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Multi-modal CT in Stroke Imaging: New Concepts

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Abstract

A multimodal CT protocol provides a comprehensive non-invasive survey of acute stroke patients with accurate demonstration of the site of arterial occlusion and its hemodynamic tissue status. It combines widespread availability with the ability to provide functional characterization of cerebral ischemia, and could potentially allow more accurate selection of candidates for acute stroke reperfusion therapy.

Introduction

Imaging has revolutionized acute ischemic stroke diagnosis and management. Previously, anatomical (structural) imaging modalities, typically noncontrast computed tomography (CT), were used to assess the presence or absence of acute ischemic stroke and exclude stroke mimics such as hemorrhage and neoplasms. With the development of functional (or physiologic) imaging such as perfusion-CT (PCT), stroke has been redefined from an all-or-none process to a dynamic and evolving process. In particular, the advent of efficacious thrombolytic therapies such as intravenous tissue plasminogen activator (IV-tPA)(¹) has served as the impetus to better define the so-called ischemic penumbra or “tissue at risk” and thus better select those patients who would be more amenable to successful therapy. Several studies have suggested favorable clinical outcomes with thrombolytic therapies which were based on imaging criteria.(2–4)

Multi-modal CT - noncontrast CT, CT-angiography (CTA), and PCT (Fig. 1)- has been shown to be fast, reliable and effective in improving stroke detection in the emergency setting.(5–7) Noncontrast CT can identify intracranial hemorrhage and detect early signs of acute ischemic stroke. CTA can identify the occlusion site, detect arterial dissection, and grade collateral blood flow, whereas PCT can accurately delineate the infarct core and the ischemic penumbra. A multi-modal CT stroke protocol might be used to properly select those patients that might be amenable to reperfusion therapy.(2) This article will discuss the individual components of multi-modal CT -noncontrast CT, CT angiography (CTA), and perfusion CT (PCT) - and address the potential role of a combined multimodal CT stroke protocol in acute stroke therapy.

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Conventional CT: Noncontrast CT

With its widespread availability, short scan time, non-invasiveness, and safety, computed tomography (CT) has been the traditional first-line imaging modality for the evaluation of acute ischemic stroke. In the acute ischemic stroke setting, noncontrast CT is typically used to rule out intracranial hemorrhage (a contraindication to thrombolysis), or other stroke mimics (e.g. tumor, infection, etc) which preclude the use of thrombolytic therapy and to detect early CT signs (i.e. scans obtained within 6 hours of the onset of stroke) (9–11). Early noncontrast CT signs of stroke include:

1. *Insular ribbon sign.* With proximal middle cerebral artery (MCA) occlusion, blood flow to the insular region is decreased. This region is particularly vulnerable because the insular cortex is the region most distal from the potential anterior and posterior collateral circulation, and as such a watershed arterial zone. When ischemic, the insular region shows loss of definition of the gray-white interface, or loss of the “insular ribbon”.(3)
2. *Obscuration of the lentiform nucleus.* An obscured outline or partial disappearance of the lentiform nucleus is another early ischemic sign on noncontrast CT.(4) As the blood supply to the basal ganglia (i.e. lenticulostriate branches of the MCA) are end-arteries, the basal ganglia are particularly vulnerable to early infarction.(4)
3. *Hyperdense artery sign.* An acute thrombus in an intracranial vessel appears as an area of increased attenuation. This radiologic sign has been called the “hyperdense artery sign.”(5–11) Contrary to other CT early signs, the hyperdense artery sign represents a thrombotic event not infarction.(11) Although this sign is highly specific, its sensitivity is poor(12), and false positives should be excluded such as those caused by a high hematocrit level or atherosclerotic calcifications, but in such cases the hyperattenuation is usually bilateral.(13) In addition, distal MCA (M2 or M3 branches of MCA) thromboemboli create punctate hyperattenuation, also known as the “MCA dot sign”.(14, 15)

Although these early ischemic changes can be helpful in stroke detection, they are subtle and difficult to detect. They also have limited sensitivity for the hyperacute stage of ischemic stroke, in particular within the first three hours after onset of symptoms, a critical window for therapeutic interventions. When compared with DWI-MR, these signs have a sensitivity of 25%.(10, 25–29) Moreover, noncontrast CT cannot reliably differentiate between irreversibly damaged brain tissue and penumbra. Finally, the relationship between early ischemic changes on CT and adverse outcomes after rt-PA treatment is not straightforward.(16, 17)

