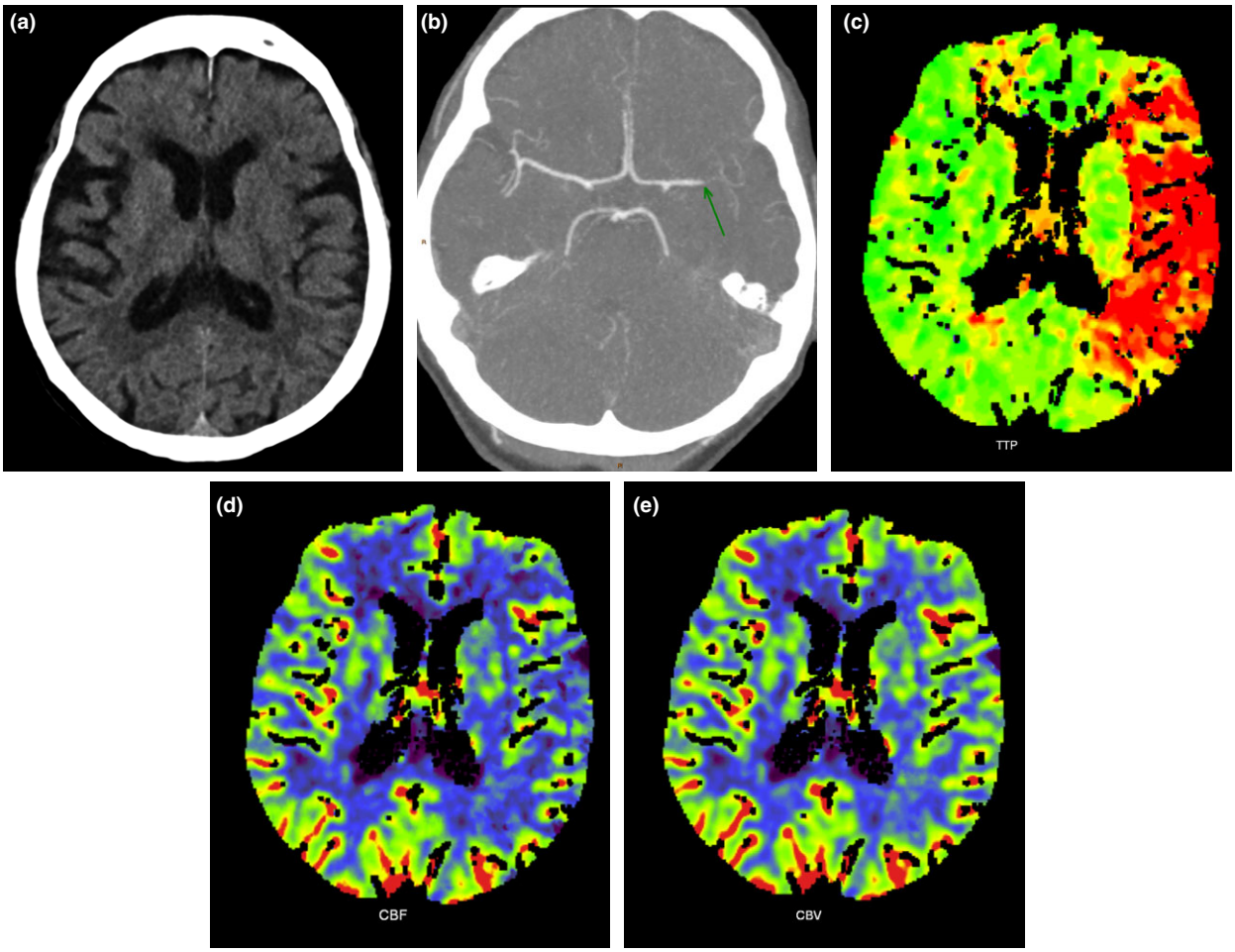


Figure 4 A 77-year-old female patient presenting with right-sided hemiparesis and aphasia on wakening (wake-up stroke). (a) Non-enhanced computed tomography performed at admission was normal. (b) Computed tomography perfusion angiography shows an occluding thrombus in the M1 segment of the left middle cerebral artery. (c) Computed tomography perfusion shows increased time to peak (TTP) in the left middle cerebral artery territory sparing the basal ganglia. (d) Relative cerebral blood flow (CBF) is reduced in the centre of this area. (e) Relative cerebral blood volume (CBV) is almost normal and indicative of salvageable tissue ('penumbra').

tomy [42]. These initially reversible lesions on an early MR (performed 24–48 h after therapy) may reappear if imaging is repeated 1–2 weeks later [43]. The higher the apparent diffusion coefficient value is, the higher the chance is that the lesion is reversible [44].

