Perfusion Computed Tomography for the Evaluation of Acute Ischemic Stroke

Strengths and Pitfalls

Jeremy J. Heit, MD, PhD; Max Wintermark, MD

Ischemic stroke results from occlusion of a cerebral artery, and it is the leading cause of disability and the fifth leading cause of death in the United States. Cerebral artery occlusion results in irreversible death of a component of cerebral tissue, which is referred to as the core infarction. There is an additional component of brain tissue that is ischemic, but viable, which is commonly referred to as the penumbra. The penumbra is at risk of irreversible infarction if timely restoration of blood flow is not achieved, and the preservation of the penumbra by restoration of arterial blood flow is the target of reperfusion therapy in the treatment of ischemic stroke.

Increasingly, perfusion computed tomography CT (PCT) is performed for physiological evaluation of the brain parenchyma in the setting of cerebral ischemia, and this technique may be used to determine volume of core infarction and of the penumbra. The physiological data derived from PCT is typically displayed in perfusion maps, including cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT; Figure 1). Regions of brain with severely reduced CBF or CBV correspond to the region of core infarction. Regions of brain with prolongation of the MTT or its derivatives, the time-to-peak and time-to-maximum (Tmax) of the residue function, have been shown to accurately measure the penumbra in patients with acute ischemic stroke.

PCT increases the sensitivity and specificity of the acute ischemic stroke diagnosis, aids in excluding stroke mimics, and informs about prognosis and treatment decisions. These important benefits of PCT must be weighed against several disadvantages of the technique. PCT necessarily results in increased radiation exposure to the patient, increased contrast administration that may result in renal injury, increased imaging time that may slightly delay treatment, and increased cost.

Here we discuss PCT in the evaluation of cerebral ischemia with an emphasis on acute ischemic stroke. The most common variations in PCT technique and processing and future directions in PCT research are also discussed.

CT Perfusion Technique: One Size Does Not Fit All

There is significant variability in PCT technique between different institutions, and the PCT parameters used are influenced by the generation of CT scanner, processing software, prior institutional optimization, and even institutional inertia. We now discuss the most common variations in PCT technique, image processing, and challenges that result from the variation in PCT technique.

Variations in Image Acquisition

The principle of PCT is to serially image a volume of brain tissue over time during the injection of an intravenous iodinated contrast bolus. CT density is linearly proportional to the time-dependent changes in iodinated contrast concentration because the contrast is delivered to the brain by arterial blood flow, saturates the brain parenchyma, and exits the brain along with normal venous egress. Serial CT imaging of the brain parenchyma allows a time–density curve to be plotted (Figure 1), and the information in this time–density curve may be used to derive CBV, CBF, MTT, Tmax, time to drain, and other perfusion maps. These maps provide capillary-level information about CBF.

PCT is generally performed after a noncontrast head CT, and it may be performed before or after a concomitant CT angiography in acute stroke protocols. A 35- to 50-mL bolus of iodinated contrast is delivered by power injection into an antecubital vein at a rate of 4 to 5 mL/s followed by a 20 mL saline chase at the same injection rate. Dynamic cine image acquisition is performed after a 5 to 7 second delay after the contrast injection. A tube voltage of 80 kV is used for image acquisition because this voltage approximates the k-edge of iodine, increases contrast enhancement, and reduces the radiation dose when compared with the standard head CT voltage of 120 to 140 kV.

The duration of image acquisition varies between protocols. Most PCT protocols acquire images for a total period of 75 to 90 seconds to ensure adequate image sampling in a later phase, which ensures complete cerebral tissue saturation of
Figure 1. Matched and Mismatched perfusion computed tomography (PCT) imaging in a patient with middle cerebral artery (MCA) occlusions. Noncontrast head CT (NCCT) and PCT images in a patient with a matched core and penumbra (patient 1) and in a patient with a mismatch between the core and penumbra (patient 2). Patient 1: NCCT images demonstrate evidence of acute ischemia within the left MCA territory, including loss of the left insular ribbon (NCCT, arrow), hypodensity within the left lentiform nuclei, and hypodensity with subtle effacement of the cerebral sulci within the left temporal lobe (NCCT, arrowhead). An axial maximum projection image from a computed tomographic angiography (CTA) demonstrates occlusion within the mid-M1 segment of the left middle cerebral artery (Continued)
Processed images show a small area of core infarction (pink region) and a penumbra that is at risk of infarction (green region). Tmax maps show perfusion delay within the right MCA territory that corresponds to the penumbra (Tmax, dashed outline). MTT images do not show significant delay, but Tmax maps show perfusion delay within the right MCA territory that corresponds to the penumbra (Tmax, dashed outline). Processed images show a small area of core infarction (pink region) and a penumbra that is at risk of infarction (green region).

