Imaging for Acute Stroke

Nine case studies detailing the impact of imaging on stroke therapy.

BY ANSAAR T. RAI, MD

Ischemic stroke is a dynamic process, and the term *stroke in evolution* precisely underscores this dynamism. Individuals respond differently to an ischemic insult, and the rate at which the stroke progresses or evolves varies from patient to patient. A diagnostic test, which can increase confidence in selecting patients for treatment, may result in better outcomes by administering therapy to those with the maximum likelihood of recovery and excluding those in whom treatment may be detrimental or futile. The progression of ischemia to irreversible brain damage is multifactorial.[1] The severity and duration of ischemia, the area of brain involved, and the oxygen content of blood are all factors that have an important bearing on how rapidly the ischemic injury becomes irreversible.[2] These factors are not constant; instead, individuals vary in their capacity to tolerate an ischemic insult.

The most widely used imaging modality in acute stroke is a noncontrast computed tomography (NCCT) scan of the brain. Although this modality is very sensitive in excluding hemorrhage,[3] it is insensitive in reflecting the functional state of the brain pertaining to its perfusion. Despite recognition of early ischemic signs,[4-6] sensitivity of NCCT remains poor in evaluating stroke within the therapeutic window of 3 hours[7] and does not substantially change when extended to 6 hours.[8] Furthermore, once ischemic changes are recognized on the NCCT, they go on to complete infarction with a very high probability.[9] Since the National Institute of Neurological Disorders and Stroke (NINDS) trials were first published, imaging modalities for assessment of brain perfusion and noninvasive angiography have been developed and are increasingly becoming part of stroke assessment at tertiary centers.[10]

PERFUSION IMAGING

Perfusion imaging in acute stroke represents the state of the brain as a function of its blood supply or the lack thereof (in contrast, a NCCT only provides anatomical data). Such imaging can be performed with either MRI or CT. After the intravenous injection of iodinated contrast, sequential cine CT data are obtained from preselected sections of the brain to which application of mathematical functions, such as deconvolution, can yield quantitative perfusion parameters, such as cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT).[11]

The CBF is generally measured as the amount of blood in milliliters delivered per 100 g of brain per minute.[12] CBV is the total volume of blood within a

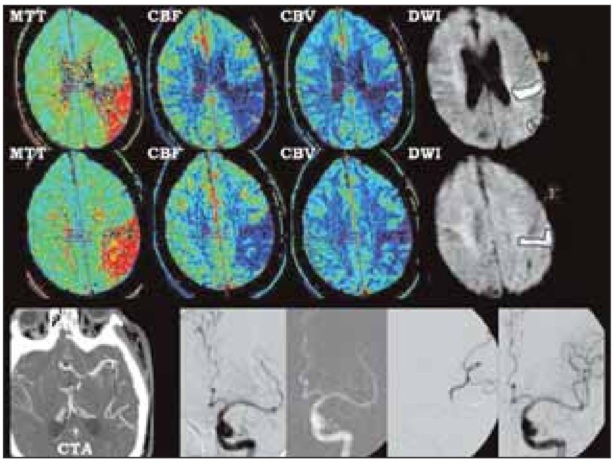

Figure 1. Case 1: A 66-year-old man presented within 3 hours of symptom onset. Endovascular therapy was performed based on perfusion imaging with restoration of flow and reversal of symptoms.

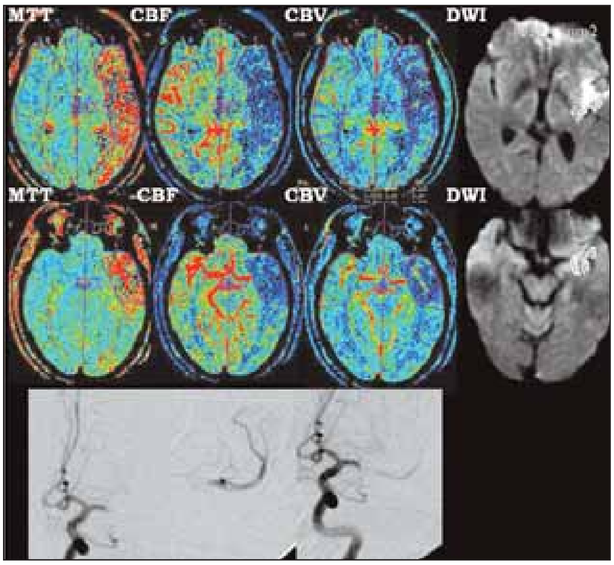

Figure 2. Case 2: A 68-year-old man presented within 6 hours of symptom onset. Partial angiographic recanalization was achieved with intra-arterial tissue plasminogen activator (tPA). Restoration of symptoms occurred during the next 24 hours.