In the anterior circulation, a large infarct with cytotoxic oedema on DWI involving more than one-third of the MCA territory, an infarct volume >100 ml or an ASPECTS < 8 are associated with poor clinical outcome [10,43–45]. In this patient group reperfusion therapy is not recommended. Some authors even discuss whether the infarct volume limit defining a therapy contraindication should be as low as 70 ml [46].

Haemorrhage on MRI

A T2*-weighted image or alternatively susceptibility-weighted imaging can be used to identify intracerebral haemorrhage and for this purpose MRI is even more sensitive than CT [47]. It may be difficult, however, to differentiate smaller acute haemorrhages from older haemosiderin deposits and their presence is a much disputed contraindication for thrombolysis [48]. One study suggests that up to five haemosiderin deposits can be ignored whilst multiple deposits (>5) are associated with an increased risk of intracerebral haemorrhage after the administration of thrombolytic therapy [49].

Vessel imaging

Time of flight (TOF) MR angiography (MRA) gives information about flow in large intracranial arteries. This technique does not require injection of contrast medium; however, it is important to be aware that stenoses may be overestimated and occlusions erroneously diagnosed. TOF MRA can be useful in

diagnosing proximal vessel occlusions but is not suitable for identification of more distal or smaller branch occlusions [13]. The advantage of contrast enhanced MRA over TOF MRA is that collaterals distal to an occlusion are visualized [50].

In some cases, it is necessary to include a pre-cerebral MRA to evaluate occlusions, stenoses or dissections of pre-cerebral arteries; alternatively, a carotid ultrasound may be performed. A fat suppressed T1-weighted series is useful in identifying a hyperintense thrombus in the vessel wall in the case of acute dissection. However, this hyperintense signal usually develops within a few days owing to the transformation of haemoglobin to methaemoglobin and is therefore not always visible in the hyperacute phase [51].

Magnetic resonance perfusion imaging

In most MR perfusion protocols in AIS patients, contrast medium containing gadolinium is administered intravenously. Classically, T2*-weighted perfusion is performed, but T1-weighted perfusion is also a possibility. The area with cytotoxic oedema on DWI is usually defined as the infarct core [52]. There is no consensus yet regarding the definition of penumbra on perfusion imaging (PI) and a variety of different methods are described in the literature [13]: variables such as thresholds of TTP, MTT or T_{max} are considered in addition to the size of the area with reduced perfusion. In the DEFUSE and EPITHET trials, mismatch is defined as a 20% difference of the area between PI and DWI [53]. As mentioned in the section on CTP, penumbra should be clearly differentiated from benign oligoaemia [54]. This distinction may be difficult using imaging alone, however, and a clinical correlate is crucial since penumbra is associated with neurological deficit and benign oligaemia is not [55].

Magnetic resonance perfusion may be helpful in identifying those patients most likely not to profit from reperfusion therapy: in the cohort from the DEFUSE and EPITHET trials, the patients with a $T_{max} > 8$ s did not benefit from reperfusion therapy. In the same study, patients without DWI−PI mismatch did not profit from reperfusion therapy [54]. In the literature, evidence for the determination of penumbra using CTP is better corroborated compared to MR perfusion [11].

Fluid attenuated inversion recovery series

The hyperintense signal on fluid attenuated inversion recovery (FLAIR) series, seen in AIS, is only first visible after some hours compared to the almost instantaneous signal changes on DWI [56]. This delay can be used to approximate the time of onset of symptoms in patients where this is unknown and to assess the presence of subacute ischaemic lesions in patients with repetitive clinical TIA. If lesions present on DWI are not visible on FLAIR series, it is regarded as safe to administer reperfusion therapy, as it is anticipated that the ischaemic event occurred within the last 4.5 h [57]. However, if small changes are visible on FLAIR the patient may yet profit from reperfusion therapy [58]. The method is dependent on imaging parameters and the magnetic field strength of the MR scanner. The abnormalities in signal are seen earlier on FLAIR images from a 3 T scanner; thus it is recommended that these examinations are performed with a field strength of 1.5 T where possible [59].

