Cerebral perfusion CT: Technique and clinical applications

Scanner de perfusion cérébrale : technique et applications cliniques

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Summary
Perfusion computed tomography (PCT) is an imaging technique that allows rapid, noninvasive, quantitative evaluation of cerebral perfusion by generating maps of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT). The concepts behind this imaging technique were developed in the 1980s', but its widespread clinical use was allowed by the recent introduction of rapid, large-coverage multidetector-row CT scanners. Key clinical applications for PCT include the diagnosis of cerebral ischemia and infarction, and evaluation of vasospasm after subarachnoid hemorrhage. PCT measurements of cerebrovascular reserve after acetazolamide challenges in patients with vascular stenoses permit evaluation of candidacy for bypass surgery and endovascular treatment. PCT has also been used to assess cerebral perfusion after head trauma and microvascular permeability in the setting of intracranial neoplasm. Some controversy exists regarding this technique, including questions regarding correct selection of an arterial input vessel, the accuracy of quantitative results, and the reproducibility of results. This article provides an overview of PCT, including details of technique, major clinical applications, and limitations.

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Introduction

Multiple imaging techniques have been used to evaluate cerebral perfusion, including positron emission tomography (PET), single photon emission computed tomography (SPECT), xenon computed tomography (CT), and magnetic resonance (MR) perfusion; these modalities, however, are hampered by limited availability, cost, and/or patient tolerance [1]. Perfusion-CT (PCT) was introduced as a timely and simple means to evaluate cerebral perfusion.

PCT can be performed rapidly with any modern spiral CT scanner and standard power injector. The PCT maps can be generated quickly and easily at a workstation equipped with the appropriate software. Multidetector-row CT scanners are desirable, as they allow for increased anatomical coverage. At our institution, PCT is routinely used in acute stroke patients to confirm a suspected diagnosis of stroke, and to distinguish between infarct and penumbra or tissue at risk, the target of reperfusion therapies [2–4]. It has been extended into the evaluation of patients with possible vasospasm after subarachnoid hemorrhage (SAH) [5] and for the evaluation of cerebrovascular reserve with acetazolamide challenge in patients with carotid artery stenosis who are potential candidates for bypass surgery or endovascular treatment [6]. PCT can also be applied to assess cerebral perfusion after head trauma [7–9] and to measure the permeability surface product area (PS) in patients with intracranial neoplasms [10–12].

Technique

PCT data acquisition technique

PCT scans at our institution are obtained using a 64-slice CT scanner. After an unenhanced CT of the whole brain, and before a CT-angiogram (CTA) of the carotid and vertebral arteries and a postcontrast CT of the brain, sixteen 5-mm-thick sections are selected to include the level of the basal ganglia and centrum semi-ovale, where all three supratentorial vascular territories can be evaluated. The CT gantry is tilted both for the unenhanced CT and the PCT, so that the selected slices are imaged parallel to the hard palate.

Forty millilitres of a nonionic contrast agent (300 mg of iodine per millilitre) are injected and flushed by 25 ml of saline chase, at a rate of 5 ml/s, using a standard power injector. Contrast administration via an 18–20 gauge line in a right antecubital vein is preferred, as it minimizes pooling of contrast, lowers the risk of extravasation, and minimizes streak artifact at the thoracic inlet during the CTA portion of the exam. All of these pitfalls are frequently observed in the case of a left antecubital vein injection, because of a compression of the left innominate vein between the sternum and the dolichoid ascending aorta often seen in elderly patients.

At 7 s after initiation of the injection, PCT scanning is initiated with the following technique: 80 kVp, 100 mA. One image per second is acquired in a cine mode for 37 s, followed by one image every three seconds for another 33 s. Total duration of the acquisition is 70 s.