given mass of tissue and is expressed as milliliters of blood per 100 g of brain tissue.[12] MTT is calculated as the ratio of CBV to CBF and, theoretically, is the time required for the blood to pass through the cerebral circulation.[12] These parameters are not only accurate but are also reproducible[13] and helpful in differentiating between irreversible and reversible brain damage.[14,15] Ischemic penumbra commonly describes the part of the brain that is hypoperfused or ischemic enough to cause cellular dysfunction but not enough to cause cell death.[16-18] The previously described perfusion parameters are helpful in identifying this penumbra. The relationship of these parameters to infarct progression varies widely between individuals and, in the same individual, between different parts of the brain.[2] Such distinction is instrumental before subjecting patients to potent thrombolytic treatment.

IMAGING THE NEUROVASCULATURE

The localization and extent of the arterial occlusion site are also important information affecting treatment decisions, especially when endovascular therapy is available. Rapid, high-resolution, noninvasive vascular imaging can be performed with CT angiography (CTA).[19] The current multidetector CT scanners allow for simultaneous performance of CTA and CT perfusion. Furthermore, the data can be obtained and processed expeditiously. In one study, the time required for entire data processing was approximately 15 minutes.[20] In the same study, CT perfusion and CTA had a very high sensitivity (90%) for predicting large territorial infarctions.[20] Small lesions and inadequate coverage of data acquisitions accounted for the false-negative cases.[20] CTA is particularly useful in posterior fossa infarcts, where perfusion CT may be limited secondary to artifacts from the skull base. Additionally, depending on the number of levels or slices utilized in perfusion imaging, the posterior fossa may be excluded from the field of view.[21] CTA and CT perfusion imaging significantly improve the assessment of infarct volume and site of vascular occlusion over that of initial clinical assessment and noncontrast CT alone.[22,23]

TECHNIQUE

Perfusion imaging can be performed utilizing either CT or MRI modalities. However, CT evaluation for stroke has logistical advantages over MRI because of its increased availability and shorter scan times.[24] MRI, however, allows for more accurate depiction of the infarcted brain and the extent of injury. At our institution, we have been incorporating CT perfusion imaging in our stroke management protocols for the past 8 years. Initially, two-level perfusion imaging was performed at the level of the basal ganglia for maximum coverage of the middle cerebral artery distribution. Currently, we use 80 mL of intravenous contrast injected at a rate of 3 to 4 mL/s to obtain eight predefined levels (each 1 cm thick) of perfusion parameters. The levels cover the posterior fossa, as well as the supratentorial brain. Concurrent CTA is performed from below the carotid artery bifurcations to the cranial vertex with an additional 80 mL of intravenous contrast. The perfusion data are immediately processed using dedicated software (CT perfusion-2, 2.6.6i., GE Healthcare Technologies, Waukesha, WI). The complete “stroke CT” information, including NCCT, CT perfusion, and

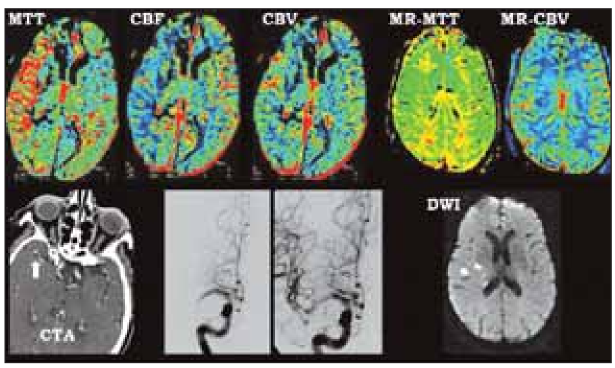

Figure 3. Case 3: A 78-year-old woman with occlusive thrombus was recanalized within 7 hours of symptom onset. Treatment was based on favorable perfusion data.

