5.1 Introduction

Acute stroke is a common cause of morbidity and mortality worldwide: it is the third leading cause of death in the United States (responsible for approximately 1 in 15 deaths in 2001) and affects approximately 700,000 individuals within the United States annually [1]. The ability to treat patients in the acute setting with thrombolytics has created a pressing need for improved detection and evaluation of acute stroke, with a premium placed on rapid acquisition and generation of data that are practically useful in the clinical setting. Recanalization methods for acute ischemic stroke remain limited to a restricted time window, since intravenous (i.v.) and intra-arterial (i.a.) thrombolysis carry hemorrhagic risk that increases with time post-ictus [2–4]. Clinical exam and unenhanced CT, the existing imaging standards for acute stroke, are limited in their ability to identify individuals likely to benefit from successful recanalization [3, 5–11].

Advanced imaging techniques extend traditional anatomic applications of imaging and offer additional insight into the pathophysiology of acute stroke, by providing information about the arterial-level cerebral vasculature, capillary-level hemodynamics, and the brain parenchyma. Our evolving understanding of acute stroke emphasizes knowledge of each of these levels to guide treatment decisions in the acute setting. As a modality, MR in particular has gained acceptance in the evaluation of acute stroke, in large part due to the rapidity and accuracy of diffusion-weighted imaging (DWI) in the detection of acute infarction when compared to traditional unenhanced CT [12, 13].
CT perfusion (CTP) expands the role of CT in the evaluation of acute stroke by providing insight into areas in which CT has traditionally suffered in comparison to MR – capillary-level hemodynamics and the brain parenchyma – and in doing so forms a natural complement to the strengths of CTA [14–17]. The imaging of acute stroke demands answers to four critical questions [10, 18, 19]:

- Is there hemorrhage?
- Is there intravascular thrombus that can be targeted for thrombolysis?
- Is there a “core” of critically ischemic irreversibly infarcted tissue?
- Is there a “penumbra” of severely ischemic but potentially salvageable tissue?

CTP attempts to address the latter two of these questions to better guide management in the acute setting. (Table 5.1).

CT perfusion (CTP) expands the role of CT in the evaluation of acute stroke by providing insight into areas in which CT has traditionally suffered in comparison to MR – capillary-level hemodynamics and the brain parenchyma – and in doing so forms a natural complement to the strengths of CTA [14–17]. The imaging of acute stroke demands answers to four critical questions [10, 18, 19]:

- Is there hemorrhage?
- Is there intravascular thrombus that can be targeted for thrombolysis?
- Is there a “core” of critically ischemic irreversibly infarcted tissue?
- Is there a “penumbra” of severely ischemic but potentially salvageable tissue?

CTP attempts to address the latter two of these questions to better guide management in the acute setting. (Table 5.1).

CTP imaging techniques are relatively new compared to MR-based methods; their clinical applications are therefore less thoroughly reported in the literature [20–22]. Despite this, because the general principles underlying the computation of perfusion parameters such as cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) are the same for both MR and CT, the overall clinical applicability of perfusion imaging using both of these modalities is likely to be similar. In addition, as will be discussed, first-pass CTP, unlike MR perfusion-weighted imaging (MR-PWI), readily provides high-resolution, quantitative data using commercially available software. In addition, CTA with CTP is fast [14], increasingly available [23], safe [24], and affordable [25]. It typically adds no more than 10 min to the time required to perform a standard unenhanced head CT, and does not hinder i.v. thrombolysis, which can be administered – with appropriate monitoring – directly at the CT scanner table immediately following completion of the unenhanced scan [8, 14, 16, 17, 20, 24, 26–49]. Like DWI and MR-PWI, CTA/CTP has the potential to serve as a surrogate marker of stroke severity, likely exceeding the NIH Stroke Scale (NIHSS) score or Alberta Stroke Program Early CT Score (ASPECTS) as a predictor of outcome [26, 50–57]. Because of these advantages, increasing evidence that advanced CT imaging can accurately characterize stroke physiology could have important implications for the management of stroke patients worldwide [32, 33, 58, 59].