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Figure 2. Mechanical thrombectomy for treatment of a right M1 occlusion. Endovascular mechanical thrombectomy was performed in patient 2 whose image is shown in Figure 1. Anteroposterior digital subtraction (DSA) images show occlusion within the M1 segment of the right middle cerebral artery (MCA; A, arrow). Robust pial collateral vessels arise from the right anterior cerebral artery that supply the ischemic right MCA territory (A, arrowhead), which likely accounts for the relative small area of infarction and modest perfusion delay shown in Figure 1. Complete recanalization of the right MCA (B, arrow) is noted after successful mechanical thrombectomy. Noncontrast head computed tomographic (CT) image shows no acute infarction on presentation (C). After endovascular treatment, there is a small cerebral infarction (D, arrow) in the right corona radiata that corresponds to the region of core infarction identified on the perfusion computed tomography (PCT) before treatment (see Figure 1, patient 2).

Figure 1 Continued. (CTA, dashed arrow), PCT time-density curves showing earlier peaking of the arterial input function (AIF; red line) and slightly later peaking of the venous outflow function (VOF; blue line). Processed PCT maps show reduced cerebral blood volume (CBV; dashed outline), reduced cerebral blood flow (CBF; dashed outline), prolonged mean transit time (MTT; dashed outline), and pro-longed time-to-maximum (Tmax) > 6 seconds (dashed outline). These PCT findings are consistent with a matched volume of core infarction and penumbra. Patient 2; NCCT images show no acute ischemic changes, and an axial maximum projection image from a CTA demonstrates occlusion within the proximal-M1 segment of the right MCA (CTA, arrow). PCT images demonstrate a subtle and small area of reduced CBV and CBF (arrows) within the right corona radiata, consistent with a small core infarction. MTT images do not show significant delay, but Tmax maps show perfusion delay within the right MCA territory that corresponds to the penumbra (Tmax, dashed outline). Processed images show a small area of core infarction (pink region) and a penumbra that is at risk of infarction (green region).

iodine. Delayed cerebral tissue iodine saturation may occur in the setting of poor cardiac output, atrial fibrillation or other cardiac arrhythmias, cervical internal carotid artery stenosis or occlusion, intracranial vessel occlusion, or a combination of these factors, which are common in patients with ischemic stroke. To minimize radiation dose in the setting of longer image acquisition times, the frequency of image acquisition may be varied. It is important to sample with high frequency in the initial acquisition period to generate accurate early-phase arterial and venous concentration curves that allow for optimal calculation of CBF, CBV, MTT, and Tmax maps. Most standard protocols acquire images every second during the first 30 to 45 seconds followed by every 2 to 3 seconds during the next 30 to 45 seconds.

The CT scanner detector array has a significant influence on the parameters used to acquire PCT images. CT scanners with ≤128 detector rows are unable to provide enough z-axis coverage to image the entire brain. There are several techniques to improve z-axis coverage when performing PCT. First, near complete brain coverage may be achieved by cine imaging of 2 separate slabs sequentially. In this technique, an initial region of brain is imaged after iodinated contrast injection in a manner as described earlier. A second intravenous contrast injection is then delivered followed by cine imaging of a second slab. The combination of these 2 perfusion data sets provides perfusion information about nearly the entire brain, but it requires increased contrast and radiation doses.

The shuttle technique may be used to increase coverage of the brain during PCT image acquisition. In this technique, the CT table moves or shuttles back and forth between 2 slabs, and cine images of each slab are obtained over a 75- to 90-second period after a single 60 mL contrast injection. Because the CT table is constantly moving between these 2 slabs, there is a relative loss of temporal resolution, which may result in iodine concentration curve degradation and less accurate perfusion maps. However, as long as images are obtained at a frequency of 2 to 3 seconds, diagnostic accuracy and clinical decision making are not altered despite information lost because of reduced temporal resolution. Helical shuttle techniques may be used to improve the temporal resolution of shuttle mode imaging.