In contrast to these early ischemic changes, frank hypoattenuation is highly specific for irreversible tissue damage(18), and its extent is predictive of the risk of hemorrhagic transformation.(19) Nevertheless, it is critical to determine the tissue at risk before irreversible tissue damage occurs and frank hypoattenuation appears, as this is essential to prevent hemorrhagic transformation. In the European Cooperative Acute Stroke Study trials (ECASS I and II), involvement of more than one-third of the MCA territory on noncontrast CT was utilized as the criterion for patient exclusion for reperfusion therapy due to the potential increased risk for hemorrhagic transformation.(20) However, subsequent studies using this “one-third MCA rule” showed poor inter-observer correlation(30, 34, 35). This outcome emphasizes the need for more reliable imaging techniques that can help determine the extent of both irreversibly damaged brain tissue and tissue at risk to avoid unnecessary thrombolytic therapy. In an attempt to provide a more quantitative approach, some authors have attempted to design algorithmic methods to quantitatively assess the extent of cerebral acute ischemia on conventional CT by using a 10-point topographic scoring system called ASPECTS (Box 1). (36, 37)

Box 1

Alberta Stroke Program Early CT Score (ASPECTS) 10-point topographic scoring system for estimating the extent of an ischemic stroke compared to the extent of the middle cerebral artery (MCA) territory (37) When three or more of the ASPECTS regions show ischemic changes, the infarct is considered to involved more than one third of the MCA territory

caudate nucleus
lenticular nucleus
insula
internal capsule
inferior anterior MCA territory
inferior middle MCA territory
inferior posterior MCA territory
superior anterior MCA territory
superior middle MCA territory
superior posterior MCA territory

CT-Angiography (CTA)

Although conventional cerebral angiography is considered to be the gold standard for the evaluation of cerebrovascular disease, the advances in multi-detector row CT (MDCT) technology have made CTA a valid alternative to conventional catheter-based cerebral angiography.(21, 22) CTA is widely available, with fast, thin-section, volumetric spiral CT images acquired during the injection of a time-optimized bolus of contrast material for vessel opacification.(23) With modern multi-section CT scanners, the entire region from the aortic arch up to the circle of Willis can be covered in a single data acquisition, with isotropic spatial resolution and acquisition time of less than 5 seconds. Multi-planar reformatted images, maximum intensity projection images (MIP) and three-dimensional (3D) reconstructions of axial CTA source images provide images comparable to those obtained with conventional angiography.(24–26)

CTA allows a detailed evaluation of the intra- and extra-cranial vasculature.(25, 27). Its utility in acute stroke lies not only in its ability to detect large vessel thrombi within intracranial vessels and to evaluate the carotid and vertebral arteries in the neck(28–30), but also in its potential in guiding therapy. In particular, the exact location (i.e. proximal vs. peripheral occlusions) and the extent of vascular occlusion have been shown to have prognostic value in the response to thrombolytics and determination of collateral circulation and possible risk of subsequent recanalization.(31) For example, “top of carotid” occlusions, proximal MCA branch occlusions, or significant thrombus burden might be poor candidates for intravenous thrombolytics, and possibly may be better candidates for intra-arterial or mechanical thrombolysis.(32)

Perfusion-CT (PCT)

Within the last few years, perfusion computed tomography (PCT) has become the third component in the multi-modal CT assessment of acute ischemic stroke. There is considerable literature on the measurement and assessment of cerebral perfusion (33) and a brief review is necessary to understand the parameters and quantitative data that PCT technique provides. In

1981, the landmark study by Jones et al (34) used a primate model to elucidate thresholds for MCA ischemia by restricting blood flow in an awake primate model with pathological correlation. Their findings form the basis of contemporary human perfusion studies:

1. 15–30 minutes of complete ischemia produced only microscopic infarcts.
2. 2–3 hours of ischemia produced moderate to severe infarcts.
3. Cerebral blood flow (CBF) $< 23 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1}$ caused reversible paralysis.
4. CBF $< 10\text{--}12 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1}$ for 2–3 hours, or CBF $< 17\text{--}18 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1}$ permanently, resulted in irreversible paralysis.

Subsequent positron emission tomography (35–37) in humans have corroborated with these earlier finding in primates (in particular, CBF $< 15 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1}$ has strongly correlated with infarction).⁽³⁶⁾

Recently, PCT has been introduced as a simple imaging technique to be used in routine clinical practice.^(38, 39) The concepts behind this imaging technique were developed about two decades ago, but its widespread clinical use has been facilitated by the advent of fast, multi-detector CT technology.

