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Přehledový článek | Review article

Role of CT perfusion in acute stroke management

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SOUHRN

Akutní ischemická cévní mozková příhoda (CMP) je celosvětově jednou z hlavních příčin invalidity dospělých osob. Moderní endovaskulární léčba akutních ischemických CMP je založena na použití vyspělých zobrazovacích metod a vyhledávání tkání, které lze ještě zachránit. Na rozdíl od nekontrastní výpočetní tomografie (CT) nebo tradiční magnetické rezonance nabízí CT zobrazení perfuze mozku (CTP) aktivní pohled na fyziologii mozkové vaskulatury s jejími četnými parametry. Přes omezení různých zařízení a analytického softwaru používaných ke kvantitativnímu hodnocení rozsahu ischemie a penumbry představuje CTP vynikající nástroj pro neurointervencionisty. Rychlost, s níž lze získat CT skeny perfuze, spolu se schopností této metody predikovat vznik infarktu mohou zkrátit dobu do provedení potřebné intervence. I když každá zobrazovací metoda má své výhody a nevýhody, představuje podle našich zkušeností použití CTP v kombinaci s klinickým vyšetřením účinný nástroj pro vyhledávání pacientů vhodných pro endovaskulární výkon.

Keywords:
CT perfusion
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ABSTRACT

Acute ischemic stroke is a leading cause of adult disability worldwide. Modern endovascular treatment for acute ischemic stroke is predicated on advanced imaging modalities and the identification of salvageable tissue. Unlike noncontrast computed tomographic (CT) imaging or traditional magnetic resonance imaging, CT perfusion (CTP) imaging offers an active view of cerebrovascular physiology with multiple parameters involved. Though limited by the different equipment and analytic software used to quantitatively assess the extent of ischemia and penumbra, CTP imaging nevertheless serves as an excellent tool for neurointerventionists. The rapidity by which CT perfusion may be obtained coupled with its potential for predicting infarct can lead to faster intervention times. Although each imaging modality offers its own set of advantages and disadvantages, we find from our experience that CTP utilized in conjunction with a clinical examination leads to an effective model for identifying patients suitable for endovascular intervention.

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Introduction

Acute ischemic stroke affects approximately 795,000 persons each year, resulting in an annual cost of $17.5 billion [1]. It remains the leading cause of adult long-term disability, with more than 50% of patients requiring discharge to a rehabilitation facility. Intravenous (IV) tissue plasminogen activator (tPA) remains the only treatment for acute ischemic stroke approved by the U.S. Food & Drug Administration. However, given the strict eligibility criteria, this treatment is administered to only a minority of patients, with less than 10% of stroke patients receiving IV-tPA [2].

Endovascular intervention is ushering in a new wave of stroke treatment. The recent publication of 5 randomized, controlled studies has demonstrated its beneficial effects on reperfusion and clinical outcome in patients with proximal, anterior-circulation occlusion [3–7]. Not limited by the strict eligibility criteria of IV tPA, endovascular treatment has expanded the number of patients undergoing treatment for acute ischemic stroke.

The treatment of patients presenting with acute ischemic stroke has its foundation on identification and reperfusion of the ischemic penumbra. Astrup et al. [8] first introduced the term "ischemic penumbra" in 1981 as "tissue within the thresholds of functional impairment (electrical failure) and morphological integrity (ion pump failure) that has the capacity to recover if perfusion is improved". Conversely, tissue in which blood flow falls below these thresholds is considered to have completed infarction and, therefore, is refractory to reperfusion [9]. Identification and differentiation of these regions versus those with potentially salvageable tissue (ischemic penumbra) is critical in the evaluation of patients with acute ischemic stroke.

Early imaging evaluation

In the National Institute of Neurologic Disorders and Stroke (NINDS) trial [10], patients presenting with acute ischemic stroke underwent a noncontrast computed tomographic (CT) scan of the head to exclude intracranial hemorrhage and evaluate for completed infarctions prior to the administration of IV tPA. Due to its rapidity and widespread availability, this technique has remained the mainstay of the radiographic evaluation of acute ischemic stroke patients. Although very sensitive for the detection of hemorrhage, a noncontrast head CT scan lacks the sensitivity for early detection of ischemic stroke (i.e., within the first 3–4 h after a stroke has occurred).