We typically increase the anatomical coverage in our PC protocol by injecting two successive boluses and acquiring two successive PCT series. This is, however, not feasible in all patients due to their level of renal function. Alternative approaches to increase the anatomic coverage of PCT include the "toggle-table" technique, in which the scanner moves between two different brain levels, obtaining data from each in turn. This method permits imaging of a larger portion of the brain with a single bolus, but sacrifices some temporal resolution due to increased time between sequential images of a single slice [13].

When an acute stroke patient is imaged within the therapeutic window, we usually do not wait for the results of creatinine testing, except in case of known history of renal failure or prior serum creatinine measurement that exceeded 1.5 mg/dl, known renal disease, solitary kidney (e.g., prior nephrectomy, congenital absence), diabetes mellitus (insulin-dependent greater or equal to two years or non-insulin dependent greater or equal to three years), collagen vascular disease (e.g. lupus), or paraproteinemia syndromes (e.g., myeloma). This approach has been demonstrated as safe in more than 1000 patients, with only a very low rate of temporary renal failure (0.19%) and no case of permanent renal failure [14].

If low kVp (80 kVp) and mAs (100 mAs) are used for PCT acquisition [15], the overall effective dose required for PCT (2.0–3.0 mSv) is only slightly higher than that required for routine head CT (1.5–2.5 mSv). This dose equivalent is less than the dose equivalent obtained with PET or SPECT, and is comparable to that of a single-level xenon CT examination [16].

PCT data processing technique

The theoretical basis for PCT imaging is the central volume principle, which relates cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) as follows: CBF = CBV / MTT. Perfusion data are obtained by monitoring the first pass of an iodinated contrast agent bolus through the cerebral vasculature. The linear relationship between contrast agent concentration and attenuation can be used to calculate the amount of contrast agent in a given region from the degree of transient increase in attenuation. Time versus contrast-concentration curves are created for an arterial and a venous region of interest, as well as for each pixel of...
the scan. The MTT map derives from deconvolution of arterial and tissue enhancement curves. CBV is calculated as the area under the curve in a parenchymal pixel divided by the area under the curve in the venous pixel. The central volume equation can then be solved for CBF [17].

Deconvolution softwares allow much lower injection rates – 5 ml/s as reported above – compared to other softwares that use different approaches, such as the maximal slope model [17]. 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 [17].

PCT data are analyzed at an imaging workstation. Post-image-collection processing involves semi-automated definition of an input artery and a ‘‘vein’’. In acute stroke patients, selection of different arterial inputs has been demonstrated to have no significant effect on PCT results for an individual patient [18]. 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, the 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.

Clinical indications

Acute stroke

PCT provides a rapid and simple means to evaluate cerebral perfusion in patients presenting with acute stroke symptoms, most of whom already undergo unenhanced head CT to rule out intracranial hemorrhage. Indeed, findings of acute cerebral ischemia, however, can be subtle or absent on unenhanced CT. In addition, the advent of thrombolytic therapy for acute nonhemorrhagic stroke has intensified the need for a rapid, readily available technique to help identify and quantify the presence and extent of the ischemic penumbra, or tissue at risk. The latter tissue may be salvageable with the administration of thrombolytic agents, whereas irreversibly damaged infarct will not benefit from reperfusion and may be at increased risk of hemorrhage after thrombolytic therapy. 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 a timely and easy means of identifying ischemic penumbra, permitting rapid triage of patients who may benefit from reperfusion. Distinction between infarct and penumbra from PCT data is based on the concept of

Figure 1  Modern CT survey in a 57-year-old male patient admitted in our emergency room with a left hemisyndrome, including an unenhanced CT (first row), a perfusion-CT (PCT) (rows 2 through 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 athemomatous plaque at the right carotid bifurcation (arrowhead).
Figure 2 Patient transferred at Day 8 to our neurovascular intensive care unit (ICU) from an outside institution after coiling of a ruptured anterior communicating artery aneurysm. Unenhanced brain CT obtained at the admission of the patient in our neurovascular ICU demonstrated extensive residual subarachnoid hemorrhage and suspicious loss of gray-white matter contrast in the left superior frontal gyrus (white arrows). The tip of a right ventricular drain catheter is also visible.