PCT involves dynamic acquisition of sequential CT slices on a cine mode during rapid intravenous administration of non-ionic iodinated contrast material. PCT allows rapid, noninvasive, quantitative evaluation of cerebral perfusion. Based on the multi-compartmental tracer kinetic model, dynamic PCT imaging is performed by monitoring the first pass of an iodinated contrast agent bolus through the cerebral circulation. As the change in CT enhancement (in Hounsfield units, HU) is proportional to the concentration of contrast, perfusion parameters are calculated by deconvolution from the changes in the density–time curve for each pixel using mathematical algorithms based around the central volume principle.^(40, 41)

1. mean transit time (MTT) indicates the time difference between the arterial inflow and venous outflow,
2. cerebral blood volume (CBV) indicates the volume of blood per unit of brain mass (normal range in gray matter, 4–6 mL/100 g)
3. cerebral blood flow (CBF) indicates the volume of blood flow per unit of brain mass per minute (normal range in gray matter, 50–60 mL/100 g/min).
4. The relationship between CBF and CBV is expressed by the equation $\text{CBF} = \text{CBV} / \text{MTT}$.

Deconvolution softwares allow much lower injection rates - 5 mL/sec as reported above - compared to other softwares that use different approaches, such as the maximal slope model.⁽⁴²⁾ These lower injection rates are more practical and tolerable for patients. They do not impair accuracy, since the deconvolution analysis controls for bolus dispersion by comparing the arterial input time-attenuation curve with that of the tissue.⁽⁴²⁾

PCT maps can be generated in a short time at an appropriate workstation.⁽⁴³⁾ PCT data are analyzed at an imaging workstation. Post-image-collection processing involves semiautomated definition of an input artery and a “vein” (Fig. 2). In acute stroke patients, selection of different arterial inputs has been demonstrated to have no significant effect on PCT results for an individual patient.⁽⁴⁴⁾ As a result, we routinely use the anterior cerebral artery as the arterial input function, to provide standardization and facilitate intersubject comparison. In patients with chronic cerebral vascular disease, situation is different, and we select for each vascular territory its own, specific arterial input function. The reference “vein” actually needs to be the

pixel with the largest area under its contrast-enhancement curve. As such, it must be selected at the center of the largest vascular structure perpendicular to the PCT slices. These requirements are usually met by pixels at the center of the superior sagittal sinus. However, in some instances, other venous structures, or even the supraclinoid internal carotid arteries, can be appropriate “veins” for PCT processing purposes.

MTT maps are more sensitive, while CBF and CBV maps are more specific for distinguishing ischemia from infarction (45, 46). PCT distinction of the infarct core from the penumbra is based on the concept of cerebral vascular autoregulation. In the penumbra, autoregulation is preserved, MTT is prolonged, but CBV is preserved because of vasodilatation and collateral recruitment as part of the autoregulation process. In the infarct core, autoregulation is lost, MTT is prolonged and CBV is down.(39) Thus, using appropriate MTT and CBV thresholds, infarct core and penumbra can be distinguished on PCT maps.(47) Direct assessment of an individual patient’s ischemic penumbra (“penumbra is brain”) may allow more personalized, appropriate selection of candidates for intervention than generalized time criteria (“time is brain”), since individuals may have different timelines for evolution of penumbra into infarct.

PCT provides equivalent results to diffusion/perfusion MRI in terms of characterizing the infarct and penumbra (Fig. 3), (38, 39, 47) and also in terms of selection of patients for acute reperfusion therapies. (48) PCT requires a shorter scan time and is usually more widely available in the emergency setting compared to MRI. As such, it represents a very appealing imaging technique to assess acute stroke patients. (49, 50) However, there are some specific situations (lacunar infarcts, posterior fossa strokes, young patients) in which MRI is warranted instead of PCT.

The main advantage of PCT is its wide availability and quantitative accuracy.(51) Its main limitation is its inability to image the whole brain as it is limited to a 2–4 cm section of brain tissue per bolus. Introduction of 256- and 320-slice CT scanners, offering whole brain coverage, is likely to overcome this limitation in the near future.(49)

Multimodal CT Stroke Protocol

Multimodal CT allows for the assessment of the four Ps (parenchyma, pipes, perfusion, and penumbra). (52) Noncontrast CT allows to rule out hemorrhage, CTA identifies intraarterial thrombus, and PCT can differentiate between “at-risk” (the so-called “penumbra”) and irreversibly damaged brain tissue.(53) Multimodal CT offers rapid data acquisition and can be performed with modern CT equipment; a typical multimodal CT stroke protocol is depicted in Box 2. Perfusion-CT is usually performed twice to increase spatial coverage and make it as close as possible as whole brain coverage.

