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Review Article

Minimal Imaging Requirements

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The minimal requirements for imaging studies prior to endovascular treatment (EVT) of acute ischemic stroke are those that can provide the information necessary to determine the indication for treatment (treatment triage) and procedural strategies without being time-consuming. An important notion is to determine whether the patient can benefit from EVT. We should recognize that the perfect diagnostic imaging technique does not yet exist, and each has advantages and disadvantages. Generally, stroke imaging protocols to triage for EVT include the following three options: 1) non-contrast CT and CTA, 2) CT perfusion and CTA, and 3) MRI and MRA. It is not known if perfusion imaging or MRI is mandatory for patients with stroke presenting within 6 hours of onset, although non-contrast CT alone has less power to obtain the necessary information. Dual-energy CT can distinguish between post-EVT hemorrhage and contrast agent leakage immediately after EVT.

Keywords ▶ acute ischemic stroke, imaging, perfusion

Introduction

Stroke imaging plays a major role in diagnosis and selection of appropriate endovascular treatment (EVT) for patients with suspected acute ischemic stroke (AIS) and large vessel occlusion (LVO). Recent advances in stroke treatment and imaging techniques have shifted from traditional time-based selection toward tissue and imaging-based selection. The natural history of many patients with untreated LVO is quite poor, but if the pretreatment ischemic core is too large, then recanalization is largely ineffective and increases the risk of reperfusion injury and hemorrhagic transformation.

Neuroimaging for acute stroke patients has not been standardized. Various imaging studies are available, but which imaging study is the best remains controversial. Whereas performing additional imaging studies may provide more information, we should avoid wasting time and delaying treatment. A minimal and effective imaging protocol should be 1) fast, 2) easily accessible and interpretable, and 3) safe. Stroke imaging protocols to triage for EVT include the following three options: 1) non-contrast CT (NCCT) and CTA, 2) CT perfusion (CTP) and CTA, and 3) MRI and MRA. Whether perfusion imaging or MRI is mandatory for patients with stroke presenting within 6 hours of onset is controversial, although NCCT alone has less power to obtain the necessary information. In this section, the minimal imaging requirements for AIS are discussed based on the advantages and disadvantages of each imaging modality.

Non-Contrast CT

NCCT is the most widely available imaging modality in clinical practice for acute stroke because of its accessibility, speed, and lack of contraindications. NCCT is not only used to exclude patients with intracranial hemorrhage but also to assess potential suitability for reperfusion therapy.

In patients with AIS, NCCT can show subtle loss of the gray–white matter interface (in terms of early ischemic changes [EICs]) due to the increased water content resulting from cytotoxic edema. A narrow window level setting of 40–60 Hounsfield units on NCCT can accentuate the

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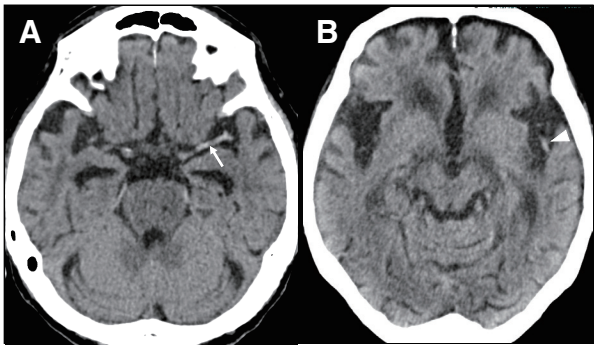


Fig. 1 Hyperdense artery signs on non-contrast CT in the M1 segment of the left MCA (arrow, **A**) and M2 segment of the left MCA (arrow head, **B**). MCA: middle cerebral artery

contrast for brain parenchyma to better visualize EICs. EICs are not contraindications to reperfusion therapy, but extensive EICs are associated with poor outcomes and higher risk of symptomatic intracerebral hemorrhage (ICH). EICs can be seen in approximately 30% of patients with anterior circulation LVO within the first 3 hours.[1] The Alberta stroke program early CT score (ASPECTS) is a widely used 10-point semi-quantitative scale for the evaluation of EICs in the middle cerebral artery (MCA) territory.[2] The AHA/ASA guidelines recommend EVT for patients with LVO and ASPECTS of 6 or more who present within 6 hours of when last known well without additional advanced imaging (e.g. perfusion imaging).[3]

EICs are mostly subtle, and exact evaluation of ASPECTS might be challenging for both inexperienced and experienced investigators in the emergency department.[4,5] Recently, some automated software solutions might support the detection and quantification of EICs.[6] However, expert analysis of ASPECTS remains mandatory.

A posterior circulation version of the ASPECTS (pc-ASPECTS) was developed to find a semi-quantitative score applicable to NCCT and CTA source images (CTA-SI). The pc-ASPECTS assigns the posterior circulation 10 points: two points each are subtracted for EIC in the midbrain or pons and 1 point each for EIC in the left or right thalamus, cerebellum, or posterior cerebral artery territory, respectively. NCCT has major limiting factors including artifact in the posterior fossa and poor spatial resolution, but accuracy is improved when calculated based on CTA-SI.[7,8]

The hyperdense artery sign (**Fig. 1**), defined as notable hyperdensity within an artery, may indicate intra-arterial acute thrombus. Patients with the hyperdense MCA (HDMCA) sign had a significantly better clinical outcome than those without the HDMCA.[9] The hyperdense artery sign can help decision-making for EVT.

CTA

CTA plays a major role in the detection of LVO or medium vessel occlusion in AIS, and it is a fast and reliable diagnostic study for extracranial and intracranial occlusive lesions. The information about vessel occlusion is mandatory to triage EVT candidates. CTA is performed by administration of an intravenous contrast agent through a line in the antecubital fossa. Stenosis of the intracranial vessels can result from a wide range of etiologies, including atherosclerosis, vasculitis, moyamoya disease, dissection, and others, which aid in the diagnosis and determination of the physiological stroke mechanism. Extracranial carotid artery stenosis is one of the acute stroke etiologies that can be directly addressed with endarterectomy or carotid stenting. CTA requires contrast agents and is therefore challenging in a patient with renal failure or allergy to contrast agents. In patients with suspected intracranial LVO and no history of renal impairment, the risk of contrast-induced nephropathy secondary to CTA imaging is relatively low.[10–15] Waiting for laboratory results of renal function may lead to delays in EVT.