On PCT, significantly abnormal brain perfusion in the distribution of the anterior and inferior branches of the left (and also, to a lesser extent, right) anterior cerebral arteries (ACA) (arrowheads) and of the posterior branches of the right middle cerebral artery (MCA) is seen primarily on MTT maps. The CBF was slightly decreased in these same territories, whereas CBV was mainly preserved (it is lowered only in the left superior frontal gyrus (star)). CTA confirmed the suspicion of moderate vasospasm of A2 and A3 segments of both ACAs (arrows), ultimately verified by gold standard digital subtracton angiography (DSA). No abnormality of the right posterior MCA branches was identified. Of note, the artifacts created by the coils on the CTA images, obscuring the A1 segments bilaterally and interfering with their evaluation.

Endovascular therapy (IA Verapamil) was performed in the ACA territories during the DSA.

Cerebrovascular reserve

In patients with known chronic cerebral ischemia related to underlying carotid artery stenotic lesions, CBF is usually preserved, at least initially, because of the cerebrovascular reserve. The cerebrovascular reserve represents the vasodi-
latation ability of cerebral arteries to compensate for a CBF tending to decrease and maintain this CBF at a normal level. In patients with chronic cerebral vascular disorders, it is necessary to quantify the residual cerebrovascular reserve, and distinguish tissue that has used only a limited fraction of its vasodilatation ability and still has cerebrovascular reserve available as a buffer, from tissue that has exhausted its vasodilatation ability and cerebrovascular reserve. The latter is at risk of ischemia, which can be triggered by any hemodynamic stress, and requires intervention to increase CBF, usually through carotid stenosis surgery or endovascular treatment, or extracranial-intracranial artery bypass [24].

Hemodynamic stress can be mimicked by using a tolerance test such as acetazolamide administration in conjunction with quantitative measurement of CBF. Although the exact mechanism of action is uncertain, acetazolamide causes vasodilatation of normal cerebral arteries and an increase in CBF in the corresponding territory. Patients with impaired cerebrovascular reserve, however, are already maximally vasodilated due to the response of cerebral autoregulatory mechanisms, and thus cannot respond further to acetazolamide. CBF does not increase, but remains stable or even decreases, because of a steal phenomenon by the “healthy” arteries [24]. Acetazolamide is generally well-tolerated, with the most common side effects being circumoral numbness, paresthesias, and headache. One case of acetazolamide-associated reversible ischemia has been reported [25].

Xenon CT [26], PET [24], SPECT [27], transcranial Doppler sonography, and perfusion MR imaging [28] have all been used to evaluate cerebrovascular reserve with the acetazolamide test. Recently, PCT has been used to perform acetazolamide challenges [6,29]. Implementation of acetazolamide challenges is always the same, independent of the technique used to assess brain perfusion. Patients first undergo a brain perfusion imaging study. Subsequently, 1g of acetazolamide is administered intravenously, followed 20 minutes later by another PCT brain perfusion imaging study.

The quantitative results potentially available with PCT may provide an advantage over qualitative techniques such as SPECT and perfusion MR imaging. The ability to measure CBV and MTT may also be an added advantage of PCT. Indeed, a recent study demonstrated that the degree of impairment in cerebrovascular reserve, as assessed by clinical history, correlated most closely with the change in MTT in response to acetazolamide [6]. This study also showed that increased baseline MTT values may be a static, quantitative indicator of compromised cerebrovascular reserve in at-risk territories [6].

Vasospasm

Vasospasm is a frequent complication after aneurysmal subarachnoid hemorrhage (SAH), causing significant morbidity during the early post-SAH clinical course. Angiographic evidence of vasospasm is present in 60–80% of patients with SAH, with approximately 32% of patients becoming symptomatic. Among patients with aneurysmal SAH who reach neurosurgical referral centers, it is estimated that 7% will be severely disabled, and another 7% will die as a result of vasospasm [30,31]. Measurement of CBF can be useful in initial identification of those patients at risk for cerebral ischemia, as well as in guiding therapeutic decisions and monitoring response to therapy [32].