The indisputable advantages of MR in AIS imaging are the absence of radiation exposure, the additional imaging information provided and that early stroke changes are more easily assessed. The main disadvantage is the limited availability on a 24/7 basis. Additionally, contraindications for MRI have to be ruled out in every patient before entering the MRI room, challenging though this might be in the hyperacute stroke setting. As the technical development evokes, it takes < 15 min to examine a patient with acute stroke using MRI, and the time used is comparable to the time used for image acquisition and analysis of a CT scan with CTA and CTP.

Magnetic resonance imaging does not necessarily prolong the door to needle time in the treatment of AIS. However, CT is often more readily available and is better incorporated into treatment routines for patients with AIS. Thus, the use of CT is recommended based on a higher level of documented evidence at present [2].

Impact on imaging of recent studies on intra-arterial thrombectomy

In February 2013 three randomized controlled studies were published showing no benefit of intra-arterial thrombectomy (IAT) over standard treatment with intravenous therapy [60–62]. However, from December 2014 to June 2015 several studies finally demonstrated the efficacy of IAT in patients with large vessel occlusions (LVOs) [63–68]. These findings have major implications on stroke organization and radiological imaging for acute stroke patients. As IAT has now been shown to be an effective treatment option, most centres emphasize that the pre-cerebral and intracranial vessels should be assessed in the acute phase and that NECT alone is no longer sufficient in the diagnostic workup of acute stroke patients. It is still not clear if NECT combined with a high National Institutes of Health Stroke Scale would be sufficient to

select the right patients for IAT, the goal being to save some time. However, most neurointerventionalists prefer to plan the IAT based on initial CT or MR images before starting the procedure.

Another important consequence of studies on radiological imaging is the impact of penumbra imaging. The Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial (EXTEND IA) study used fully automated CTP software to define irreversibly injured brain [64]. Ischaemic core was defined as tissue where the relative CBF was < 30% of that in normal tissue. Penumbra was defined as the surrounding tissue with a time to maximum (T_{max}) delay of more than 6 s. Some sites used MRI in the acute setting and used the DWI–PI mismatch instead of CT stroke imaging. Inclusion criteria were as follows: mismatch ratio > 1.2, absolute mismatch volume > 10 ml and ischaemic core lesion volume < 70 ml. Findings on CTP led to exclusion of 25% of the patients who probably would have been enrolled to IAT based on NECT and CTA alone. The selection criteria in this study led to good results in the IAT group where 71% reached functional independence compared to 40% in the control group ($P = 0.01$). There are still many questions to be answered regarding patient selection for IAT with radiological imaging remaining the cornerstone of the selection criteria in combination with clinical findings.

Another implication of the positive IAT trials addresses the organization of stroke treatment: patients with LVO must have access to IAT. This may imply centralization of stroke treatment or fast transport to a stroke centre offering IAT after initiation of intravenous thrombolysis in the case of LVO (drip and ship) [69].

Imaging of patients with transient ischaemic attack

As already mentioned, the former clinical diagnosis TIA is now defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia without signs of acute infarction on neuroimaging [41]. In this patient group it is particularly important to perform a thorough and rapid neuroradiological, neurological and cardiac workup. The most sensitive and specific method for this patient group to exclude signs of acute infarction is MRI including DWI [70,71].