Multiphase CTA or Dynamic CTA

Multiphase CTA or dynamic CTA can evaluate the collateral circulation. The collateral circulation consists of extracranial (external carotid artery branches) and intracranial routes (communicating arteries of the circle of Willis and leptomeningeal collaterals). Leptomeningeal collaterals consist of pre-existing collateral routes between the cortical vessels that may be recruited in the event of a proximal occlusion. Good collateral circulation maintains the blood supply to the penumbral area in the acute phase and is associated with a higher recanalization rate, smaller infarct volume, lower rate of hemorrhagic transformation, and better neurological outcomes after intravenous thrombolysis or EVT.[16–19]

A whole-body CT immediately after CTP imaging makes it easier to evaluate the extracranial vessels including the aortic arch than with NCCT because of the residual contrast agent in the vessels. A bovine aortic arch, hostile abdomen, calcified plaque, and aortic dissection (**Fig. 2**) can be identified, which aids in planning the access to the intracranial artery for the EVT procedure on.

MRI and MRA

Diffusion-weighted imaging (DWI) is superior to NCCT for the detection of ischemic lesions at earlier time points,

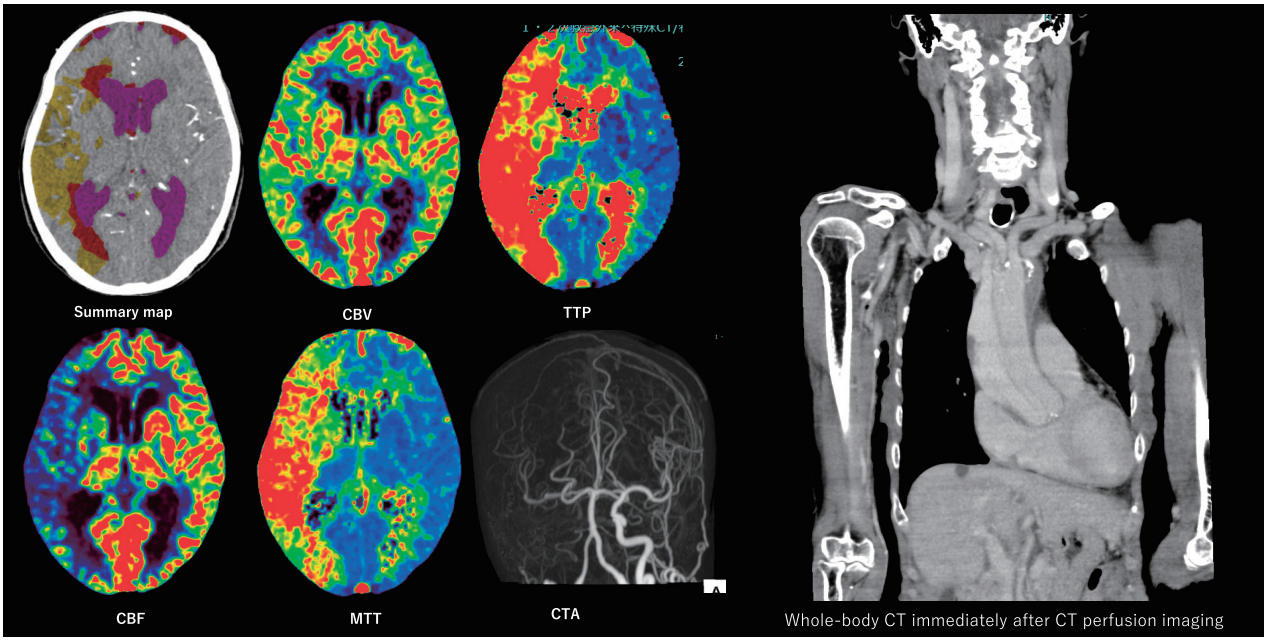


Fig. 2 A 90-year-old woman with sudden dysarthria, left hemispatial neglect, and left hemiplegia with an NIHSS score of 19. CTP shows perfusion lesions in the right hemisphere, and CTA shows right carotid artery occlusion. Contrast-enhanced CT of the trunk just after CTP shows a false lumen in the ascending aorta, suggesting Stanford A-type aortic dissection with a dissected lumen and thrombus from the brachiocephalic artery to the common carotid artery of the right side. She was considered to have neurological symptoms because of decreased blood flow in the right ICA caused by the stenosis due to the aortic dissection. CTP: CT perfusion; ICA: internal carotid artery; NIHSS: National Institutes of Health Stroke Scale

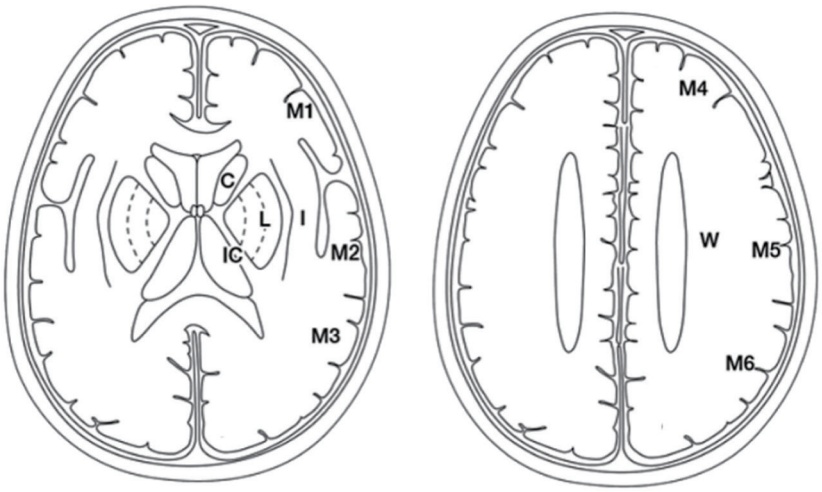
as well as smaller or vertebrobasilar lesions. DWI can detect early ischemic lesions within minutes, appearing as a hyperintensity lesion due to restricted water diffusion. On the other hand, MRI is expensive and contraindicated in patients with metallic implants or older generation implantable devices. Screening for metallic implants in acute stroke patients in the emergency department is challenging.