The European Cooperative Acute Stroke Study (ECASS) trial excluded patients in whom "parenchymal hypodensity, and/or effacement in more than 33% of the middle cerebral artery (MCA) territory" was present [11]. These findings are considered indicative of completed infarct and, therefore, are not useful in identifying salvageable tissue. This concept was formalized with the creation of the Alberta Stroke Programme Early CT Score (ASPECTS) in 2000, which was developed in an effort to predict outcome of hyperacute stroke [12]. This score divides the MCA territory into 6 territories, with each assigned one point (Fig. 1). One point is subtracted for each area de-

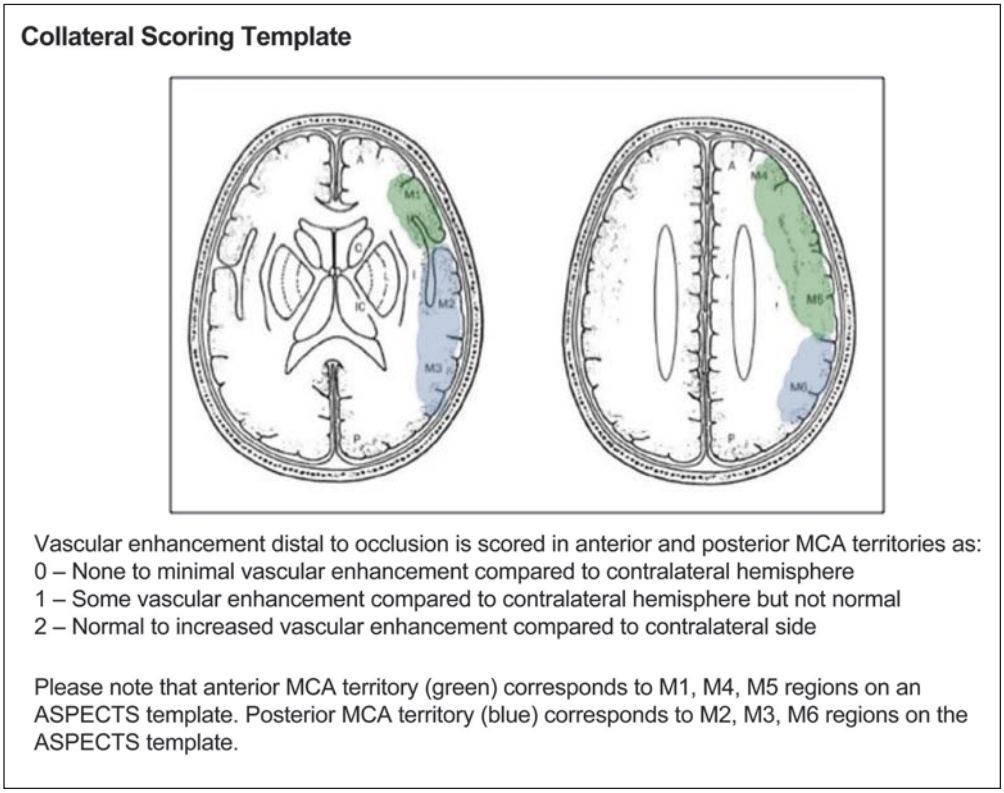

Fig. 1 – Schematic illustrations of head CT scans demonstrating ASPECTS collateral scoring. Reproduced with permission from http://www.aspectsinstroke.com/collateral-scoring/training-cases/13681c2226/ (accessed 11. 12. 2015).