Acute ischaemic stroke beyond 4.5 h and wake-up strokes

Under current guidelines, the restricted time window for thrombolytic therapy after symptom onset (> 4.5 h) is a challenging limitation: as many as 20%–25% of stroke patients wake from sleep with AIS [72]. A substantial number of acute stroke patients are admitted to hospital with unknown onset of stroke symptoms. It is also known that some patients arriving at hospital beyond the 4.5 h time window can still profit from thrombolytic treatment as the infarct core is relatively small, surrounded by a larger penumbra. A subgroup analysis of the EPITHET trial revealed that reperfusion and thrombolytic therapy between 4.5–6 h reduced infarct size and improved functional outcome [73]. The recent Cochrane analysis confirms that thrombolytic therapy can be profitable even up to 6 h after stroke onset, although the greatest benefit is seen if therapy is initiated within the first 3 h [74]. The DWI–FLAIR mismatch was initially used to identify patients with symptom onset < 3 h, but was later proved to be useful up to 4.5 h [57,75]. In patients arriving between 4.5 and 6 h after stroke onset it is a matter of discussion whether PI can select patients suitable for reperfusion therapy; suggested criteria are patients with infarct core less than a third of the MCA territory and MTT–CBV mismatch > 20% (Fig. 4) [76].

Conclusion

The goal of imaging in AIS patients should be to ensure the optimal treatment for each patient in the shortest time possible. As door to needle time is crucial, it is recommended that each stroke centre uses the imaging methods readily available, thus leading to the quickest, most reliable diagnosis. Both CT and MRI have a high specificity in AIS imaging. Independent of the imaging modality, current guidelines strongly recommend that an evaluation of the arteries also should be performed. In case of pre-cranial or intracranial stenoses or occlusions, the different therapeutic options such as thrombectomy or early carotid thromboendarterectomy should be discussed and appropriate medical therapy initiated [13,63–68]. Although PI shows promising results in identifying patients not eligible for thrombolytic therapy, it remains controversial whether PI can be used to predict if a patient will profit from reperfusion therapy or not [62,64]. As fast, precise and reliable radiological imaging and interpretation is crucial for important therapeutic decisions and outcome of patients with AIS, the neuroradiology department has to be tailored to provide this function on a 24/7 basis.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