DWI quantitative assessment is done by manual tracing or an automated imaging postprocessing system. In the acute phase, manual tracing is time-consuming; therefore, automated tracing is preferable, although analysis software is required. Semi-quantitative ASPECTS assessed using DWI (DWI-ASPECTS) and the original ASPECTS based on CT are highly correlated, and the DWI-ASPECTS scored approximately 1 point lower than CT-ASPECTS in patients within 3 hours of stroke onset.[20] A modified scoring method, the 11-point ASPECTS + W score, including deep white matter lesions on DWI (DWI-W) (**Fig. 3**) in addition to the original ASPECTS regions, is a useful tool for predicting subsequent intracranial hemorrhage independent of intravenous thrombolytic therapy.[21]

DWI-negative stroke can be seen in approximately 7% of AIS patients, especially those with posterior circulation ischemia.[22] DWI sometimes fails to detect early CT ischemic lesions showing parenchymal hypoattenuation, which is termed reverse discrepancy (RD), in short, underestimation.[23] Because RD is observed in a quarter of AIS patients within 3 hours of stroke onset, RD should be taken into consideration to prevent underestimating the extent of ischemic lesions on DWI (**Fig. 4**).[24] Some other studies raised concern that the DWI lesion is not precise in distinguishing between irreversible and reversible ischemia, and it cannot therefore be considered equivalent to the infarcted core in the acute phase.[25–26] However, reversal of DWI lesions or DWI reversal is infrequent and unlikely to be clinically relevant.[27]

Apparent diffusion coefficient (ADC) maps can help distinguish between true restricted diffusion and T2 shine-through. FLAIR hyperintense vessels (FHVx) (**Fig. 5A**), indicative of slow or collateral flow, and the susceptibility vessel sign (SVS) on T2*-weighted imaging (**Fig. 5B**) or susceptibility-weighted imaging due to acute intra-arterial thrombus can also be seen. The SVS on MRI, as well as the hyperdense vessel sign on NCCT, reflects red blood cell-dominant clot,[28] and these lesions may have a better response to a stent retriever than contact aspiration.[29]

MRA is a powerful diagnostic modality for the detection of occlusive or stenotic lesions and does not require a contrast agent, but it may be more time-consuming than CTA. MRA can be used instead of CTA in patients with contrast agent allergy or severe renal impairment.



C: caudate
L: lentiform
I: insular ribbon
IC: internal capsule
M1: anterior MCA cortex
M2: MCA cortex lateral to insular ribbon
M3: posterior MCA cortex
M4~6: immediately superior to M1, M2, and M3, rostral to basal ganglia
W: deep white matter

Fig. 3 ASPECTS is a score derived from evaluating ten regions for evidence of early ischemic changes in the MCA territory. Two axial slices, one at the level of the thalamus and basal ganglion and one adjacent to the most superior margin of the ganglionic structures, determine the ASPECTS. A W lesion is defined as a lesion in the corona radiata. A single point is subtracted for an area of early ischemic change, such as focal swelling or parenchymal hypoattenuation, for each of the defined regions. ASPECTS: acute stroke prognosis early CT score; MCA: middle cerebral artery

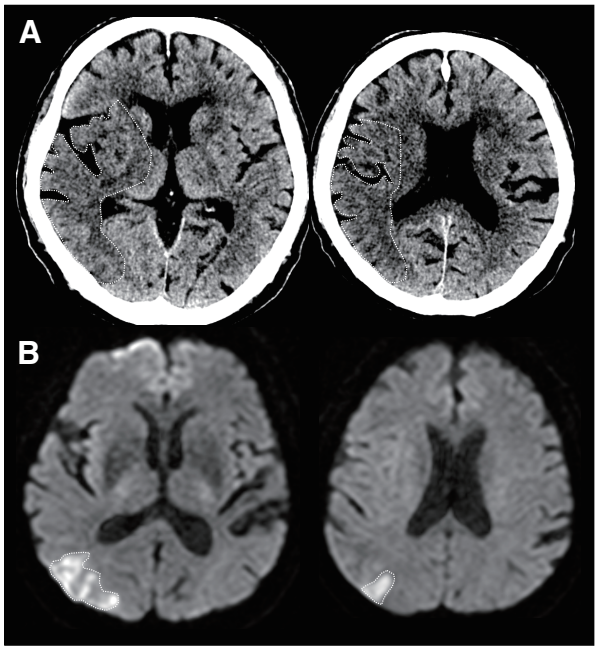


Fig. 4 Non-contrast CT 7 hours after onset shows early ischemic changes in the right L, I, IC, M2, M3, M5, and M6 regions (CT-ASPECTS, 3) (**A**). DWI 7.5 hours after onset shows hyperintense lesions in the M3 and M6 regions (DWI-ASPECTS, 8) (**B**). ROIs for hypoattenuation and DWI hyperintensity are placed manually on CT and DWI (in dashed lines). Therefore, the patient has RD in the right L, I, IC, L, M2, and M5. ASPECTS: acute stroke prognosis early CT score; DWI: diffusion-weighted imaging; RD: reversed discrepancy; ROIs: regions of interest

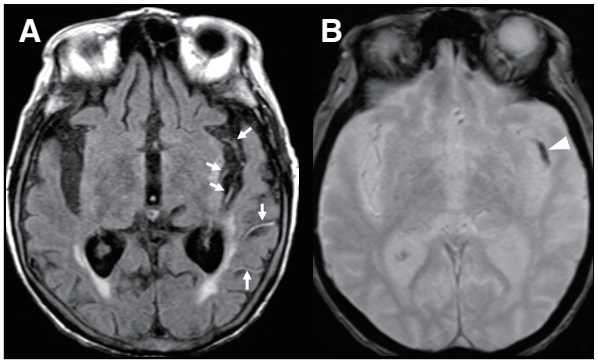


Fig. 5 FHVx on FLAIR imaging in the left MCA territory (arrows, **A**). The SVS on T2*-weighted imaging of the M2 segment of the left MCA (arrowhead, **B**). FHVx: hyperintense vessels; MCA: middle cerebral artery; SVS: susceptibility vessel sign

