CT Brain Perfusion: A Clinical Perspective

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Abstract. Computed tomography perfusion (CTP) is an important exam performed in neuroradiology that adds functional information regarding hemodynamics to that obtained from morphological imaging and thereby supports clinical decision-making in several vascular and non-vascular conditions.

This paper outlines the clinical applications of CTP, its advantages over MRI and disadvantages. Factors affecting the results of CTP will also be discussed. Finally, a clinically oriented overview of the calculated perfusion parameters and their value will be provided.

Keywords: CT · Perfusion · Stroke

1 Clinical Applications of CTP

CTP is applied in different conditions, and its uses are divided into vascular and non-vascular applications.

1.1 Vascular Applications

CTP is necessary to identify infarction core and penumbra and their mismatch in cases with acute cerebral ischemia, which is not possible using conventional scans; it is therefore very important in triaging patients and deciding whether recanalization therapy (i.e., thrombectomy or thrombolysis) is needed. Many institutes consequentially implement CTP (or MR perfusion) as part of their stroke-imaging algorithm, based on evidence and/or experience [1, 2]. It is particularly valuable in patients with extended time window, such as those exhibiting symptoms for longer than six hours or with an unknown symptom onset (such as wake-up stroke), to approximate the risk benefit ratio for aggressive stroke therapy and to identify eligible patients in whom CTP can be used to estimate the tissue at risk [3].

Patients with classic thromboembolic stroke may benefit from CTP, as can those with other conditions that may lead to ischemic lesions, such as sickle cell anemia [4], which can cause vascular occlusion, or myomoya disease [5] and other types of occlusive diseases. The detection of perfusion disturbance appears to be helpful in predicting the risk of developing stroke in patients with extracranial internal carotid stenosis or occlusion [6].

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Vasculitis results in narrowing of intracranial vessels, leading to a reduction in the blood supply to the brain, and in these cases perfusion can help detect affected territories [5].

Perfusion imaging is also helpful in evaluating the stages of hypoxic ischemic injury after resuscitation [7, 8], and assessing the ischemic effects of hypotensive cerebral syndrome [9].

Sudden onset of neurological symptoms can potentially be due to stroke but can also be present in other disorders that cause stroke-like symptoms; some of these symptoms are not easy differentiated from stroke clinically and therefore called stroke mimics. The most important members in this group of diseases are seizures and migraine in which perfusion imaging plays an important role not only in excluding stroke but also in demonstrating the pattern characteristic of these diseases [10, 11].

Because CTP can be used to evaluate macro- and microvascular circulation, it is important to be added to CT angiography in patients with delayed cerebral ischemia and vasospasm after subarachnoid hemorrhage [12] because it can predict which patients that may develop ischemia [13], identify the extent and degree of ischemia [14], helps in selecting patients for treatment [15], including either triple-H therapy (hypertension, hypervolemia, and hemodilution) or catheter-based management, such as intra-arterial vasodilator and balloon angioplasty.

CTP can also help to confirm brain death [16].

1.2 Non-vascular Applications

Neoplastic

CTP parameters, especially CBV and permeability, can be used to differentiate low- from high-grade gliomas, predict progression from low- to high-grade glioma, and differentiate between high-grade glioma and lymphoma [17, 18]. Perfusion imaging also plays a role in monitoring patients under therapy, as it can differentiate radionecrosis from recurrent tumor [17]. It is also helpful in differentiating neoplastic lesions, such as high-grade tumors, from inflammatory lesions, such as tumefactive demyelinating lesions, a process that is difficult when using only conventional imaging.

Traumatic

Another non-vascular indication is traumatic squeal, in which CTP provides some benefits. It has a higher sensitivity than non-enhanced CT for detecting cerebral contusions; It can show changes related to mass effects caused by edema, swelling, and extra-axial hematomas related to trauma; and the number of territories involved with perfusion changes may help to predict outcomes in severe trauma [19].

Degenerative

CTP can play a role in degenerative diseases of the brain by detecting decreased perfusion in characteristic locations [20].