References

1. Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; **359:** 1317–1329.
2. European Stroke Organisation Executive C, Committee ESOW. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008 **25:** 457–507.
3. Chalela JA, Kidwell CS, Nentwich LM, *et al*. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. *Lancet* 2007; **369:** 293–298.
4. Srinivasan A, Goyal M, Al Azri F, Lum C. State-of-the-art imaging of acute stroke. *Radiographics* 2006; **26** (Suppl 1)**:** S75–S95.
5. El-Koussy M, Schroth G, Brekenfeld C, Arnold M. Imaging of acute ischemic stroke. *Eur Neurol* 2014; **72:** 309–316.
6. Kim EY, Lee SK, Kim DJ, *et al*. Detection of thrombus in acute ischemic stroke: value of thin-section noncontrast-computed tomography. *Stroke* 2005; **36:** 2745–2747.
7. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke* 2011; **42:** 1775–1777.
8. Cerase A, Grazzini I. Early relapsing calcified cerebral embolism. *J Stroke Cerebrovasc Dis* 2015; **24:** 125–126.
9. Walker BS, Shah LM, Osborn AG. Calcified cerebral emboli, a 'do not miss' imaging diagnosis: 22 new cases and review of the literature. *Am J Neuroradiol* 2014; **35:** 1515–1519.
10. Hacke W, Kaste M, Fieschi C, *et al*. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995; **274:** 1017–1025.
11. Campbell BC, Weir L, Desmond PM, *et al*. CT perfusion improves diagnostic accuracy and confidence in acute ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2013; **84:** 613–618.
12. Rajajee V, Kidwell C, Starkman S, *et al*. Diagnosis of lacunar infarcts within 6 hours of onset by clinical and CT criteria versus MRI. *J Neuroimaging* 2008; **18:** 66–72.
13. Jauch EC, Saver JL, Adams HP Jr, *et al*. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; **44:** 870–947.
14. Puetz V, Sylaja PN, Coutts SB, *et al*. Extent of hypoattenuation on CT angiography source images predicts functional outcome in patients with basilar artery occlusion. *Stroke* 2008; **39:** 2485–2490.
15. Sabarudin A, Subramaniam C, Sun Z. Cerebral CT angiography and CT perfusion in acute stroke detection: a systematic review of diagnostic value. *Quant Imaging Med Surg* 2014; **4:** 282–290.
16. Devlin TG, Phade SV, Hutson RK, *et al*. CT perfusion imaging in the selection of acute stroke patients to undergo emergent carotid endarterectomy. *Ann Vasc Surg* 2015; **29:** 1–11.
17. Schramm P, Schellinger PD, Fiebach JB, *et al*. Comparison of CT and CT angiography source images with diffusion-weighted imaging in patients with acute stroke within 6 hours after onset. *Stroke* 2002; **33:** 2426–2432.
18. Higashida RT, Furlan AJ, Roberts H, *et al*. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke* 2003; **34:** e109–e137.
19. Yeo LL, Paliwal P, Teoh HL, *et al*. Assessment of intracranial collaterals on CT angiography in anterior circulation acute ischemic stroke. *AJNR Am J Neuroradiol* 2015; **123:** 662–669.
20. Schramm P, Schellinger PD, Klotz E, *et al*. Comparison of perfusion computed tomography and computed tomography angiography source images with perfusion-weighted imaging and diffusion-weighted imaging in patients with acute stroke of less than 6 hours' duration. *Stroke* 2004; **35:** 1652–1658.
21. Rosenthal ES, Schwamm LH, Roccatagliata L, *et al*. Role of recanalization in acute stroke outcome: rationale for a CT angiogram-based 'benefit of recanalization' model. *AJNR Am J Neuroradiol* 2008; **29:** 1471–1475.
22. Yoo AJ, Chandra RV, Leslie-Mazwi TM. Catching strokes before they happen: the importance of early neuroimaging findings in TIA and minor ischemic stroke. *Expert Rev Cardiovasc Ther* 2012; **10:** 847–850.
23. Calamante F, Christensen S, Desmond PM, Ostergaard L, Davis SM, Connelly A. The physiological significance of the time-to-maximum (Tmax) parameter in perfusion MRI. *Stroke* 2010; **41:** 1169–1174.
24. Fieselmann A, Kowarschik M, Ganguly A, Hornegger J, Fahrig R. Deconvolution-based CT and MR brain perfusion measurement: theoretical model revisited and practical implementation details. *Int J Biomed Imaging* 2011; **2011:** 467563.
25. Thierfelder KM, von Baumgarten L, Baumann AB, *et al*. Penumbra pattern assessment in acute stroke patients: comparison of quantitative and non-quantitative methods in whole brain CT perfusion. *PLoS One* 2014; **9:** e105413.
26. Bivard A, Levi C, Krishnamurthy V, *et al*. Defining acute ischemic stroke tissue pathophysiology with whole brain CT perfusion. *J Neuroradiol* 2014; **41:** 307–315.
27. Campbell BC, Christensen S, Levi CR, *et al*. Cerebral blood flow is the optimal CT perfusion parameter for assessing infarct core. *Stroke* 2011; **42:** 3435–3440.
28. Heiss WD, Graf R. The ischemic penumbra. *Curr Opin Neurol* 1994; **7:** 11–19.
29. Parsons MW, Levi CR. Reperfusion trials for acute ischaemic stroke. *Lancet* 2012; **380:** 706–708.
30. Parsons MW, Miteff F, Bateman GA, *et al*. Acute ischemic stroke: imaging-guided tenecteplase treatment in an extended time window. *Neurology* 2009; **72:** 915–921.
31. Payabvash S, Souza LC, Wang Y, *et al*. Regional ischemic vulnerability of the brain to hypoperfusion: the need for location specific computed tomography perfusion thresholds in acute stroke patients. *Stroke* 2011; **42:** 1255–1260.
32. Falcao AL, Reutens DC, Markus R, *et al*. The resistance to ischemia of white and gray matter after stroke. *Ann Neurol* 2004; **56:** 695–701.
33. Koga M, Reutens DC, Wright P, *et al*. The existence and evolution of diffusion-perfusion mismatched tissue