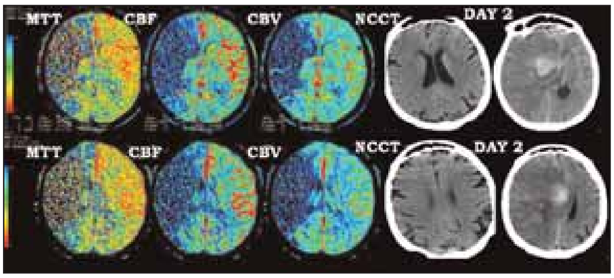

Figure 4. Case 4: An 85-year-old woman presented within 3 hours of symptom onset with matched perfusion deficits. Treatment failure occurred with thrombolytics despite administration within 3 hours.

CTA, is available for review within 10 minutes. A Web-based server allows remote access to these images, which is helpful in treatment planning (especially an endovascular intervention). Currently, almost all vendors offer perfusion packages as part of the new multidetector scanners.

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CASE STUDIES

The utility of CT perfusion and its potential role in stroke management are further highlighted by specific case examples. The interrelationship of the perfusion parameters is categorized into matched or mismatched defects. Strokes of unknown onset and posterior circulation strokes are discussed separately.

"Mismatched" Perfusion Defects

In case 1 (Figure 1), a 66-year-old man presented to the emergency room approximately 2.5 hours after onset of right-sided weakness, with a National Institute of Health Stroke Scale (NIHSS) of 8. The NCCT (not included in the figure) did not show any early ischemic changes. The CT perfusion imaging performed at two contiguous levels shows a distinctly increased MTT and decreased CBF in the posterior middle cerebral artery distribution on the left side. However, the CBV was decreased around a much smaller area. Simultaneously performed CTA showed occlusion of an M2 branch confirmed by the catheter angiography. Local intra-arterial tPA was administered via a microcatheter with lysis of the clot and restoration of blood flow. MRI performed the next day showed an infarct on the diffusion-weighted images (DWI). The diffusion abnormality representing the infarct closely corresponded to the area of decreased CBV. The rest of the brain, which showed abnormal MTT and CBF (but preserved CBV) was spared, suggesting potentially reversible perfusion changes. The DWI slices are at the same level as the CT perfusion images. The patient was discharged after 2 days with a near-baseline neurologic examination. The decision to treat this patient was based on the mismatch between the CBF and the CBV or the MTT and the CBV, which is believed to represent the salvageable tissue of the penumbra. Simultaneous CTA allows for clot localization, sparing the need for a full-catheter angiogram.

In case 2 (Figure 2), a 68-year-old man presented approximately 4 hours after symptom onset of right hemiparesis and aphasia, with an NIHSS of 12. The NCCT was unremarkable. The CT perfusion showed increased MTT and decreased CBF over almost the entire left middle cerebral artery distribution; the CBV was, however, decreased over a relatively much smaller area. CTA (not shown) showed an occlusive left middle cerebral artery thrombus, which was confirmed angiographically. Local intra-arterial thrombolysis was performed with 12 mg of tPA, resulting in partial recanalization (bottom row). MRI performed the next day showed the infarct localized to the anterior temporal and inferior frontal lobes on slice-matched DWI. This case again highlights the utility of CT perfusion parameters in guiding therapy. The part of the brain that has an abnormal CBV is most likely to infarct. Although perfusion abnormalities involving CBF and MTT may be reversed following successful recanalization, a significantly decreased CBV is least likely to come back. The CBV abnormality therefore can be

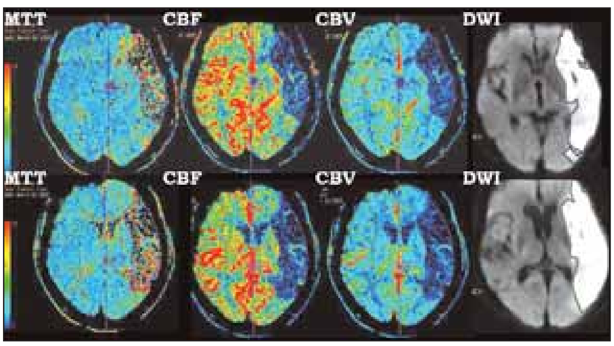

Figure 5. Case 5: A 79-year-old man presented within 6 hours of symptom onset with severe matched perfusion deficits. A large infarct despite angiographic recanalization occurred with endovascular therapy.