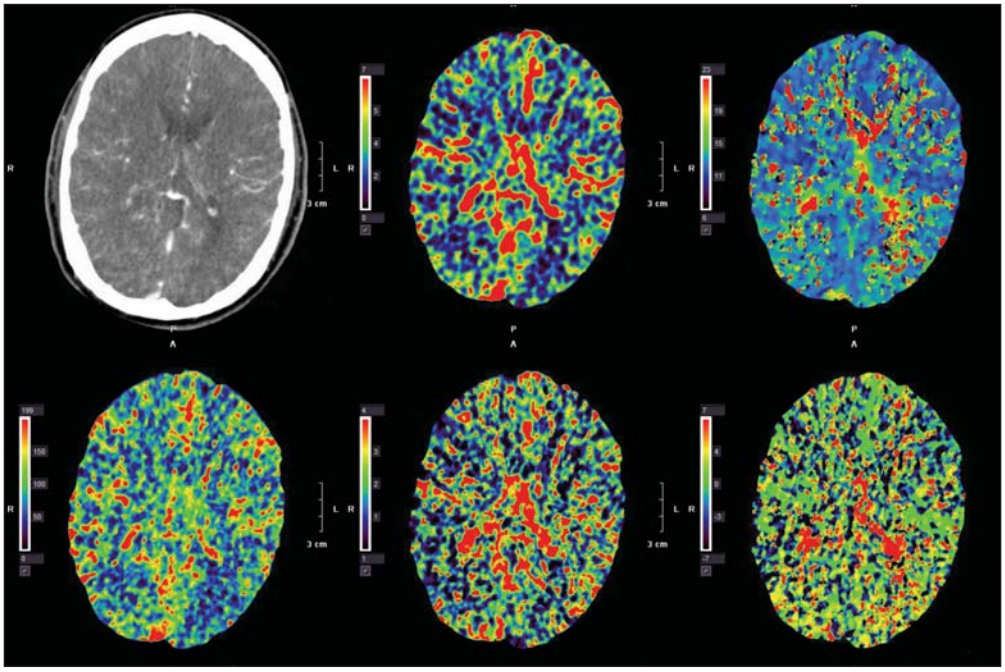

Fig. 2 – Normal computed tomographic perfusion (CTP) imaging study. Upper left, noncontrast head CT scan without evidence of any abnormality. Notice the symmetry in color for each component of the CT perfusion maps (remaining images), indicating normal flow without any evidence of large-vessel occlusion.

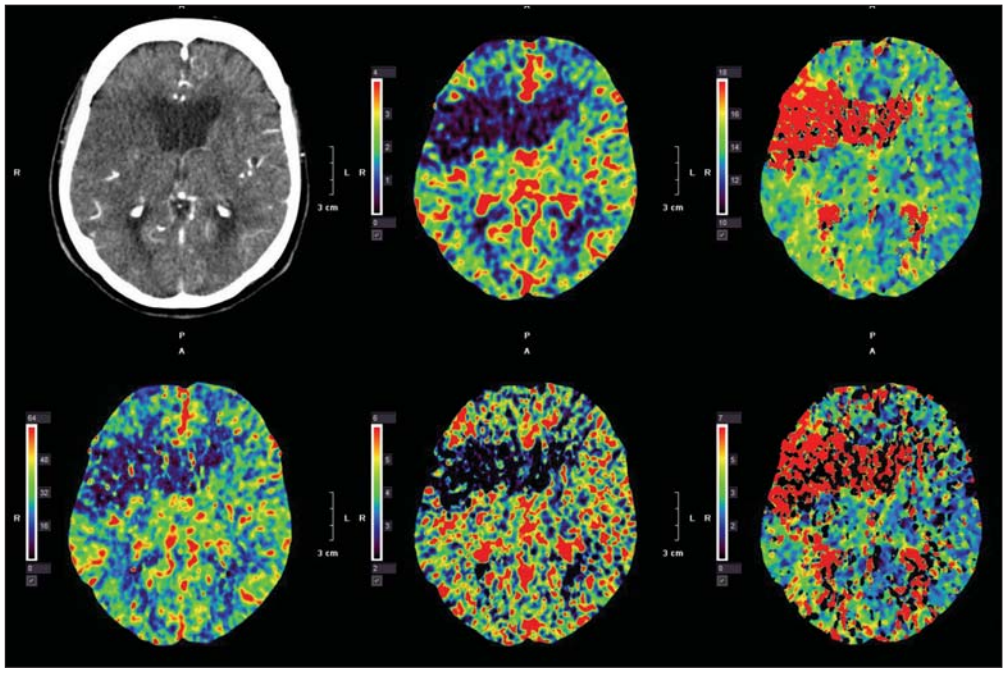

Fig. 3 – CTP imaging study showing a right-sided middle cerebral artery (MCA) stroke without any salvageable penumbra. Of the six-image panel, the upper right image represents time to peak (TTP), which indicates a delay in blood flow to the region of the brain seen as bright red on the color map. The upper middle component of the six-image panel represents cerebral blood volume (CBV). Notice the dark blue within that image, which highlights significant core infarct and large volume loss. Regions of irreversibly infarcted tissue show matched areas of decreased CBF and TTP. No stroke intervention was offered for this patient.

monstrating early ischemic changes (e.g., focal swelling or parenchymal hypoattenuation). Though the ASPECTS correlated with the presenting National Institutes of Health Stroke Scale (NIHSS) score and predicted functional outcome, it remains unable to predict impending ischemia. In other words, it predicts tissue that is *already* ischemic.