in white and gray matter after acute stroke. *Stroke* 2005; **36:** 2132–2137.
34. Forster A, Gass A, Kern R, *et al*. Brain imaging in patients with transient ischemic attack: a comparison of computed tomography and magnetic resonance imaging. *Eur Neurol* 2012; **67:** 136–141.
35. Nezu T, Koga M, Nakagawara J, *et al*. Early ischemic change on CT versus diffusion-weighted imaging for patients with stroke receiving intravenous recombinant tissue-type plasminogen activator therapy: stroke acute management with urgent risk-factor assessment and improvement (SAMURAI) rt-PA registry. *Stroke* 2011; **42:** 2196–2200.
36. Hjort N, Butcher K, Davis SM, *et al*. Magnetic resonance imaging criteria for thrombolysis in acute cerebral infarct. *Stroke* 2005; **36:** 388–397.
37. Schaefer PW, Copen WA, Lev MH, Gonzalez RG. Diffusion-weighted imaging in acute stroke. *Magn Reson Imaging Clin N Am* 2006; **14:** 141–168.
38. Hotter B, Kufner A, Malzahn U, Hohenhaus M, Jungehulsing GJ, Fiebach JB. Validity of negative high-resolution diffusion-weighted imaging in transient acute cerebrovascular events. *Stroke* 2013; **44:** 2598–2600.
39. Inatomi Y, Kimura K, Yonehara T, Fujioka S, Uchino M. DWI abnormalities and clinical characteristics in TIA patients. *Neurology* 2004; **62:** 376–380.
40. Simonsen CZ, Madsen MH, Schmitz ML, Mikkelsen IK, Fisher M, Andersen G. Sensitivity of diffusion- and perfusion-weighted imaging for diagnosing acute ischemic stroke is 97.5%. *Stroke* 2015; **46:** 98–101.
41. Easton JD, Saver JL, Albers GW, *et al*. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke* 2009; **40:** 2276–2293.
42. Inoue M, Mlynash M, Straka M, *et al*. Clinical outcomes strongly associated with the degree of reperfusion achieved in target mismatch patients: pooled data from the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution studies. *Stroke* 2013; **44:** 1885–1890.
43. Kidwell CS, Saver JL, Mattiello J, *et al*. Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging. *Ann Neurol* 2000; **47:** 462–469.
44. Fung SH, Roccatagliata L, Gonzalez RG, Schaefer PW. MR diffusion imaging in ischemic stroke. *Neuroimaging Clin N Am* 2011; **21:** 345–377, xi.
45. Pexman JH, Barber PA, Hill MD, *et al*. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *AJNR Am J Neuroradiol* 2001; **22:** 1534–1542.
46. Campbell BC, Mitchell PJ, Kleinig TJ, *et al*. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015; **12:** 1009–1018.
47. Fiebach JB, Schellinger PD, Gass A, *et al*. Stroke magnetic resonance imaging is accurate in hyperacute intracerebral hemorrhage: a multicenter study on the validity of stroke imaging. *Stroke* 2004; **35:** 502–506.
48. Kidwell CS, Chalela JA, Saver JL, *et al*. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. *JAMA* 2004; **292:** 1823–1830.
49. Dannenberg S, Scheitz JF, Rozanski M, *et al*. Number of cerebral microbleeds and risk of intracerebral hemorrhage after intravenous thrombolysis. *Stroke* 2014; **45:** 2900–2905.
50. Ernst M, Forkert ND, Brehmer L, *et al*. Prediction of infarction and reperfusion in stroke by flow- and volume-weighted collateral signal in MR angiography. *AJNR Am J Neuroradiol* 2015; **36:** 275–282.
51. Rizzo L, Crasto SG, Savio D, *et al*. Dissection of cervicocephalic arteries: early diagnosis and follow-up with magnetic resonance imaging. *Emerg Radiol* 2006; **12:** 254–265.
52. Wheeler HM, Mlynash M, Inoue M, *et al*. Early diffusion-weighted imaging and perfusion-weighted imaging lesion volumes forecast final infarct size in DEFUSE 2. *Stroke* 2013; **44:** 681–685.
53. Mlynash M, Lansberg MG, De Silva DA, *et al*. Refining the definition of the malignant profile: insights from the DEFUSE-EPITHET pooled data set. *Stroke* 2011; **42:** 1270–1275.
54. Olivot JM, Mlynash M, Thijs VN, *et al*. Optimal Tmax threshold for predicting penumbral tissue in acute stroke. *Stroke* 2009; **40:** 469–475.
55. Best AC, Acosta NR, Fraser JE, *et al*. Recognizing false ischemic penumbras in CT brain perfusion studies. *Radiographics* 2012; **32:** 1179–1196.
56. Lansberg MG, Lee J, Christensen S, *et al*. RAPID automated patient selection for reperfusion therapy: a pooled analysis of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Study. *Stroke* 2011; **42:** 1608–1614.
57. Thomalla G, Cheng B, Ebinger M, *et al*. DWI−FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4.5 h of symptom onset (PRE-FLAIR): a multicentre observational study. *Lancet Neurol* 2011; **10:** 978–986.
58. Odland A, Særvoll P, Advani R, *et al*. Are the current MRI criteria using the DWI−FLAIR mismatch concept for selection of patients with wake-up stroke to thrombolysis excluding too many patients? *Scand J Trauma Resusc Emerg Med* 2015; **19:** 22.
59. Emeriau S, Serre I, Toubas O, Pombourcq F, Oppenheim C, Pierot L. Can diffusion-weighted imaging-fluid-attenuated inversion recovery mismatch (positive diffusion-weighted imaging/negative fluid-attenuated inversion recovery) at 3 Tesla identify patients with stroke at <4.5 hours? *Stroke* 2013; **44:** 1647–1651.
60. Broderick JP, Palesch YY, Demchuk AM, *et al*. Endovascular therapy after intravenous r-PA versus t-PA alone for stroke. *N Engl J Med* 2013; **368:** 893–903. [Erratum, *N Engl J Med* 2013 **368:** 1265.]
61. Ciccone A, Valvassori L, Nichelatti M, *et al*. Endovascular treatment for acute ischemic stroke. *N Engl J Med* 2013; **368:** 904–913.
62. Kidwell CS, Jahan R, Gornbein J, *et al*. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med* 2013; **368:** 914–923.