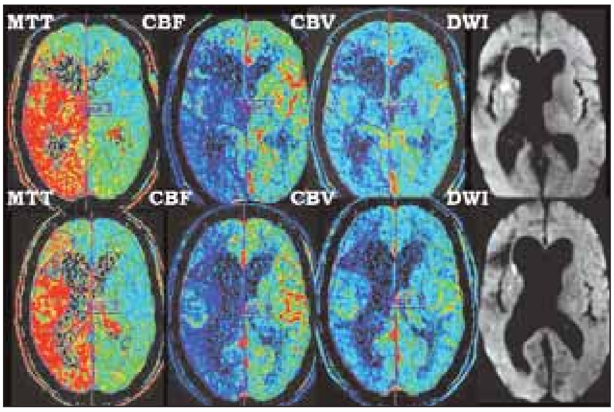

Figure 6. Case 6: An 82-year-old man awoke with stroke symptoms. Treatment guided by perfusion imaging led to neurologic improvement.

characterized as the core of the ischemic brain likely representing irreversible damage surrounding which is a zone of potentially reversible ischemia. The increase in MTT is possibly secondary to the cerebral vasodilatation and development of collaterals in response to an intracranial vascular occlusion, thereby maximizing oxygen extraction.

In case 3 (Figure 3), a 78-year-old woman presented 5.5 hours after onset of left hemiparesis. NCCT showed no acute ischemic changes. Perfusion imaging, although slightly degraded by patient motion, showed increased MTT and decreased CBF in a large part of the right middle cerebral artery distribution, representing the area at risk for infarction. The CBV, however, was decreased over considerably smaller and localized areas that amounted to <10% of the area of perfusion abnormalities on the CBF and MTT. CTA localized a middle cerebral artery occlusion, which was angiographically confirmed and successfully recanalized (Figure 3, bottom row, center two images) using the Merci retriever device (Concentric Medical, Inc., Mountain View, CA) more than 6.5 hours into the stroke. MRI performed 2 days after admission showed minimal infarcts only limited to the area of CBV abnormality. An MRI perfusion study performed at the same time showed normalization of the CBF and MTT as well. The fact that the final infarct size correlates most closely with the CBV highlights the importance of this parameter in identifying areas most likely to infarct, although the reversibility of the CBF and MTT suggest areas of reversible ischemia. It is this difference between the potentially reversible ischemic brain (represented by the MTT and CBF) versus the infarcted brain (most closely reflected by the CBV) that can help determine the penumbra and individualize treatment.

"Matched" Perfusion Defects

Cases 4 and 5 describe patients who had matched defects in terms of their perfusion parameters. In other words, there was no difference between the ischemic and infarcted brain indicating no penumbra or salvageable brain.

In case 4 (Figure 4), an 85-year-old woman presented with dense left hemiparesis within 3 hours of symptom onset. Her NCCT showed mild early ischemic changes along the insular cortex and the basal ganglia. The CT perfusion study shows marked perfusion abnormalities involving the entire left middle cerebral artery distribution; however, unlike the previous cases, the abnormal perfusion in this patient is matched across the three parameters. The MTT is also mostly decreased, indicating the lack of any cerebral autoregulation and collateral reserve; the CBF is significantly decreased, and the CBV is also markedly decreased in an almost identical configuration. The findings in this case indicate an area of the brain that is severely ischemic with almost no perfusion reserve and a very high likelihood of complete infarction. The patient was given intravenous tPA without any neurologic recovery. NCCT performed the next day (Figure 4, images labeled "Day 2") showed a very large infarct with mass effect, edema, and localized hemorrhagic conversion. Despite this patient presenting well within 3 hours of symptom onset, her stroke was so severe that it limited any chances of meaningful recovery despite any intervention.