Perfusion Imaging

A concept fundamental to the rationale for recanalization therapy is that of mismatch between the ischemic core (irreversibly damaged tissue) and the ischemic penumbra (severely hypoperfused, functionally impaired, at risk but not yet infarcted tissue, but destined to undergo infarction without recanalization). The goal of recanalization therapy is to recanalize an occluded blood vessel, restoring blood flow to penumbral tissue before the ischemic core

expands and saving the penumbral tissue. If early reperfusion is not achieved, the ischemic core expands over the next several hours and the penumbra shrinks. Salvaging penumbral tissue increased disability-free life expectancy.[30] Advanced neuroimaging including perfusion imaging allows noninvasive evaluation of the ischemic core and penumbral tissue, although the ischemic penumbra is difficult to discern clinically or by non-contrast imaging alone.

Cerebral perfusion refers to capillary level blood flow. Both CTP and MR perfusion bolus-tracking studies involve obtaining serial scans during a 1- to 2-minute interval following the injection of an intravenous contrast bolus. Dynamic signal time-course data are transformed into a tissue-concentration time-course for each voxel. The perfusion parameters of interest, mean transit time (MTT), cerebral blood volume (CBV), cerebral blood flow (CBF), time to peak (TTP), time to peak of the residue function (T_{max}), and delay time (DT), are derived from the tissue–concentration time curves. CBV is the total volume of blood in a unit volume of the brain. CBF is the volume of blood moving through a given unit volume of the brain per unit time. MTT is the average of the transit time of blood through a brain region. MTT is calculated using the CBV and CBF, as MTT = CBV/CBF. Automated post-processing software can be used to quickly calculate the location and volume of the ischemic core and ischemic penumbra (**Table 1**). Optimal thresholds are specific to particular perfusion software platforms, or even versions of each software, and acquisition parameters used for each CTP scanner.

CTP can be performed quickly for almost every stroke patient, and it is performed with rapid injection of contrast agent in the antecubital vein, repeating intermittent scanning many times. The CBV or CBF is used to detect the core infarction by automated post-processing software (**Table 1**). On CTP, the ischemic penumbra is considered areas of preserved CBF and CBV but increased MTT, TTP, T_{max}, or DT (**Table 1**).

Evaluation of MR perfusion and DWI mismatch is another method of imaging-based selection of patients for recanalization therapy. The target mismatch criteria include (a) a ratio between the volumes of critically hypoperfused tissue and the ischemic core of 1.8 or greater, with an absolute difference of 15 mL or greater; (b) ischemic core volume less than 70 mL; and (c) volume of tissue with a severe delay in bolus arrival (T_{max} >10 seconds) less than 100 mL[31] using the RAPID software program. However, patients with renal impairment cannot undergo MR perfusion imaging because the administration of gadolinium is associated with the development of nephrogenic systemic fibrosis. Arterial spin labeling does not require gadolinium; however, it has not reached an equivalent level of validation.

Even if perfusion imaging is performed, NCCT should also be evaluated. The influx of a contrast agent in a chronic infarcted area or chronic cerebral hemorrhage may lead to the depiction of an ischemic core or ischemic penumbra on perfusion imaging. NCCT evaluation can avoid this misinterpretation.

Deciding whether the occluded vessel identified on imaging is eligible for EVT is important. When a new occlusion occurs on the same side as the chronic infarcted area, it may be difficult to assess from the angiography alone whether the occluded vessel is eligible for EVT. Perfusion imaging can identify the tissue at risk that should be salvaged in EVT (**Fig. 6**).

Pitfall of perfusion imaging: underestimation or overestimation

In patients with rapid reperfusion in the early time window, current thresholds of ischemic core on the perfusion imaging prior to EVT may overestimate the extent of the infarct core[32–34] or underestimate it.[35–37] Infarct overestimation can result in patients inappropriately being excluded from reperfusion therapy, whereas infarct underestimation is preferred to allow for inclusion of patients in EVT to achieve neurological improvement, but this may lead to an increase in the likelihood of poor clinical outcomes due to hemorrhagic transformation. The following factors are thought to delay the arrival of contrast agent in the brain and may result in overestimation or underestimation of the ischemic core: 1) inadequate intravenous access, such as a small caliber vein in the distal hand can result in an insufficient bolus profile; and (2) nontechnical factors that can affect insufficient contrast bolus include low cardiac function, severe valvular disease, aortic dissection, severe internal carotid artery (ICA) stenosis, ICA dissection, and high intracranial pressure.

Perfusion imaging for stroke mimics

Stroke mimics such as seizures, hypertensive encephalopathy, and hemiplegic migraines can be falsely classified as ischemic penumbra. Seizures are a common stroke mimic, and CTP findings depend on ictal vs postictal stage. The ictal

Table 1 Automated post-processing software for perfusion imaging

	RAPID	Vitrea (CT 4D-Perfusion)	Abierto Reading Support Solution	PMAneo	MIStar
	iSchemaView (Menlo Park, CA, USA)	Canon Medical System (Tochigi, Japan)	Canon Medical System (Tochigi, Japan)	Micron (Tokyo, Japan)	Apollo Medical Imaging (Melbourne, VIC, Australia)
FDA/CE	Approved	Approved	Approved	Unapproved	Approved
Pharmaceuticals and Medical Devices Law in Japan	Approved	Approved	Approved	Approved	Unapproved
Covered by health insurance in Japan	Not yet	Not yet	Not yet	Not yet	Not yet
Definition of ischemic core lesion	rCBF <30%	Bayesian: relative CBV <38% Reformulated SVD: relative CBV <41%	Relative CBV <40%	rCBF <30%	rCBF <30%
Definition of perfusion lesion	T_{max} >6 seconds	Bayesian: difference TTP >5.3 seconds difference T_{max} >2.2 second (latest version) Reformulated SVD: difference TTP >6.8 seconds	Difference T_{max} >2.2 seconds	T_{max} >6 seconds	DT >3 seconds
Analysis algorithm	Delay- and dispersion-insensitive SVD	Bayesian Reformulated SVD	Bayesian	Block-circulant SVD	Delay- and dispersion-corrected SVD