63. Berkhemer OA, Fransen PSS, Beumer D, *et al*. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; **372:** 11–20.
64. Campbell BC, Mitchell PJ, Kleinig TJ, *et al*. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015; **372:** 1009–1018.
65. Goyal M, Demchuk AM, Menon BK, *et al*. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015; **372:** 1019–1030.
66. Saver JL, Goyal M, Bonafe A, *et al*. Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial: protocol for a randomized, controlled, multicenter study comparing the Solitaire revascularization device with IV tPA with IV tPA alone in acute ischemic stroke. *Int J Stroke* 2015; **10:** 439–448.
67. Jovin TG, Chamorro A, Cobo E, *et al*. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015; **372:** 2296–2306.
68. Saver JL, Goyal M, Bonafe A, *et al*. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015; **372:** 2285–2295.
69. Sheth KN, Smith EE, Grau-Sepulveda MV, *et al*. Drip and ship thrombolytic therapy for acute ischemic stroke: use, temporal trends, and outcomes. *Stroke* 2015; **46:** 732–739.
70. Cerase A1, Vallone IM, Tassi R, *et al*. Neuroimaging of transient ischemic attack. *Arch Neurol* 2010; **67:** 772–773.
71. Casaubon LK, Boulanger JM, Blacquiere D, *et al*. Canadian stroke best practice recommendations: hyperacute stroke care guidelines, update 2015. *Int J Stroke* 2015; **10:** 924–940.
72. Rimmele DL, Thomalla G. Wake-up stroke: clinical characteristics, imaging findings, and treatment option – an update. *Front Neurol* 2014; **5:** 35.
73. Picanco MR, Christensen S, Campbell BC, *et al*. Reperfusion after 4.5 hours reduces infarct growth and improves clinical outcomes. *Int J Stroke* 2014; **9:** 266–269.
74. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2014; **7:** CD000213.
75. Thomalla G, Rossbach P, Rosenkranz M, *et al*. Negative fluid-attenuated inversion recovery imaging identifies acute ischemic stroke at 3 hours or less. *Ann Neurol* 2009; **65:** 724–732.
76. Garcia-Bermejo P, Calleja AI, Perez-Fernandez S, *et al*. Perfusion computed tomography-guided intravenous thrombolysis for acute ischemic stroke beyond 4.5 hours: a case–control study. *Cerebrovasc Dis* 2012; **34:** 31–37.