Various methods have been employed to measure cerebral perfusion, including PET, SPECT [33], xenon-CT [32], and transcranial Doppler sonography [34]. Of these modalities, sonography has been the most widely used, but has many limitations, as it is operator dependent, cannot quantify CBF at the tissue level, and, alone, may not be specific enough to guide therapy.

![Figure 3](image-url) Patient fallen from a 6-m height, admitted with a Glasgow Coma Scale score of 9. Neurological examination in the emergency room revealed an asymmetry of tone and deep tendon reflex involving both right upper and lower limbs. Admission contrast-enhanced cerebral CT demonstrated a displaced left parietal skull fracture, associated with a large cephalohematoma. A small left parieto-occipital sub-dural hematoma (white arrowhead) and a small contusion area (white star) could also be identified on the conventional CT images. PCT demonstrated a much wider area of brain perfusion compromise (white arrows), with involvement of the whole left temporal and parietal lobes, the latter showing increased MTT and decreased CBF and CBV. Thus, PCT afforded a better understanding of the neurological examination findings on admission than conventional CT.

**Figure 3** Patient victime d’une chute de 6 mètres, admis avec un score de 9 sur l’échelle du coma de Glasgow. L’examen neurologique aux urgences révéla une asymétrie de tonus et des réflexes impliquant les membres supérieur et inférieur droits. Le scanner cérébral avec injection de produit de contraste montre une fracture déplacée pariétale gauche et un céphalhématome. Un hématome sous-dural pariéto-occipital (tête de flèche blanche) et une contusion minime (étoile) sont aussi identifiables sur les images de scanner conventionnel. Le PCT montre une région beaucoup plus étendue d’altération de la perfusion cérébrale (flèches blanches), impliquant les lobes pariétal et temporal gauches, avec un MTT augmenté et des CBF et CBV diminués. Le PCT explique mieux le déficit neurologique clinique que les images de scanner conventionnel.
Figure 4 Eighty-three-year-old women with known meningiomas presented in the emergency room with left-sided face, arm and leg weakness of one-day duration, following a seizure episode. The CT survey demonstrated two extra-axial masses, containing calcifications and characterized by heterogeneous enhancement, in the right frontal region and right parafalcine location, consistent with meningiomas. On PCT, these meningiomas demonstrated increased CBV and CBF, but also increased permeability. Increased permeability translated on the time-density curves into a large and rapid increase in density within the meningiomas (red and orange curves), without significant return to baseline compared to normal white matter (green curve). On the Patlak plot, increased permeability is responsible for the steep slope of the curves calculated within the meningiomas.

At our institution, PCT is used in combination with CTA to monitor cerebral perfusion in SAH patients with a positive Doppler study (Fig. 2). MTT maps are reviewed for arterial territories with prolonged MTT values. Such a territory is considered at risk for vasospasm, and the artery supplying this territory is then evaluated by CTA for vasospasm. If CTA of the corresponding artery is abnormal, the diagnosis of vasospasm is made. Finally, the arterial territories with MTT and CTA suggestion of vasospasm are carefully assessed for a decrease in cortical CBF values. If present, the latter prompts a conventional angiogram for possible endovascular treatment. This approach, which is as sensitive as, and more specific than performing Doppler alone, allows to obviate unnecessary invasive angiograms in selected lower risk patients [5].

Head trauma

PCT has been used in severe head trauma patients, as it affords insight into regional brain perfusion alterations due to head trauma, with the major advantage of being able to detect regional heterogeneity (Fig. 3). Its results show specific patterns, linked to cerebral edema and intracranial hypertension. PCT allows differentiation between patients with preserved autoregulation (or pseudoautoregulation) and those with impaired autoregulation. It may help monitor cytotoxic and vasogenic edema, and guide their treatment [8,9].