CBV: cerebral blood volume; CE: manufacturer or importer affirms conformity with European health, safety, and environmental protection standards; DT: delay time; FDA: Food and Drug Administration; rCBF: relative cerebral blood flow; SVD: singular value decomposition; T_{max}: time to peak of the residue function; TTP: time to peak

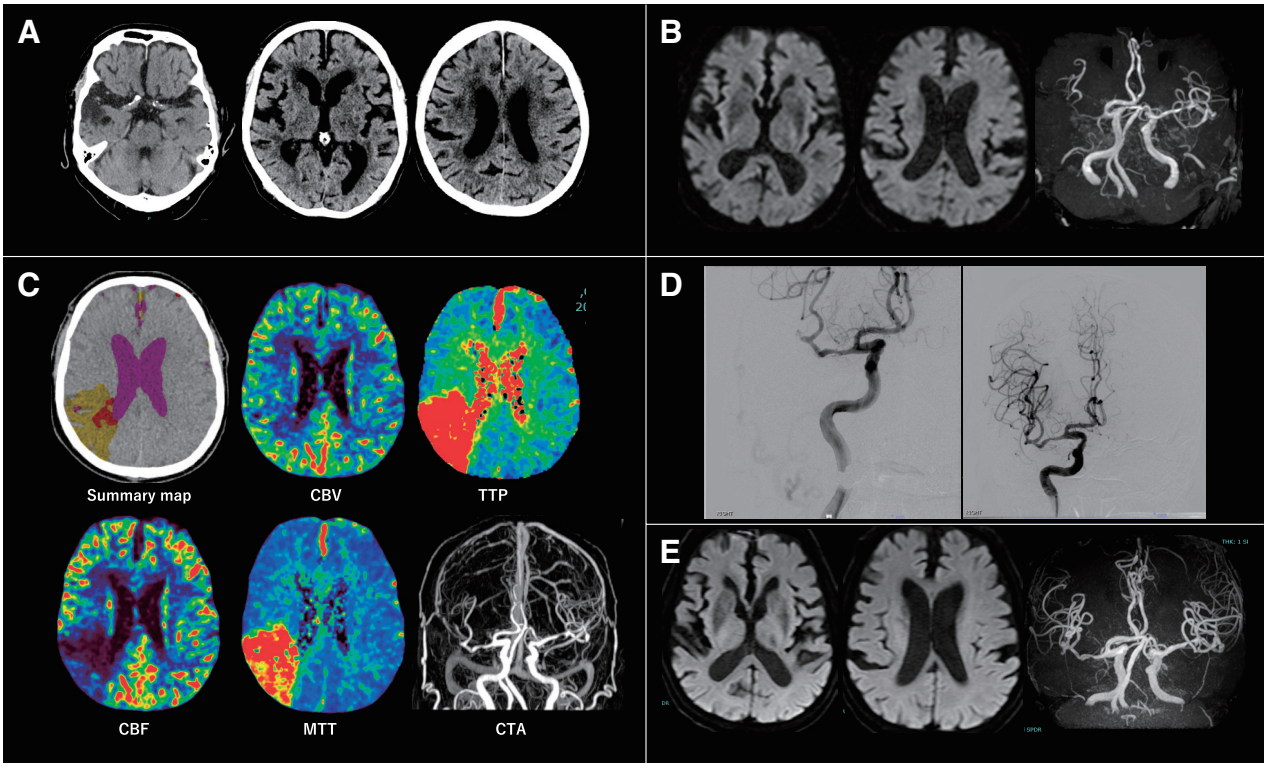


Fig. 6 Case presentation: an 80-year-old man with a history of ischemic stroke. He was transferred to our hospital by ambulance because of sudden-onset left-sided weakness. When he came to the hospital, he had left hemispatial neglect, left motor weakness, and sensory disturbance with an NIHSS score of 9. (**A**) Non-contrast CT 55 minutes after onset shows an old infarction in the right temporal lobe. (**B**) MRI diffusion-weighted image 75 minutes after onset shows no high signal intensity lesions, and MRA shows the right M1–M2 segment weakly compared to the left one. It is difficult to determine whether the right MCA lesion is residual occlusion due to old infarction or new onset due to recurrent stroke. His symptoms suggest a right parietal lobe lesion. (**C**) CTP image (Vitrea; Canon Medical System, Tochigi, Japan) 85 minutes after onset. There are areas of prolonged TTP, prolonged MTT, and decreased CBV in the right parietal lobe; ischemic core of 24 mL; and ischemic penumbra of 95 mL. CTA shows the right M2. Perfusion imaging shows recurrent cerebral infarction. (**D**) DSA. Endovascular therapy was performed for the right M2 occlusion, and TICI grade 3 recanalization has been obtained. (**E**) Diffusion-weighted image on the next day shows no ischemic lesions, and MRA shows sustained recanalization. He was discharged without any neurological disability. CBF: cerebral blood flow; CBV: cerebral blood volume; CTP: CT perfusion; MCA: middle cerebral artery; MTT: mean transit time; NIHSS: National Institutes of Health Stroke Scale; TICI: thrombolysis in cerebral infarction; TTP: time to peak

stage often shows ipsilateral hyperperfusion with increased CBF and CBV and decreased MTT or TTP (**Fig. 7**). However, in the postictal phase, the perfusion patterns can overlap with ischemic stroke including hypoperfusion. It is important to consider whether perfusion abnormalities correlate with clinical symptoms and CTA. The discordance among the CTP findings, clinical symptoms, and CTA findings can provide an additional evidence suggesting the diagnosis of a stroke mimic.