In case 5 (Figure 5), a 79-year-old man presented slightly more than 5 hours after onset of aphasia and dense right hemiparesis. The CT perfusion images again

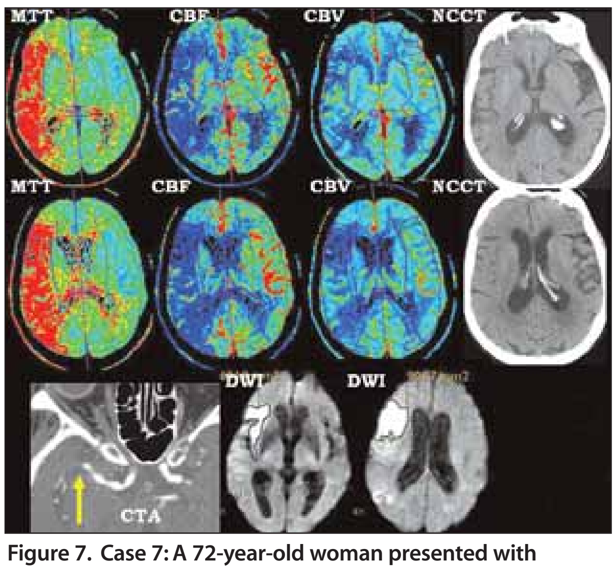

Figure 7. Case 7: A 72-year-old woman presented with unknown onset of neurologic symptoms. Endovascular recanalization was performed based on favorable perfusion data.

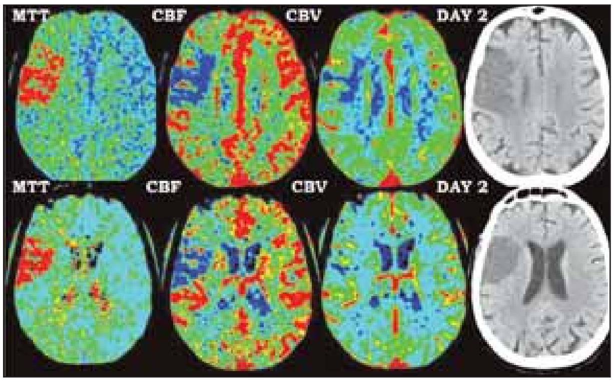

Figure 8. Case 8: A 79-year-old woman with improving neurologic symptoms.

show severe matched perfusion abnormalities involving the entire left middle cerebral artery distribution. The MTT, unlike the first three cases, was barely increased, again indicating a lack of cerebral vascular reserve. The matched and significant CBV decrease suggests irreversible damage and infarcted tissue. The patient had an occlusive left middle cerebral artery thrombus that was recanalized utilizing intra-arterial tPA and angioplasty (not shown). However, despite angiographic recanalization, the patient had complete infarction of the left middle cerebral artery distribution. Both cases 4 and 5 were treated according to the suggested treatment guidelines based on time of symptom onset, and in case 5, despite achieving angiographic recanalization, this treatment failed to affect the outcome.

Unknown Time of Onset and "Wake-Up" Strokes

Patients with an unknown time of onset or those waking up with neurologic deficits are typically excluded from treatment based on the current guidelines.[25] It is in these cases that perfusion imaging can play an extremely important role in selecting patients for therapy. Also, patients with improving deficits in the face of obvious perfusion abnormalities and documented vascular occlusion can be at risk of eventual infarction if left untreated and can be potential candidates for therapy based on the imaging findings.

In case 6 (Figure 6), an 82-year-old man presented approximately 7 hours after waking up with left hemiparesis. His NIHSS was 12. A CT perfusion scan showed decreased CBF over almost the entire right middle cerebral artery territory; the MTT was significantly increased over the same region indicating good vascular reserve. The CBV showed only subtle localized decrease at the basal ganglia. The large difference in the perfusion abnormalities between the CBV and the MTT or the CBF is suggestive of a large penumbra. CTA (not shown) identified an occlusive thrombus within the proximal right middle cerebral artery. Because of the large amount of potentially salvageable brain, endovascular recanalization was offered and performed utilizing the Merci retriever device (images not shown). The patient demonstrated significant neurologic improvement, and follow-up MRI showed minimal infarcts in the basal ganglia corresponding to the CBV abnormality.

In case 7 (Figure 7), similar imaging findings were seen in a 72-year-old woman who presented with unknown onset of neurologic symptoms. Based on the mismatch in the perfusion images (MTT and CBV or CBF and CBV), local intra-arterial thrombolysis was performed with tPA for an M1 thrombus with complete recanalization with limited infarction on the subsequent DWIs.