PCT is more sensitive than conventional unenhanced CT in the detection of cerebral contusions, with a sensitivity reaching 87.5% versus 39.6% [7]. PCT can detect altered brain perfusion as a result of compression by an epidural/subdural hematoma [7]. Finally, PCT offers prognostic information with respect to the functional outcome, and this as early as on admission. Normal brain perfusion or hyperemia is observed in case of favorable outcome, and oligemia in case of unfavorable outcome [7]. Head trauma patients with altered brain PCT results might be considered for more aggressive and early treatment to prevent intracranial hypertension, whereas patients with preserved brain perfusion might benefit from less invasive treatment [7–9].

Tumors

Tumors are inherently associated with increased angiogenic activity and neovascularization that results in increased...
blood volume and hyperpermeability related to the immature vessels. [35] Results of previous studies have indicated that microvascular permeability increases with increasing biologic aggressiveness of tumors, while a reduction in permeability in response to antiangiogenic therapy correlates with decreased tumor growth. Results of initial studies in which measurements of CBV and permeability surface product area (PS), a measure of microvascular permeability, were obtained from PCT show PS to be predictive of pathologic grade and to correlate with tumor mitotic activity [35]. Elevated PS values are evident only in the tumor and not in the surrounding tissues [10,11]. Finally, PCT may help in distinguishing primary glial neoplasms from extraaxial tumors and metastases (Fig. 4) [12]. PCT may prove to be advantageous over MR imaging in the assessment of tumor angiogenesis, given the linear relationship between contrast agent concentration and attenuation changes, the lack of sensitivity to flow, the high spatial resolution, and the absence of susceptibility artifacts. However, the exposure to ionizing radiation, the potential for adverse reaction to the contrast agent, and the limited anatomic coverage are limitations of CT, compared with MR, for evaluation of the microvasculature [10,11].

There are also reports describing the use of PCT to evaluate squamous cell carcinomas of the head and neck. Initial results revealed elevated PS, CBF, and CBV and a lower MTT in the primary tumor site, compared with those values in normal structures [36,37]. PCT may provide a way to noninvasively measure tumor malignancy, guide biopsies to the most malignant portion of the tumor, and assess response to treatment. However, further investigation is still necessary to validate such an approach.

**Controversies**

The quantitative accuracy of the PCT CBF results is debated. PCT CBF results were demonstrated in a few small studies to be highly correlated with PET [38] and xenon-CT [39] quantitative values. As mentioned above, this however requires appropriate selection of accurate arterial input functions [18].

The reproducibility of PCT postprocessing has also not been fully validated. Software to analyze the PCT data is commercially available and relatively simple to use, although training is required. Results of initial investigations indicate that postprocessing findings are reproducible between different operators [40,41].

Another limitation of PCT is its limited anatomic coverage. We described above two alternative approaches to increase PCT coverage (two separate PCT boluses and the toggle-table technique). The limited coverage of PCT is becoming less and less of an issue with the advent of large coverage, whole-brain multidetector CT scanners, as a note, perfusion-weighted MRI is often advocated because it provides whole-brain coverage, but it can do so only at a cost. Indeed, on most scanners, either of a long time of repetition (2000 ms), limiting the temporal resolution of the acquisition and the accuracy of the perfusion measurements, or of a low matrix size or large slice thickness or interslice gap, limiting the spatial resolution of the PWI maps. The limited coverage of PCT has been demonstrated not to be an obstacle when assessing the extent of a stroke for making treatment decision [2].

**Conclusion**

PCT is a very easy-to-use imaging technique to assess brain perfusion. Its main application is the evaluation of stroke patients, but clinical applications are quickly expanding to include assessment of patients with chronic cerebrovascular diseases, vasospasm, head trauma and brain tumors. Several limitations, including mainly standardization and automation of the processing, remain to be addressed, hopefully in a close future.

**References**