2 Advantages and Disadvantages of CTP

CTP has many advantages, CT scanners are widely available and more affordable than MRI. CT is also readily available in emergency and acute settings and suitable for intensive care patients without the need for the special equipment required to monitor the patient during MRI. The high temporal resolution of CTP is advantageous in uncooperative patient and CT can be performed in patients with different types of implants that are contraindicated in MRI, such as a pacemaker. A change in CT density observed after the application of contrast agent is linearly related to the concentration of iodine, and this allows a more robust quantification with absolute measures of perfusion parameters [21]. CTP benefits from the high spatial resolution of the CT scanner.

However, small lesions can be missed by a CT exam. Because of the usual beam hardening artifacts, visualization of the posterior fossa is not optimal in CT exams. The limited soft tissue contrast in CT is also a drawback that renders MRI more superior in evaluating brain tissues. The application of contrast agents could be contraindicated in certain patients, such as those with kidney failure or allergy. However the most important drawback of CTP is the high radiation dose, which differs according to the technique applied and the coverage required on the Z-axis; this limits the use of such exams, especially in younger patients. High doses of radiation can be delivered to the radiosensitive eye lens during CTP.

Several strategies can be used to reduce the radiation dose in CT; these include reducing the tube voltage and/or current. Ultra-low-dose CTP decreases radiation by approximately 20%, but should be combined with denoising techniques [22]. Modern scanners that use iterative reconstruction allow the radiation dose to be reduced without an associated reduction in image quality. Reducing the frequency of image acquisition and the number of CTPs performed per patient are important factors. CTP should be performed only when indicated, and whenever possible, other radiation-free methods should be used, such as MR perfusion [23].

3 Acquisition and Post-processing

A variety of factors may affect the results of CTP.

3.1 Factors Related to Acquisition

Injection Rate

Typically, 4–7 ml/s flow of contrast agent given via an antecubital vein is advised, but this is not feasible in every patient, such as those with a smaller venous caliber. A higher injection rate leads to a maximum but brief peak, which is more suitable for rapid data collection during acquisition. A lower injection rate leads to a shorter but prolonged peak, which is more suitable for slower data collection [24]. Therefore, both the injection rate and the frequency of data collection should be jointly considered.

Duration of Image Acquisition
Generally, an acquisition duration of 45 s is enough to include the tissue attenuation curve (TAC) in patients without a cardiac condition, but there is a risk of acquiring an incomplete TAC in patients with low cardiac output, atrial fibrillation or severe vascular stenosis. To avoid these instances, a prolonged duration time (60–90 s) is advised.

Frequency of Image Acquisition
As was previously stated, the injection rate and frequency of data collection should both be optimized to record the maximum enhancement. Using a low frequency may miss the peak point of the curve, while using a high frequency rate can lead to increased radiation exposure. Accordingly, a multiphase protocol with variation in image acquisition over three different phases is sometimes advised [25].

Coverage
The volume of brain included in the perfusion exam depends on the detector width, which can reach 16 cm in 256 and 320-slice scanners. Patients scanned with a lower detector number can be scanned twice at two different levels if clinically indicated. Some scanners include a toggle table with shuttle mode (instead of a static table during scanning), and this allows for larger coverage.

3.2 Factors Related to Mathematical Modeling

Deconvolution and Non-deconvolution
There are two major methods for mathematical calculations; deconvolution and non-deconvolution.
The non-deconvolution method is based on Fick's principle of conservation of mass, and the Mullani Gould formula, which neglects venous return, and therefore requires a high injection rate. This method is easier to calculate, but the non-venous return assumption is considered an oversimplification. Absolute quantification is not possible with this method [21].

There are two different methods of performing deconvolution techniques; parametric and non- parametric. Non-parametric methods include the Fourier transformation, which is very sensitive to noise, and singular value decomposition (SVD), which is the most common method used in perfusion calculations. This type of deconvolution contains other subtypes, such as standard SVD, oscillation SVD, circular SVD and Bayesian methods.