Invoking the mantra that "time is brain," the ideal imaging study in the triage of patients presenting with symptoms of acute ischemic stroke would be: (1) rapid, (2)

accurate, (3) capable of identifying and differentiating tissue at risk, but salvageable, from tissue that is already infarcted and at risk for hemorrhage with reperfusion. As mentioned, although a noncontrast head CT scan can be obtained rapidly, this imaging modality is relatively inaccurate for detecting hyperacute stroke and incapable of identifying and differentiating the ischemic penumbra. However, these principles are fulfilled by CT perfusion (CTP) imaging.

Computed tomographic perfusion imaging

A detailed description of the theoretical and technical bases of CTP is beyond the scope of this text, but we refer the reader to thorough reports by Konstas et al. [13,14]. The basis of CT perfusion imaging is the "tracking" of a single injected bolus of iodinated contrast material through the cerebral circulation via sequential spiral CT scanning. Using this technique, the following parameters are measured: cerebral blood flow (CBF), cerebral blood volume (CBV), time to peak (TTP), and mean transit time (MTT). CBF is measured in mL of blood per 100 g of parenchyma per minute (normal: 50 mL/100 g/min), whereas CBV is measured in mL of blood per 100 g of parenchyma (normal: 5 mL/100 g) [15,16]. MTT is a measurement of the mean time for blood to travel through a given volume of brain, thereby reflecting the amount of time it takes for the bolus of contrast material to pass from the arterial to the venous circulation. TTP is the delay between the first arrival of contrast material intracranially and the time at which the contrast reaches its peak concentration in a given region of parenchyma.

Using these parameters, one can utilize hemodynamic differences to assess the intracranial vascular physiology. In cases of normal intracranial perfusion, there is symmetry of all CTP parameters, with CBV and CBF being higher in gray matter than white matter secondary to normal hemodynamic differences between these tissues (Fig. 2) [17]. In this way, CTP is a form of "physiologic imaging," representing active cerebrovascular physiology, rather than just its result (e.g., hypodensity on a CT scan, reflecting a completed infarct).

Utilization of CTP in evaluating acute ischemic stroke

An acute infarct is easily visualized using CTP. Due to loss of cerebral autoregulation, areas of irreversible infarction demonstrate matched decreases in CBF and CBV, with increased MTT and TTP (Fig. 3). Severe decreases in CBV (<30–40% compared to CBV in the normal, contralateral side) have been shown to accurately reflect core infarct when compared to diffusion-weighted magnetic resonance imaging (MRI) sequences [18]. Concomitant decreases in CBF (<30% compared to the normal, contralateral side) further support the prediction of core infarct [19–22].

Conversely, in areas of ischemic penumbra, there may be a mild decrease in CBF with preserved CBV (Fig. 4) [19–21]. However, because of the impairment of blood supply to this region, TTP and MTT are increased, reflecting the fact that the blood is taking alternative (i.e., collateral) routes to supply the territory [22]. These findings are consistent with intact, but stressed, autoregulation in which vasodilation and recruitment occur. Consequently, CBF is typically >30% of that in the normal, contralateral hemisphere, whereas CBV is 60% of normal. However, relative (r) MTT has been shown to be the CTP parameter that most accurately describes salvageable penumbra [18].

Determination of these CTP patterns has traditionally been done through simple visual inspection and, therefore, is affected by the subjectivity and biases inherent to this approach. However, increasingly, utilization of analytic software is being implemented to provide quantitative assessments of ischemia and penumbra [23,24]. This quantitation has also led to the development of "CTP thresholds" for defining area of infarct. For example, some investigators have suggested that CBF <25 mL/100 g/min and CBV <2 mL/100 g are thresholds below which tissue has experienced completed infarct [18,25]. Variations in scanning equipment, protocols, and software may limit extrapolation of these thresholds across different institutions [18]. Therefore, although these thresholds should be interpreted and applied with caution, their development suggests that CTP is moving from a tool for qualitative assessment to one of quantitative assessment. Further development and investigation of the CTP thresholds are needed and may permit more precise analysis of ischemia and penumbra.