Mismatch concept for EVT to predict benefit from reperfusion

The concept of mismatch among clinical, morphological, and imaging findings might help identify patients who could benefit from EVT. Two successful thrombectomy trials beyond 6 hours used DWI–perfusion mismatch[38] or imaging–clinical mismatch.[39]

Imaging mismatch (CTP mismatch, diffusion–perfusion mismatch)

Imaging mismatch is a profile promising for patient selection for EVT. In the DEFUSE 2 trial,[31] the target mismatch profile was defined as (a) a ratio between perfusion (T_{max} >6 seconds) and the diffusion lesion of 1.8 or more; (b) an absolute difference between perfusion (T_{max} >6 seconds) and the DWI lesion of 15 mL or more; (c) DWI lesion less than 70 mL; and (d) a severe perfusion (T_{max} >10 seconds) lesion less than 100 mL. Responses to reperfusion in patients selected according to target mismatch criteria were different; the odds ratio for a good clinical outcome associated with reperfusion was 8.8 (95% CI: 2.7–29) in patients with target mismatch and 0.2 (95% CI: 0.0–1.6) in those without target mismatch ($P = 0.003$).[31]

Two of the positive EVT trials for patients within 6 hours of stroke onset, EXTEND-IA, which used 100% CTP,[40]

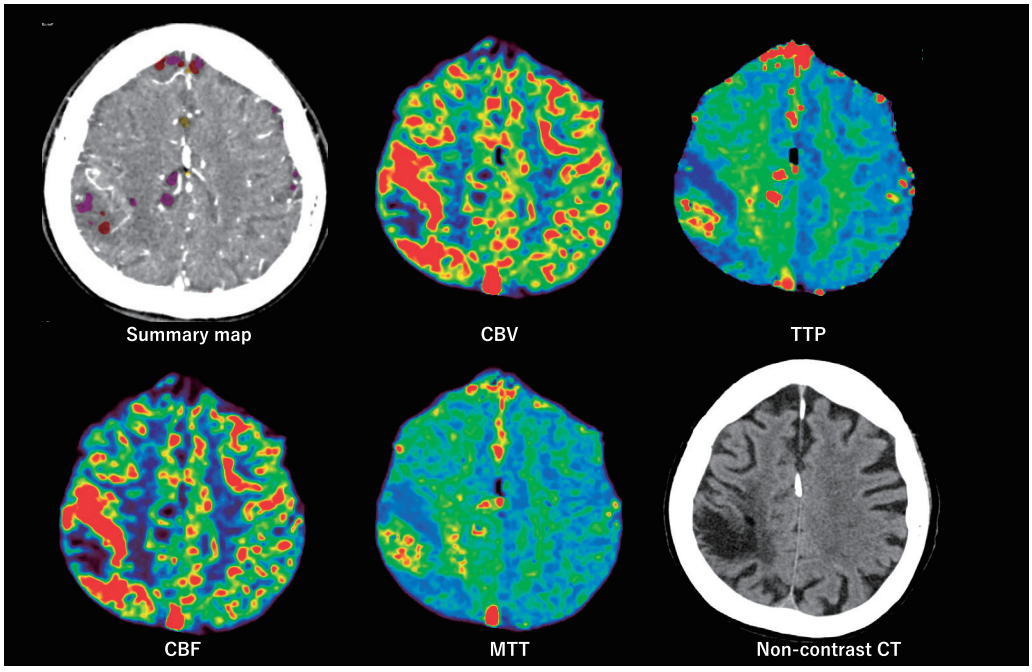


Fig. 7 A 70-year-old man with a history of ischemic stroke in the right MCA. He was transferred to our hospital by ambulance because of sudden-onset consciousness disturbance and left-sided weakness. Non-contrast CT shows old infarction in the right MCA area. CTP in the ictal stage shows hyperperfusion with increased CBF and CBV and decreased MTT or TTP around the old infarct area (Vitrea; Canon Medical System, Tochigi, Japan). DWI shows no acute ischemic lesions. CBF: cerebral blood flow; CBV: cerebral blood volume; CTP: CT perfusion; DWI: diffusion-weighted imaging; MCA: middle cerebral artery; MTT: mean transit time; NIHSS: National Institutes of Health Stroke Scale; TTP: time to peak

and SWIFT-PRIME, in which the majority of patients had CTP,[41] demonstrated high rates of good functional outcomes and the large absolute benefit of EVT.

The DEFUSE 3 trial focused exclusively on patients with unknown stroke onset and last known well 6 to 16 hours before and ICA or proximal MCA occlusion.[38] Inclusion criteria were an initial infarct size of less than 70 mL and a ratio of the volume of ischemic tissue on perfusion imaging to infarct volume of at least 1.8 from CTP or MRI diffusion. EVT was associated with a favorable shift in the distribution of functional outcomes on the modified Rankin score (mRS) at 90 days and a higher percentage of patients with functional independence (mRS score 0 to 2), with 45% in the EVT group vs. 17% in the group with medical treatment alone (P <0.001). The 90-day mortality was 14% in the EVT group vs. 26% in the medical therapy group (P = 0.05), and there were no significant between-group differences in the frequency of symptomatic intracranial hemorrhage (7% vs. 4%, P = 0.75).

Clinical–imaging mismatch

The clinical–DWI mismatch model is an alternative to imaging mismatch. This is based on the assumption that patients with severe clinical deficits, but with relatively small lesion volumes on DWI, are likely to have an ischemic penumbra. The original definition of clinical–DWI mismatch was a DWI lesion less than 25 mL and an National Institutes of Health Stroke Scale (NIHSS) score of 8 or higher.[42]

In the DAWN trial involving patients who had last been known well 6 to 24 hours before being considered for EVT because of occlusion of the ICA or the proximal MCA on CTA or MRA,[39] patients had to have clinical–imaging mismatch, which was defined according to the following criteria: those in Group A were 80 years of age or older, had a score of 10 or higher on NIHSS scores, and had an infarct volume of less than 21 mL; those in Group B were younger than 80 years of age, had an NIHSS score of 10 or higher, and had an infarct volume of less than 31 mL; and those in Group C were younger than 80 years of age, had an NIHSS score of 20 or higher, and had an infarct volume of 31 to less than 51 mL. Infarct volume was assessed by DWI MRI or CTP and was measured with RAPID software. The rate of mRS score 0 to 2 at 90 days was 49% in the EVT group and 13% in the control group, and neither the symptomatic intracranial hemorrhage rate (6% vs. 3%, P = 0.50) nor the 90-day mortality rate (19% vs. 18%, P = 1.00) differed significantly between the two groups.