Delay and Dispersion
In cases of vessel occlusion, there will be a delay in contrast approaching the tissue voxel, and there may be dispersion of the contrast bolus before it reaches the occlusion site [26]. The opinions of authors differ in this matter, with some advising delay correction, and others suggesting that delay is a part of the pathological process and should not be corrected. Therefore, some software corrects for delay (delay-invariant), while others do not (delay-sensitive). Methods that can be used to correct for delay include Fourier transformation, block circulant decomposition matrix, the use of an arterial input function (AIF) obtained from smaller vessel near the region of interest, and curve fitting [21].

3.3 Factors Related to Post-processing

Motion
Uncooperative patients tend to move during the exam, and this can lead to motion artifacts, the loss of accurate results, or in some instances an inability to process the data. Thus motion correction, which is usually performed by software packages developed for perfusion analysis, is an important step.

Vessel Definition
To avoid partial volume, the artery used for the AIF and the vein used for venous reference should be perpendicular to the slice orientation; hence the anterior cerebral artery is usually used for AIF, and the superior sagittal sinus is used for a venous reference. Most modern software performs this step automatically.

Accordingly, the results of CTP can vary widely according to the previously mentioned factors. There are various models to perform this processing, each of which produces different results. Therefore, care should be taken, especially in multicenter studies, as the results obtained in different centers may be not comparable.

4 Interpretation of Perfusion Parameters

Several parameters can be generated from CT perfusion, and these vary among software packages. In this section, an overview is provided of the value of each parameter and how it can be interpreted from a clinical point of view. Understanding of each parameter will improve interpretation of imaging findings. Each parameter should not be interpreted separately, but should instead be interpreted with other parameters and morphological images.

4.1 Cerebral Blood Flow (CBF)

CBF is defined as the volume of blood moving through a given unit volume of brain per unit time [24]. On the TAC, it is the upward slope of the curve. A more vertical line indicates a faster flow. This parameter is measured in ml of blood/100 g brain tissue/s. The flow, according to Ohm's law (applied to fluids), is directly proportional to the pressure (or pressure gradient) and indirectly proportional to the resistance [27]. Consequently, the flow will decrease when the difference between the arterial and venous sides is reduced, as is observed in cases of arterial occlusion, or when resistance increases, which can be caused by the vascular wall in cases of vasospasm or by the surrounding structures in cases of brain edema or hydrocephalus, and by other causes that can increased intracranial pressure. Another important factor that affects CBF is the vascular diameter; according to the Hagen-Poiseuille equation the volumetric flow is directly proportional to the fourth power of the internal radius of a tube [28]. Thus, a reduction in the vascular diameter by half leads to a 16-fold decrease in the flow, which results in a reduction in CBF when autoregulation is exhausted. A reduction in the vascular diameter occurs in cases of stenosis, such as that observed in vasospasm and other vaso-occlusive diseases.

In summary, CBF can be affected by pressure gradients, resistance and vessel diameter, which are altered in many conditions and is therefore one of the most important parameters.

4.2 Cerebral Blood Volume (CBV)

CBV is the total volume of blood in a given unit volume of brain [24]. In the TAC CBV is the area under the curve represents the total amount of contrast (blood) in the tissue of interest (ROI) regardless of time. Generally, it indicates whether blood reaches a tissue, even when it does so in a reduced rate or delayed manner [29]. It is measured in ml of blood/100 g brain tissue.

In certain conditions the flow of blood may be significantly reduced, even though the volume may be normal or even increased. This is because of autoregulation phenomena, which are physiological process that aims to adjust hemodynamics when there are changes in cerebral blood pressure. Additionally, the hypoxia and hypoglycemia caused by hypoperfusion can cause vasodilatation, leading to increased blood volume.

4.3 Time to Peak (TTP)

TTP is defined as the time taken for the contrast to achieve maximum enhancement. In the TAC, this is the time from when the contrast injection is initiated until the peak of the curve is reached. TTP is very sensitive to flow changes. However, many factors (technical, or patient-related), such as a lower injection rate, or low cardiac output, can prolong TTP without the presence of cranial pathology. Hence, some vendors define TTP in an alternative method in which the time is calculated from the earliest enhancement of the cerebral arteries until the peak is reached on the tissue curve. This method (tracer delay-insensitive or delay-invariant) reduces extracranial factors that may cause delay and thereby increases specificity.