Comparison with magnetic resonance imaging

Many consider diffusion-weighted MRI to be the standard noninvasive imaging technique for the evaluation of ischemic brain tissue. With the introduction of MRI perfusion imaging, MRI increasingly is being utilized for evaluation of the penumbra and the subsequent triage of patients presenting with symptoms of acute ischemic stroke. Given the greater expense and time associated with MRI compared to CT imaging, it is critical to compare the two techniques.

In their analysis of 64 patients presenting within 3–6 h of symptom onset, Campbell et al. [26] demonstrated concordance between CTP mismatch (i.e., the area of mismatch between increased TTP/MTT and loss of CBV, or the ischemic penumbra [18–21,27]) and perfusion–diffusion MRI in 90% of studied cases. Similar findings were reported by Schramm et al. [28], who concluded that CTP and CTA were as effective, efficient, and accurate as MRI in determining infarct extent and perfusion deficit. The utilization of CTP in the setting of hyperacute stroke (patients presenting <3 h from symptom onset) also has been shown to be as accurate as diffusion-weighted MRI in defining the infarct volume [29]. Perhaps most importantly and clinically relevant, Wintermark et al. [30] concluded, in their study consisting of 42 patients in whom CTP or MRI was obtained within 3–9 h of symptom onset, that relying on either MRI or CTP imaging would have led to the same treatment decisions. Though diffusion-weighted MRI remains the noninvasive imaging standard for defining the extent of core infarct, these data support the notion that CTP is capable of rapidly and accurately predicting infarct core. Although the speed of MR

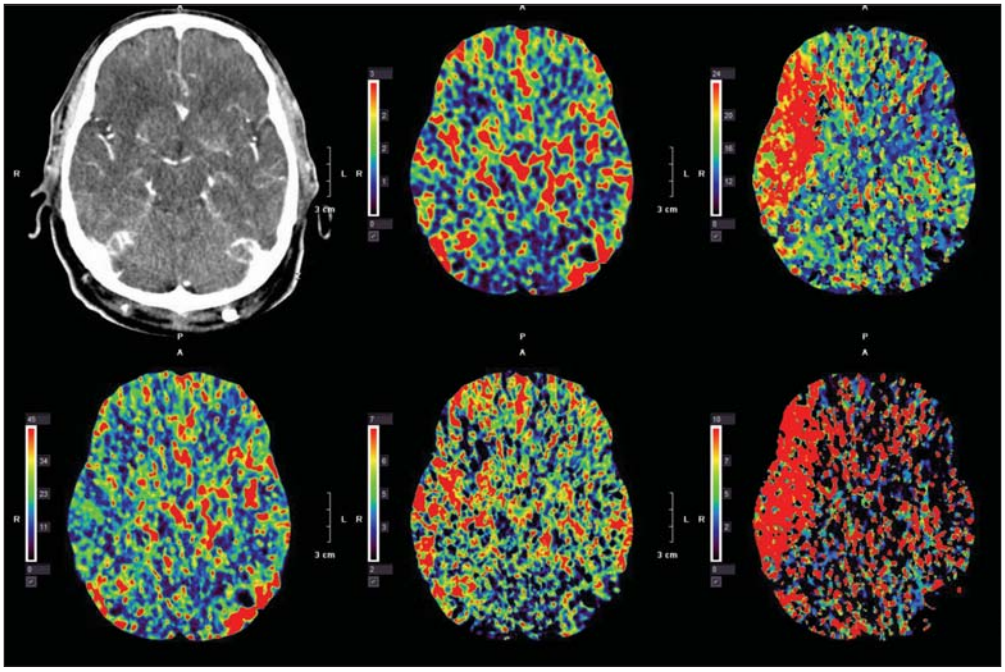

Fig. 4 – CTP imaging study showing an acute stroke of the right MCA territory with salvageable penumbra. The upper right panel indicates increased TTP (red area on perfusion map), whereas the upper middle panel indicates no significant CBV loss as seen by the minimal blue coloring in the right MCA territory. This patient underwent thrombectomy on the basis of CTP imaging findings and National Institutes of Health Stroke Scale score.