MRA–DWI mismatch

The MRA–DWI mismatch model appears to present a viable alternative to the MR perfusion–DWI mismatch model. Patients with an MRA–DWI mismatch have a documented vessel occlusion on MRA and a small ischemic core on DWI that corresponds with the involved vascular territory. The MRA–DWI mismatch is defined as (1) a DWI lesion volume less than 25 mL in patients with an ICA or MCA-M1 occlusion or (2) a DWI lesion volume less than 15 mL in patients with a proximal vessel stenosis or an abnormal finding of an MCA-M2 occlusion.[43] Reperfusion was associated with an increased rate of a good clinical response in patients with an MRA–DWI mismatch (OR 12.5, 95% CI: 1.8 to 84) and a lower rate in patients without mismatch (OR 0.2, 95% CI: 0.0 to 0.8).[43] However, the clinical utility of MRA–DWI mismatch has yet to be demonstrated in randomized, controlled trials.

Malignant profile for EVT to predict harm from reperfusion and poor outcomes

The malignant profile was defined as a DWI lesion with a volume of 100 mL or greater and/or a perfusion (T_{max} >8 seconds) volume of 100 mL or more, and it appeared to be associated with symptomatic intracranial hemorrhage and poor outcomes following reperfusion.[44] In malignant profile patients with DWI lesions of 80 mL or more, poor outcomes and parenchymal hematoma were both more common with reperfusion than without (89% vs. 39%, $P = 0.02$ and 67% vs. 11%, $P < 0.01$).[45] Patients with large baseline DWI lesions more than 70 mL who were treated with EVT had a high rate of poor outcomes.[46] These studies suggest worse outcomes and possibly a lack of clinical benefit from reperfusion in patients with a large baseline ischemic score volume.

Predicting hemorrhage

A large ischemic core is associated with an increased risk of ICH. The presence of tissue with very low CBV[47] or T_{max} more than 14 seconds[48] is a stronger predictor of hemorrhagic transformation in patients treated with intravenous thrombolysis. CTP-derived blood–brain barrier permeability may be a promising predictor of hemorrhagic transformation in patients treated with intravenous thrombolysis[49–50] and/or EVT.[51]

Recently, several randomized, controlled trials have reported the efficacy of EVT for patients with large ischemic cores.[52–54] The RESCUE-Japan LIMIT trial was the first published randomized, clinical trial that evaluated the efficacy and safety of EVT in patients with LVO and an established large ischemic region (ASPECTS of 3 to 5) on NCCT or DWI. In this population, a better functional outcome (mRS 0 to 3 at 90 days) was observed in the EVT group than in the medical management group (31.0% vs. 12.7%, $P = 0.002$).[52] We should pay attention to the latest information on how to consider treatment for patients with a larger ischemic core than those described in the current treatment guidelines.[3]

Ultrasonography

Ultrasonography provides noninvasive real-time monitoring of CBF. Ultrasonography including duplex carotid ultrasonography and transcranial Doppler (TCD) ultrasonography is noninvasive real-time monitoring, inexpensive, and available in many hospitals. Carotid ultrasound can evaluate extracranial carotid stenosis, plaque morphology, and intimal flaps due to acute aortic dissection. When a patient has ICA occlusion detected by intracranial CTA or MRA, carotid ultrasound can provide morphological information regarding the ICA origin. TCD can provide real-time information about stenosis and occlusion and the collateral circulation, and monitor vasomotor reactivity, embolization, and recanalization following recanalization therapy. However, ultrasonography is highly operator dependent, and in many facilities, it is difficult to arrange to perform ultrasonography on short notice before EVT.

Single-photon emission CT and positron emission topography

Although both single-photon emission CT (SPECT) and positron emission topography (PET) provide important physiological information in patients with LVO, they are very limited and not preferred because of difficulty in emergent access before EVT, time delay, and the complex infrastructure required. These imaging studies are inappropriate as the minimal requirement before EVT.

NCCT vs. perfusion imaging

Although both MR CLEAN[55] and ESCAPE[56] used conventional imaging (NCCT and CTA), both SWIFT-PRIME[41] and EXTEND IA[40] used advanced imaging (CTP or diffusion/MR perfusion mismatch) for patient selection. Although the success of SWIFT-PRIME[41] and EXTEND IA[40] was overwhelming, it remains unclear whether the success of these studies can be attributed to advanced imaging.

MRI-based selection was associated with decreased futile recanalization and improved clinical outcomes