Modern multiarray CT detectors are able to image ≤16 cm of coverage because of their large number of detectors. Therefore, these CT scanners offer a large enough detector array to allow for PCT imaging of nearly the entire brain without any movement in the table position. Furthermore, this increased slab thickness will result in a reduced radiation exposure. These scanners may have additional benefits such as the ability to perform temporally resolved CT angiography, although the...
utility of this technique in the evaluation of cerebral ischemia has not yet been demonstrated in a large number of patients.

PCT necessarily results in an increased radiation dose to the patient, but the use of shuttle mode, low 80 kVp and 100 mAs, and CT scanners with higher detector array numbers minimizes the radiation dose to the 2 mSv range or even lower, which is equivalent to the dose of a single head CT. Most physicians agree that this modest increase in radiation dose is worth the additional information provided by PCT in evaluating patients with acute ischemic stroke.

Processing of Images
Mathematical manipulation of the PCT time–density curves is necessary to derive CBF, CBV, MTT, and T_max maps. There is wide variation in the algorithms used to generate these perfusion maps, but, generally speaking, the 2 techniques used to process the raw PCT data are (1) nondeconvolution and (2) deconvolution methods. Nondeconvolution methods are based on first-pass iodine extraction measurements, which results in a simplified and less computationally intensive processing algorithm. By contrast, deconvolution methods account for physiological variations in arterial delivery of contrast, the effects of collateral flow, and venous outflow components of cerebral perfusion, all of which increase the computational complexity of this method. The number of variables and the specific algorithm used to process these variables result in significant variability in the volume of core infarction and penumbra. Furthermore, each variable and the assumptions associated with assigning a value to each variable result in noise in the PCT data, which may limit the ability of this technique to accurately measure the region of core infarction and the penumbra.

Despite these complex issues and wide variety in techniques, the method of PCT processing does not seem to influence the decision of whether to perform reperfusion therapy.

Additional variation in deconvolution algorithms is introduced by whether the data are processed using manual or automated placement of the arterial input function and the venous outflow function. The A2 segment of the anterior cerebral artery and the superior sagittal sinus are most commonly selected for the arterial input function and venous outflow function, respectively, because these structures are perpendicular to the axis of imaging, which minimizes volume averaging with adjacent brain parenchyma. Manual selection of the arterial input function and venous outflow function is inherently variable depending on the operator, and automated selection of the arterial input function and venous outflow function may be more prone to volume averaging errors or inappropriate vascular structure selection. To date, no consensus exists as to whether manual or automated processing is superior, although many centers have elected to use automated processing to reduce personnel workload.

Determination of the region of core infarction and of the penumbra requires interpretation of the CBF, CBV, and MTT maps. The MTT is prolonged, and the CBF is reduced in both the core infarction and penumbra because of occlusion of a proximal artery that results in slowed passage of blood through the affected brain. The CBV differs between the core and the penumbra and may be used to distinguish these regions of ischemia. The penumbra remains viable by inducing compensatory vasodilatation of collateral vessels that result in an increased CBV. By contrast, these compensatory mechanisms fail in the irreversibly injured core infarction, which results in a decreased CBV.

There is wide variation between vendor software, institutional methods, and threshold values by which the core is distinguished from the penumbra using PCT, and recommended thresholds are based on relatively few studies and a small number of patients. The most commonly used thresholds for determining the region of core infarction are (1) an absolute CBV < 2.0 to 2.2 mL/100 g and (2) a decrease in CBF by 38% to 50% relative to the normal hemisphere. Despite these studies demonstrating that PCT may be used to accurately determine the core infarction, other studies have found relatively poor correlation between these measures and diffusion-weighted imaging assessment of core infarction.

Difficulty in Standardization
The wide variability in these techniques has resulted in controversy in the stroke imaging community about the most accurate measurement of core infarction and penumbra and the most optimal PCT processing techniques. Furthermore, the lack of consensus and standardization in PCT technique likely contributes to the difficulty in accurately measuring the core infarction relative to diffusion-weighted imaging. It will be of interest to determine whether a mechanism to standardize PCT between vendors and institutions can be developed to address these deficiencies. Despite these issues, once a PCT protocol has been optimized at an institution and is internally reproducible, it has value in clinical decision.