In case 8 (Figure 8), a 79-year-old woman presented within 3 hours with left hemiparesis; however, her symptoms had started to improve significantly in the emergency room and no treatment was instituted. Her perfusion images showed a mismatch between the CBV, which was not altered, and the MTT and the CBF, which were increased and decreased respectively. The MTT abnormality was helpful in localizing an occlusion within an M3 branch of the right middle cerebral artery. The patient was admitted and the next morning was found to have significant left hemiparesis. NCCT performed the following day (Figure 8, images labeled "Day 2") showed an acute infarct corresponding to the earlier perfusion abnormalities (MTT and CBF) in the right frontal lobe. The patient initially had a penumbra based on the perfusion parameters; however, the continuous branch-vessel occlusion led to completion of the infarct in the area of the reversible ischemia represented by the CBF/CBV mismatch. In this case, a sustained decrease in the perfusion pressure secondary to the continuous occlusion probably overcame the brain's autoregulatory response and the collateral reserve. Although it is still difficult to justify a potentially risky treatment in someone with improving

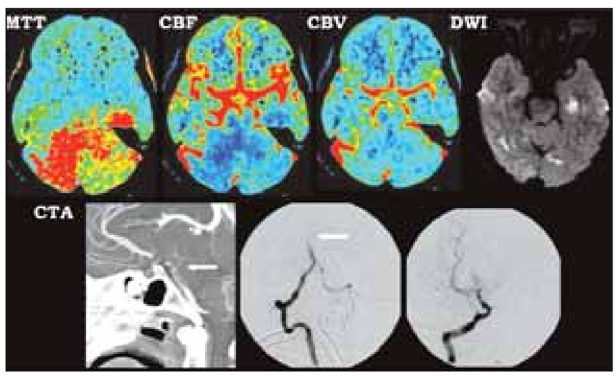

Figure 9. Case 9: A 49-year-old woman with basilar artery occlusion.

symptoms or minimal neurologic deficits, perfusion imaging can be useful in identifying this patient subset that may need much closer neurologic monitoring.

> "Because basilar artery occlusions carry a much worse prognosis and are almost fatal if left untreated, time-based therapies are even less applicable than for anterior circulation strokes."

Posterior Circulation Strokes

Because basilar artery occlusions carry a much worse prognosis and are almost fatal if left untreated, time-based therapies are even less applicable than for anterior circulation strokes. CTA plays a very important role in localizing the site of occlusion, as well as for evaluation of the vertebral arteries for endovascular treatment planning. Our CT perfusion protocol now includes imaging through the posterior fossa in addition to the supratentorial brain.

In case 9 (Figure 9), a 49-year-old woman was found unresponsive and brought to the emergency room. NCCT showed a hyperdense basilar artery indicating possible occlusion, which was confirmed by CTA. The perfusion imaging showed increased MTT and decreased CBF in most of the posterior circulation distribution. The CBV was equivocally decreased in some areas. Angiographic evaluation confirmed the basilar occlusion. Endovascular recanalization was performed with local intra-arterial tPA, as well as mechanical thrombectomy with the Merci device. The patient's clinical condition progressively improved during the days that followed, and MRI showed scattered infarcts with preservation of most of the basilar artery distribution. An MRI perfusion study also showed almost complete normalization of the previous abnormalities.

DISCUSSION

These cases illustrate how perfusion imaging may help in tailoring stroke treatment. Whether the perfusion data are obtained from MRI or CT is a matter of institutional preference and experience. Both modalities allow identification of the reversible ischemic zones, which is the guiding concept. Optimum patient selection can not only lead to consistently better outcomes, but it can also prevent treatment-related complications in patients with irreversible damage and little chance of recovery. Interplay among cerebral perfusion pressure, cerebral vascular resistance, and the metabolic demand of the brain contribute in maintaining a steady oxygen extraction for viable brain metabolism and function.[12,26] Our understanding of the behavior of cerebral hemodynamics in stroke can guide therapy. Parametric perfusion imaging reflects these hemodynamic alterations. With continual technological advancement, both in scanning hardware and processing software and increasing experience in functional brain imaging, image-based, patient-specific treatment has the potential to become the accepted strategy for acute stroke management. ■