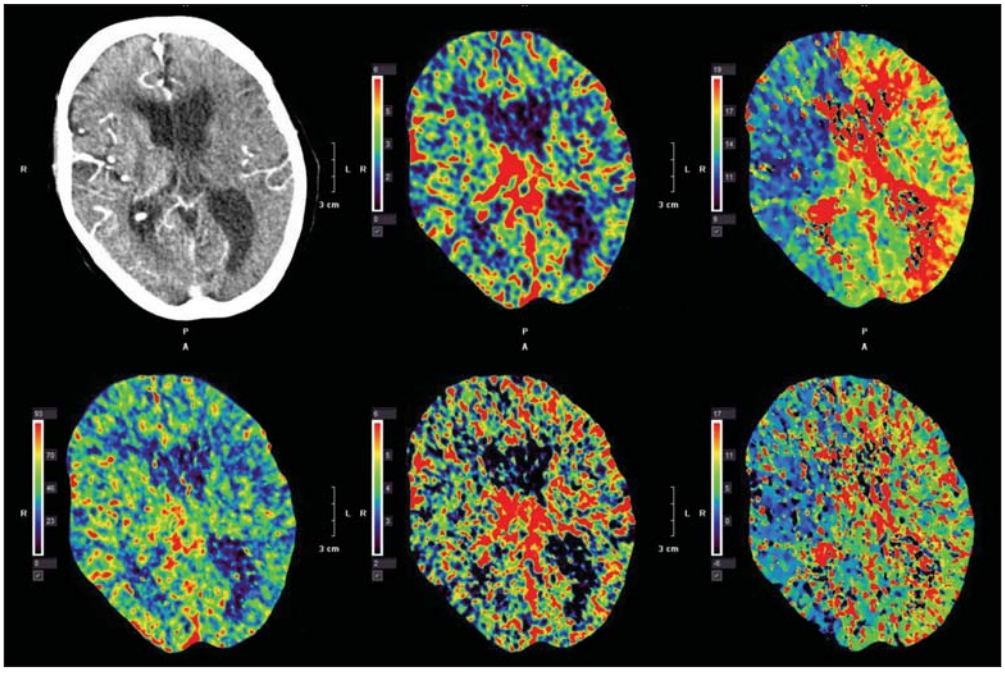

Fig. 5 – CTP imaging study that is abnormal due to *extracranial* carotid stenosis. The left cerebral hemisphere has increased TTP as demonstrated by the upper right panel. Notice the bottom right image is relatively symmetrical because intracranial flow is normalized to the carotid artery at the skull base. It is imperative during interpretation of imaging to account for possible overestimation of areas of acute ischemic penumbra by evaluating concurrent CTA findings.

stroke imaging is improving, the greater availability and decreased cost of CT imaging may make CTP a more attractive option for the imaging triage of patients with acute ischemic stroke.

CTP pitfalls

Early CTP imaging was capable of assessing a region surrounding the basal ganglia and, therefore, was primarily

focused on detecting events involving the MCA territories. Therefore, with early protocols, ischemia affecting other vascular distributions or distal territories (e.g., watershed regions) could be easily missed. Similarly, the poor resolution of these studies could miss small regions of infarct that could be highly symptomatic if located in eloquent regions. Current techniques, including the one applied at our institution, are now capable of scanning the entire brain, thereby increasing image resolution and generating perfusion maps for all vascular territories [22].

CTP parameters are calculated from time–attenuation curves that rely on differences between arterial inflow and venous outflow. Therefore, appropriate selection of arterial input and venous output functions from the source images is critical to accurate perfusion representation. Inaccurate arterial input and/or venous output functions can result in both qualitative and quantitative errors [31]. We typically obtain the arterial input from the A2 segment of the anterior cerebral artery because of its orthogonal orientation on axial CTP source images and its ease of identification on multiple slices. Venous output routinely is obtained from a dural venous sinus [22].

Because both CBV and CBF are calculated using a deconvolution technique, these parameters are affected by any condition causing a delay in passage of the contrast bolus from the arterial to the venous circulation (e.g., extracranial arterial stenosis, congestive heart failure, atrial fibrillation). As a result of such a delay, core infarct may be overestimated. Interpretation of CTP in conjunction with assessment of a CTA of the head *and neck* easily can identify the potentially confounding factor of extracranial stenosis (Fig. 5). Additionally, the application of algorithms that shift the tissue time–density baseline curve generating a delay map can also help clarify any potential overestimation.