PCT in Acute Ischemic Stroke
There has been recent and unprecedented advancement in the treatment of ischemic stroke patients using endovascular mechanical thrombectomy. Within the past year, 5 randomized trials (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN], Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset [REVASCAT], Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times [ESCAPE], Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment [SWIFT PRIME], and Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial [EXTEND-IA]) that demonstrate a marked improvement in patient outcomes after endovascular stroke therapy have been published. The success of these trials is starkly contrasted with several prior randomized trials that demonstrated no significant benefit of endovascular stroke therapy compared with medical management alone. The 2 advances that are most credited with the success of the more recent trials are (1) the use of next-generation mechanical thrombectomy devices that result in better recanalization and (2) more stringent neuroimaging criteria for the selection of endovascular treatment candidates.
Each of the trials demonstrating the efficacy of endovascular stroke therapy included at minimum a noncontrast head CT and vascular imaging with a CT angiography. However, there was variation in these studies with respect to additional neuroimaging that was performed. The ESCAPE trial included a CT angiography-based measure of collateral score, and both the SWIFT PRIME and EXTEND-IA trials included an assessment of penumbra, largely by PCT (Figures 1 and 2). Interestingly, the SWIFT PRIME and EXTEND-IA trials demonstrated the best outcomes in patients undergoing endovascular treatment with functional independence in 60% and 71% at 3 months of follow-up, respectively. These data demonstrate that PCT is not necessary for the selection of endovascular reperfusion candidates. However, the superior patient outcome in SWIFT PRIME and EXTEND-IA compared with MR CLEAN, REVASCAT, and ESCAPE may indicate that the use of PCT in the neuroimaging selection criteria may lead to superior patient outcomes. Future studies should investigate the most optimal imaging selection in patients considered for endovascular stroke therapy to address this hypothesis.

PCT provides important information to the neurologist and neurointerventionalist when evaluating patients for endovascular reperfusion therapy beyond identifying the size of core infarction and penumbra. First, the physiological information derived from perfusion imaging may indicate the likelihood of the infarction increasing in size regardless of whether endovascular reperfusion is achieved. The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) 2 trial, which was based on magnetic resonance perfusion, found extreme delays in Tmax to be a marker of infarct growth and a poor outcome even if reperfusion was achieved. Next, regions of low CBV are at high risk of hemorrhagic transformation after endovascular treatment, and this information may be helpful in describing the risks of this therapy to the patient, their family, and the physicians caring for the patient.

Clinical Application of PCT: Beyond Ischemic Stroke

Neurological deficits because of acute ischemic stroke are often strongly suggestive of the diagnosis, but there are numerous conditions that may present with symptoms similar to acute ischemic stroke, such as intracranial hemorrhage, seizures, migraine headaches, posterior reversible encephalopathy syndrome, hypoglycemia, tumors, and drug-related toxicity. Although a detailed discussion of these entities is beyond the scope of this review, we briefly highlight the utility of PCT in the evaluation of the most common stroke mimics.

Nonvascular stroke mimics include seizures, posterior reversible encephalopathy syndrome, and intracranial tumors. Both seizures and posterior reversible encephalopathy syndrome may be identified on PCT as regions of increased CBF and CBV and reduced MTT. In seizure disorders, these perfusion changes are typically localized to the cortex, and they do not conform to expected vascular territories. Similarly, primary or metastatic brain tumors may display increased CBF and CBV. Prompt recognition of these perfusion changes with patterns that are inconsistent with acute infarction help to expeditiously identify the correct diagnosis.

Future Directions in PCT Research

PCT for triage of endovascular stroke patients is likely to increase in the coming years, but much work remains to validate further this technique in acute stroke imaging. Ongoing studies in which endovascular stroke candidates are selected for endovascular stroke treatment with or without perfusion-weighted imaging are likely to determine whether PCT results in superior patient selection. Efforts to standardize PCT imaging or to develop a means by which PCT data can be normalized across vendors and institutions should be aggressively pursued. If a method to standardize PCT is developed, it would open the door for data pooling meta-analyses of large amounts of imaging data, which we expect would provide important insights into the imaging triage of acute stroke patients. Finally, the DEFUSE 3 will begin enrollment this year, and this study will use perfusion-weighted imaging to randomize stroke patients with a mismatch profile to endovascular treatment or no treatment in the 6- to 16-hour window. The results of this study may be the first to determine whether neuroimaging may replace the clock in determining stroke patient treatment eligibility, which may provide a treatment option to a large number of patients.

Disclosures

None.

References


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