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1. Baron JC. Perfusion thresholds in human cerebral ischemia: historical perspective and therapeutic implications. Cerebrovasc Dis. 2001;11(suppl 1):2-8.
2. Eskey CJ, PC Sanelli. Perfusion imaging of cerebrovascular reserve. Neuroimaging Clin N Am. 2005;15:367-381.
3. Larrue V, von Kummer RR, Muller A, et al. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian acute stroke study (ecass ii). Stroke. 2001;32:438-441.
4. Kucinski T, Koch C, Grzyska U, et al. The predictive value of early CT and angiography for fatal hemispheric swelling in acute stroke. Am J Neuroradiol. 1998;19:839-846.
5. Inoue Y, Takemoto K, Miyamoto T, et al. Sequential computed tomography scans in acute cerebral infarction. Radiology. 1980;135:655-662.
6. Tomura N, Uemura K, Inugami A, et al. Early CT finding in cerebral infarction: obscuration of the lentiform nucleus. Radiology. 1988;168:463-467.
7. Patel SC, Levine SR, Tilley BC, et al. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. JAMA. 2001;286:2830-2838.
8. von Kummer R, Nolte PN, Schnittger H, et al. Detectability of cerebral hemisphere ischaemic infarcts by CT within 6 hours of stroke. Neuroradiology. 1996;38:31-33.
9. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ecass ii). Second European-Australasian acute stroke study investigators. Lancet. 1998;352:1245-1251.
10. Schaefer PW, Romero JM, Grant PE, et al. Perfusion magnetic resonance imaging of acute ischemic stroke. Semin Roentgenol. 2002;37:230-236.
11. Wintermark M, Thiran JP, Maeder P, et al. Simultaneous measurement of regional cerebral blood flow by perfusion CT and stable xenon CT: a validation study. Am J Neuroradiol. 2001;22:905-914.
12. Derdeyn CP. Positron emission tomography imaging of cerebral ischemia. Neuroimaging Clin N Am. 2005;15:341-50, x-xi.
13. Gillard JH, Antoun NM, Burnet NG, et al. Reproducibility of quantitative CT perfusion imaging. Br J Radiol. 2001;74:552-555.
14. Butcher K, Parsons M, Baird T, et al. Perfusion thresholds in acute stroke thrombolysis. Stroke. 2003;34:2159-2164.
15. Shih LC, Saver JL, Alger JR, et al. Perfusion-weighted magnetic resonance imaging thresholds identifying core, irreversibly infarcted tissue. Stroke. 2003;34:1425-1430.
16. Hossmann KA. Viability thresholds and the penumbra of focal ischemia. Ann Neurol. 1994;36:557-565.
17. Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia—the ischemic penumbra. Stroke. 1981;12:723-725.
18. Fisher M. The ischemic penumbra: identification, evolution and treatment concepts. Cerebrovasc Dis. 2004;17(suppl 1):1-6.
19. Xavier AR, Farkas J. Catheter-based recanalization techniques for acute ischemic stroke. Neuroimaging Clin N Am. 2005;15:441-453.
20. Maruya J, Yamamoto K, Ozawa T, et al. Simultaneous multi-section perfusion CT and CT angiography for the assessment of acute ischemic stroke. Acta Neurochir (Wien). 2005;147:383-391; discussion 391-382.
21. Wintermark M, Fischbein NJ, Smith WS, et al. Accuracy of dynamic perfusion CT with deconvolution in detecting acute hemispheric stroke. Am J Neuroradiol. 2005;26:104-112.
22. Ezzeddine MA, Lev MH, McDonald CT, et al. CT angiography with whole brain perfused blood volume imaging: added clinical value in the assessment of acute stroke. Stroke. 2002;33:959-966.
23. Latchaw RE, Yonas H, Hunter GJ, et al. Guidelines and recommendations for perfusion imaging in cerebral ischemia: a scientific statement for healthcare professionals by the writing group on perfusion imaging, from the Council on Cardiovascular Radiology of the American Heart Association. Stroke. 2003;34:x1084-1104.
24. The national institute of neurological disorders and stroke (ninds) RT-PA stroke study group. A systems approach to immediate evaluation and management of hyperacute stroke. Experience at eight centers and implications for community practice and patient care. Stroke. 1997;28:1530-1540.
25. The national institute of neurological disorders and stroke RT-PA stroke study group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581-1587.
26. Liebeskind DS. Collateral circulation. Stroke. 2003;34:2279-2284.