4.4 Time to Maximum (Tmax)

Tmax is defined as the time to maximum of the residue function. Hence, Tmax is also a "time to peak" but after processing the residue. This is one of the more complex parameters, because it is affected by many factors. It reflects bolus delay but is also affected by temporal dispersion and, to a lesser extent, mean transit time. These factors increase the complexity of analyzing this parameter as a prolonged Tmax can represent any one of these factors, and this should be taken into consideration when interpreting results. However, a significant delay in Tmax is most likely not caused by a prolonged MTT.

Tmax is considered a measure of macrovascular parameters [30] and one of the important parameters in stroke imaging. It is understood that elevated Tmax in acute ischemia coexists with hypoperfusion and delayed poor collateral supply. In addition, regions with highly elevated Tmax, even when well-perfused, are the most vulnerable to further perfusion pressure reduction.

Quantifying Tmax is helpful in stroke management, in which a threshold between 4–6 s appears to be optimal for the early identification of critical hypoperfused brain tissues [31].

4.5 Time to Start (TTS)

TTS indicates the interval between contrast material injection and the beginning of contrast enhancement. This is the time between the start of contrast administration until the bolus arrival time (BAT) in seconds and is affected by multiple factors, as in TTP. Thus, the delay-invariant method can increase specificity by calculating the time from the beginning of the earliest enhancement of the cerebral artery until BAT at the tissue side. When using this definition (time spent from beginning enhancement of the arteries until the contrast reaches the tissue), this is the time spent on the arterial side (mostly inside the large- and medium-sized vessels), so TTS can be considered as a marker of macrovascular structures that reflects the bolus arrival delay [32].

4.6 Mean Transit Time (MTT)

MTT is, with CBF and CBV, one of the three basic parameters used in CTP. It may be calculated by the central volume principle, CBF = CBV/MTT (i.e., MTT = CBV/CBF). It is the average transit time of blood through a given brain region [9]. It also represents the time spent between inflow and outflow of contrast on a tissue curve. In other words, it indicates the time spent in capillary vessels, and can therefore be considered a marker of microvascular circulation. It can be used to detect changes due to microvascular alterations and lesions due to vasospasms of the microvasculature as it is highly sensitive to hemodynamic disturbances.

MTT is inversely proportional to perfusion pressure. Compensatory vasodilatation (which is preserved in the penumbra) occurs when cerebral blood pressure drops, leading to prolongation of the MTT. Therefore, MTT is a useful parameter for identifying penumbras.

4.7 Time to Drain (TTD)

TTD describes the time to washout. It is the time from when the enhancement is started until the outflow of contrast in the tissue curve; in other words, TTD represents the sum of TTS and MTT, making this parameter very sensitive to both macro- and microvascular disturbances. This parameter appears to condense both types of pathologies into one image. Therefore, it is sensitive to different types of changes in hemodynamics, and a normal TTD predicts normal perfusion with a high probability [33].

4.8 Flow Extraction Products (Extraction Flow Products)

This parameter is also called the volume transfer constant (K^{trans}) [34] and reflects the passage of contrast between the blood and the extravascular extracellular space [35]. K^{trans} is considered a marker of blood brain barrier disturbances and depends on the flow of a tracer (F) in addition to permeability (P) and the vascular surface area (S).

Surface area and permeability cannot be separated in practice, so they are commonly called permeability-surface products (PS). Thus K^{trans} can vary according to these two factors (F and PS) [36]. This parameter is important in neoplastic conditions.

5 Conclusion

New methods for automated image analysis are currently developed in many domains. For appropriate clinical application of artificial intelligence technologies in this domain, it remains important to understand processing steps in CTP and factors that affect final lesion load prediction so that solutions can be reached that will help clinicians in decision-making even in challenging situations.

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