As discussed previously, interpretation of CTP parameters and assessment of ischemic infarct versus penumbra is based on relative values with the contralateral hemisphere used as a reference. The inherent limitation with this approach is the requirement for a normal, unaffected hemisphere. For example, a patient in whom CTP is performed for evaluation of a left MCA thrombus will have a potentially distorted CTP map in the presence of a concomitant right extracranial carotid artery stenosis that causes a contrast delay. Although various delay-sensitive software/algorithms are now available, this pitfall nonetheless is one that should not be overlooked by the clinician.

Inherent to CTP is exposure to radiation and iodinated contrast medium. In our experience, the mean dose-length product to the head in patients undergoing evaluation with CTP plus CTA was 4807 mGy, and the mean dose--length product to the body was 619.8 mGy (unpublished data). Absolute contraindications to the administration of iodinated contrast medium are rare and include previous anaphylactic reactions. Routine preoperative preparation for patients with non-anaphylactic allergies at our institution includes the administration of hydrocortisone and diphenhydramine. Patients with underlying renal dysfunction present additional concerns for the administration of iodinated contract material. In our experience, the risk of acute kidney injury in patients undergoing CTP plus CTA followed by digital subtraction angiography for the evaluation of acute ischemic stroke symptoms was 4.7% (unpublished data).

Clinical experience

At our institution, all patients presenting with symptoms concerning for acute ischemic stroke undergo CTP and CTA imaging immediately upon arrival to the emergency room. Patients are taken for endovascular revascularization based on a favorable CTP profile and regardless of time from symptom onset (our patient selection protocol is summarized in Fig. 6). In this way, we frequently treat patients considered outside the traditional time windows.

Furthermore, the decision to proceed to intervention is based not on only the findings on CTP but also on the patient's clinical condition. Placing greater emphasis on CTP findings over those on the clinical examination is not recommended, as the examination findings may be worse than, or better than, those indicated by CTP imaging. Therefore, endovascular therapists work alongside the stroke neurologists to determine a clear and agreed upon NIHSS score prior to any intervention. The combination of CTP and clinical examination drives the endovascular team's desire to treat acute stroke; nevertheless, we urge providers to be cognizant of even basic noncontrast head CT studies where tissue changes may be noted even prior to the injection of any contrast material. Although our institution heavily favors the utilization of CTP as an excellent and proven tool in the assessment of stroke, it is incumbent and imperative that interventionists pay close attention to the clinical examination along with the standardized NIHSS score.

Additionally, we have also used CTP imaging to predict which patients may be high risk for post-revascularization hemorrhage and outcome [32]. We found rCBV to have a statistically significant association with post-revascularization hemorrhagic transformation: rCBV of the basal ganglia region was significantly lower in patients with hemorrhage than those without. Though this finding did not hold true for the rCBV in the cortical regions, cortical rCBV was found to be significantly lower in patients with poor clinical outcomes than those with favorable outcomes.

Conclusions

Acute ischemic stroke remains a leading cause of adult disability. Rapid clinical and imaging evaluation is critical to rapid intervention. CTP is another valuable imaging tool in the growing toolbox of neurointerventionists, providing information on cerebrovascular physiology. By permitting identification and differentiation of penumbra from areas of ischemic core, CTP may be better able to select patients most suitable for endovascular intervention. Our experience with CTP combined with the clinical examination has led to an efficient, effective, and algorithmic model for identifying patients amenable for intervention. Lastly, we have demonstrated its utility in identifying patients at risk for reperfusion hemorrhage, as well as patients likely to achieve favorable outcome.