Box 2

Summary of multimodal computed tomography (CT) imaging acquisition protocol on a 64-slice CT scanner. Series are obtained in this chronological order, each series being separated from the subsequent one by 2 minutes. Perfusion-CT is usually performed twice to increase spatial coverage and make it as close as possible as whole brain coverage

1. Noncontrast head CT:
 - a. 2.5-mm axial cuts from skull base to vertex
 - b. 120 kVp, 200 mAs
2. Dynamic CT perfusion (performed two consecutive times)

- a. 40 mL (370 mg I/mL) iodinated contrast
 - b. 18- or 20-gauge IV access; 5 mL/sec injection rate
 - c. 6-second scan delay, 45-second scan time
 - d. 80 kVp, 100 mAs
 - e. cine scan mode, 5-mm slices
3. CT angiogram:
- a. 40 mL (300 mg I/mL) iodinated contrast
 - b. 5cc/sec injection rate
 - c. 18- or 20-gauge IV access; 4 mL/sec injection rate
 - d. 25-second scan delay
 - e. 100 kV, 250 mAs
 - f. spiral CT acquisition, 0.625-mm slices, pitch of 1:1
 - g. coverage from left atrium to vertex

The advantages of multimodal CT include short protocol time (5–6 mins), and the availability in the emergency setting. The new generation of portable multislice CT scanners may bring CTP to the patient's bedside in the emergency room or the intensive care unit. The principle disadvantages of this CT based stroke protocol would be ionizing radiation exposure (recent technological CT advancements such as dose modulation have effectively reduced the amount of radiation exposure) and its limited ability to assess ischemia in areas which have a propensity to create so-called “beam hardening” artifacts (e.g. posterior fossa ischemia). We also use lower kV for CTA and PCT to reduce the radiation dose and to improve the signal to noise ratio.

Conclusion

Thus, a multimodal CT protocol provides a comprehensive non-invasive survey of acute stroke patients with accurate demonstration of the site of arterial occlusion and its hemodynamic tissue status. It combines widespread availability with the ability to provide functional characterization of cerebral ischemia, and could potentially allow more accurate selection of candidates for acute stroke reperfusion therapy.

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Fig. 1.

Modern CT survey in a 57-year-old male patient admitted in our emergency room with a left hemisindrome, including an unenhanced CT (first row), a PCT (PCT) (rows 2 thru 5) and a CT-angiogram (CTA) (right column). The unenhanced CT ruled out a cerebral hemorrhage. From the PCT raw data, three parametric maps were extracted, relating to mean transit time (MTT, second row), cerebral blood flow (CBF, third row), and cerebral blood volume (CBV, fourth row), respectively. Application of the concept of cerebral vascular autoregulation led to a prognostic map (fifth row), describing the infarct in red and the penumbra in green, the latter being the target of acute reperfusion therapies. CTA identified an occlusion at the right M1–

M2 junction (*arrow*) as the origin of the hemodynamic disturbance demonstrated by PCT. CTA also revealed a calcified atheromatous plaque at the right carotid bifurcation (*arrowhead*).

Fig. 2.

Representation of the typical location of the two perfusion-CT boluses and of the typical selection of the anterior input function (*cross* over the anterior cerebral artery) and of the venous output (*cross* over the superior sagittal sinus)

Fig. 3.

Fig. 3a–f. **a** Admission PCT demonstrates mixed infarct and penumbra in the left sylvian territory in a patient with a right hemisindrome, whereas **b** CT-angiography (CTA) relates it to an occlusion at the left M1–M2 junction (*arrow*). The patient underwent intravenous thrombolysis and his clinical condition evolved favorably. Twenty-four hours after admission, **d** follow-up CTA features recanalization of the left sylvian artery, later confirmed on the MR-angiography (MRA) **f**. **c** Follow-up PCT shows an almost complete resolution of the penumbra, afforded by the early arterial recanalization. The final PCT infarct has progressed in only a very limited fashion when compared to the admission PCT infarct; its extent closely correlates with that of the abnormality on the delayed DWI trace image (**e**).