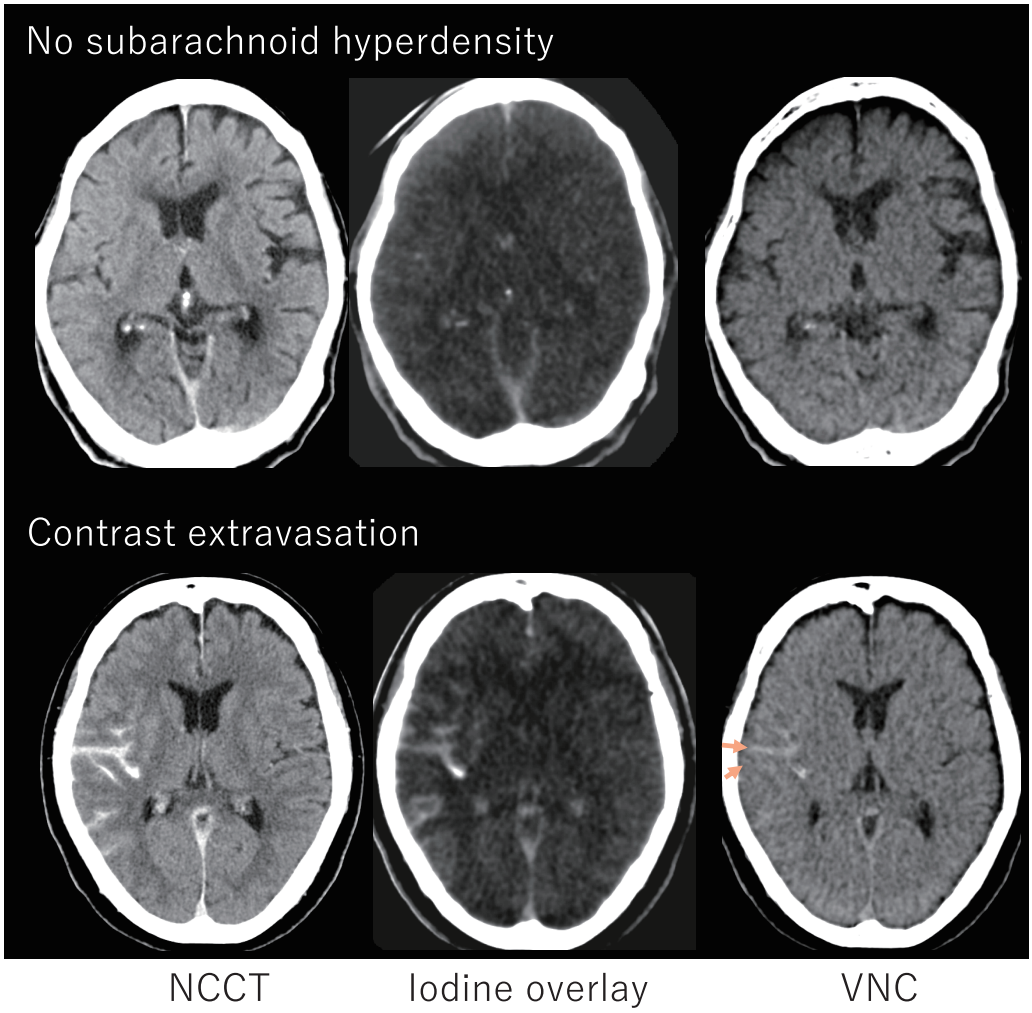


Fig. 8 Representative cases of contrast extravasation on dual-energy CT-derived NCCT, iodine overlay, and VNC maps. NCCT: non-contrast CT; VNC: virtual non-contrast

compared to CT-based selection in an observational registry of patients presenting within 6 hours of onset.[57] On the other hand, CT- and MRI-guided patient selection for intravenous thrombolysis and/or EVT was similar in terms of functional outcome and safety (symptomatic ICH or mortality).[58] Other researchers also reported that there were no significant differences in the clinical outcomes of patients selected with NCCT compared with those selected with CTP or MRI in patients with proximal anterior circulation occlusion stroke presenting within 6 to 24 hours of last known normal.[59–60] However, interpretation of the studies comparing CT, CTP, versus MRI-based selection requires caution, because most patients in the NCCT group underwent CTA and because it is unclear how many patients were excluded from EVT triaged by NCCT, CTP, or MRI. Since an experienced investigator decided on EVT eligibility, the selected patients should have benefited from EVT regardless of imaging modality.

Early vs. Extended Time Window

Is perfusion imaging a waste of time? No

The requirement for CTP to identify EVT candidates within the early time window remains a question. Guidelines do not recommend the routine use of perfusion imaging for EVT selection in patients within 6 hours of last known normal with LVO and ASPECTS of 6 or more.[3] When selecting patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, CTP or DWI, with or without perfusion, is recommended to aid in patient selection for EVT.[3] In short, when selected based on CT, CTA is recommended regardless of early or extended time window.

Table 2 Neuroimaging modalities for AIS

	Proposed imaging modalities
Brain imaging	
Ischemic core (mandatory)	ASPECTS on NCCT ASPECTS on DWI (DWI-ASPECTS, ASPECTS + W) Volume of severely decreased CBV or CBF on CTP with automated software Volume of DWI lesion on automated software
Ischemic penumbra	Volume of prolonged MTT, TTP, T_{max}, or DT on CTP or MRP with automated software ASL on MRI
Vessel imaging	
Artery occlusion (mandatory)	CTA, MRA (HDAS on NCCT or SVS on T2*WI or SWI)
Cerebral collateral	Multiphasic or dynamic CTA CTA source image (FHV on FLAIR)
Extracranial artery	CTA, MRA

AIS: acute ischemic stroke; ASL: arterial spin labeling; ASPECTS: Alberta stroke program early CT score; ASPECTS + W: 11-point ASPECTS including deep white matter lesions on DWI; CBF: cerebral blood flow; CBV: cerebral blood volume; CTP: CT perfusion; DT: delay time; DWI-ASPECTS: ASPECTS using DWI; FHV: flair hyperintense vessel; HDAS: hyperdense artery sign; MRP: MR perfusion; MTT: mean transit time; NCCT: non-contrast CT; SVS: susceptibility vessel sign; SWI: susceptibility-weighted imaging; T_{max}: time to peak of the residue function; TTP: time to peak

There is little time wasted by adding CTP, because both CTP and CTA can be obtained with a single contrast bolus, and post-processing image analysis with automated software takes only a few minutes. Perfusion imaging combined with automated software can decrease the time required.

Post-EVT imaging

The presence of postinterventional subarachnoid hyperdensities in the hemisphere ipsilateral to the treated vessel is a relatively common finding after EVT. On routine CT, it can be difficult to differentiate the hyperdensities resulting from the iodinated contrast agent from those related to blood extravasation. Dual-energy CT is a technique based on the different attenuation effects of normal brain tissue, iodine, and blood at different irradiation energy levels that allows reliable differentiation between hyperdensities secondary to iodine contrast extravasation or hemorrhage (**Fig. 8**).[61–62] Diffuse subarachnoid hyperdensities, but not local collections of blood or contrast extravasations, were found to be associated with an increased risk of a poor outcome and mortality. Diffuse subarachnoid hyperdensities were associated with M2 occlusions, more thrombectomy passes, and concurrent parenchymal hematomas.[63]

What is the minimum requirement for AIS?

Generally, stroke imaging protocols to triage for EVT include the following three options: 1) NCCT and CTA, 2) CTP and CTA, and 3) MRI and MRA. We should understand the strong and weak points of each imaging modality (**Table 2**). Of the three options, we believe that the fastest, safest, and easiest-to-interpret imaging technique at each hospital should be used, and that is the minimum requirement for imaging prior to EVT.

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