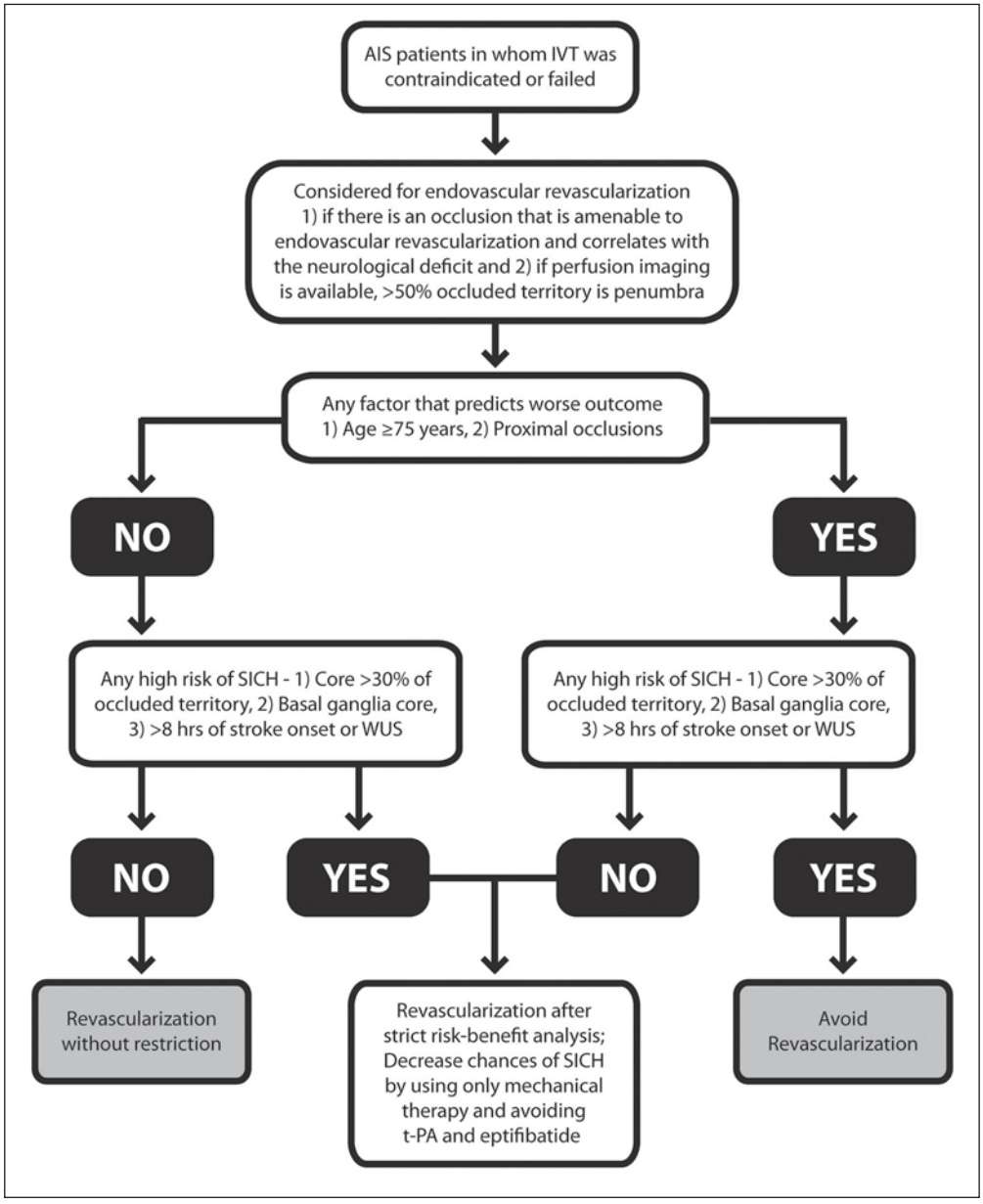

Fig. 6 – Protocol for patient and therapy selection at Gates Vascular Institute. With permission from Kan PT, Snyder KV, Yashar P, Siddiqui AH, Hopkins LN, Levy EI. Utility of CT perfusion scanning in patient selection for acute stroke intervention: experience at University at Buffalo Neurosurgery-Millard Fillmore Gates Circle Hospital. *Neurosurg Focus* Jun 2011;30(6):E4.

Contributions

Conception and design: all authors; data acquisition: all authors; data analysis and interpretation: all authors; drafting the manuscript: Munich; critically revising the manuscript: both authors; Final approval of the manuscript: all authors.

Conflict of interest

Munich and Shakir: None. Snyder: Boston Scientific: Research and major stockholder; Cordis: Research and significant financial interest; EndoTex: Research and significant financial interest; Medtronic: Research and consultant support; Abbott Vascular: Research and consultant support; ev3: Research and consultant support; Toshiba: Research and consultant support; Micrus: Research and consultant support and significant financial interest; Zimmer: Research and consultant support; Access Closure Inc.: Significant financial interest and major stockholder; Niagara Gore Medical: Major stockholder; EPI: Research and significant financial interest; Primus: Significant financial interest; Guidant: Research; Kerberos: Research

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Ethical statement

I declare, on behalf of all authors that the research was conducted according to Declaration of Helsinki.

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