5.2 CTP Technical Considerations

Acute Stroke Protocol. A protocol for the imaging of acute stroke should address the central questions necessary to triage patients appropriately (Table 5.1). The acute stroke protocol employed at our institution has three components: the unenhanced CT, an “arch-to-vertex” CTA, and dynamic first-pass cine CTP (Table 5.2). A similar CTA/CTP protocol, or its equivalent, could be applied using any commercially available multidetector row helical CT scanner with only minor variations that should not adversely alter image quality. The protocol is routinely completed within 10 min. Perhaps the most important aspect of patient preparation for CTP imaging may be to have an 18- or 20-gauge catheter already placed in an appropriately large vein prior to the patient’s arrival in the CT suite. It is similarly useful for the power injector to be loaded prior to patient arrival. Total scanning time can be drastically reduced if such details are attended to before the examination. It is important to secure the head with tape or Velcro straps, as motion artifact can severely degrade CTA/CTP image quality.
The role of unenhanced CT in stroke triage, discussed in more detail in Chapter 3, is principally to exclude hemorrhage prior to thrombolytic treatment [60]. A large, greater than one-third middle cerebral artery (MCA) territory hypodensity at presentation is considered by most to be a contraindication to thrombolysis [61]. CT remains suboptimal in its ability to correctly subtype stroke, localize embolic clot, predict outcome, or assess hemorrhagic risk [3, 5–11]. Early ischemic signs of stroke are typically absent or subtle, and their interpretation is prone to significant inter- and intra-observer dependency [11, 56, 62–65].

The technical considerations and interpretation of the second portion of the acute stroke protocol, CTA, are discussed in detail in Chapter 4. Importantly, however, the source images from the CTA vascular acquisition (CTA-SI) also supply clinically relevant data concerning tissue-level perfusion. It has been theoretically modeled that the CTA-SI are weighted predominantly by blood volume rather than blood flow [22, 29, 66]. The potential utility of the CTA-SI series in the assessment of brain perfusion is discussed in detail below. This perfused blood volume technique requires the assumption of an approximately steady-state level of contrast during the peri-

<table>
<thead>
<tr>
<th>Series</th>
<th>Unenhanced</th>
<th>CTA head</th>
<th>CTA neck</th>
<th>Cine perfusion ×2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>C1 to vertex</td>
<td>Biphasic contrast injection: 4 ml/s for 40 ml, then 0.8 ml for 30 ml</td>
<td>Arch to C1</td>
<td>7 ml/s for 40 ml for each CTP acquisition</td>
</tr>
<tr>
<td>Gantry angle</td>
<td>0</td>
<td>C1 to vertex</td>
<td>0</td>
<td>5 s; each is a 60-s cine acquisition</td>
</tr>
<tr>
<td>Algorithm</td>
<td>Standard</td>
<td>C1 to vertex</td>
<td>Arch to C1</td>
<td>0</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>5 mm</td>
<td>Standard</td>
<td>5 mm</td>
<td>0</td>
</tr>
<tr>
<td>Gantry angle</td>
<td>0</td>
<td>0</td>
<td>Arch to C1</td>
<td>0</td>
</tr>
<tr>
<td>Algorithm</td>
<td>Standard</td>
<td>0</td>
<td>Arch to C1</td>
<td>0</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>5 mm</td>
<td>Standard</td>
<td>5 mm</td>
<td>0</td>
</tr>
<tr>
<td>Table feed</td>
<td>5.62 mm</td>
<td>5.62 mm</td>
<td>5.62 mm</td>
<td>0</td>
</tr>
<tr>
<td>Pitch</td>
<td>0.562</td>
<td>0.562</td>
<td>0.562</td>
<td>5 mm</td>
</tr>
<tr>
<td>Mode</td>
<td>0.562:1</td>
<td>0.562:1</td>
<td>0.562:1</td>
<td>5 mm</td>
</tr>
<tr>
<td>kVp</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>5 mm</td>
</tr>
<tr>
<td>mA</td>
<td>220</td>
<td>200</td>
<td>250</td>
<td>5 mm</td>
</tr>
<tr>
<td>Rotation time</td>
<td>0.5 s</td>
<td>0.5 s</td>
<td>0.5 s</td>
<td>5 mm</td>
</tr>
<tr>
<td>Scan FOV</td>
<td>Head</td>
<td>Head</td>
<td>Head</td>
<td>5 mm</td>
</tr>
<tr>
<td>Display FOV</td>
<td>22 cm</td>
<td>22 cm</td>
<td>22 cm</td>
<td>5 mm</td>
</tr>
<tr>
<td>Retrospective helical reconstructions</td>
<td>Thick 1.25 mm Interval 0.625 mm FOV 18 cm</td>
<td>Thick 1.25 mm Interval 1.0 mm FOV 18 mm</td>
<td>5 mm</td>
<td></td>
</tr>
</tbody>
</table>
of image acquisition [29]. It is for this reason – in order to approach a steady-state – that our protocols call for a biphasic contrast injection that can achieve a better approximation of the steady-state [67, 68]. More complex methods of achieving uniform contrast concentration with smaller doses have been proposed that may eventually become standard, such as exponentially decelerated injection rates [69] and biphasic boluses constructed after analysis of test bolus kinetics [68, 70].

CTP Acquisition. The cine acquisition of CTP forms the final step in the acute stroke imaging evaluation. With dynamic, quantitative CTP, an additional contrast bolus is administered (at a rate of 4–7 ml/s) during continuous, cine imaging over a single brain region. Using the “standard” cine technique, imaging occurs for a total of 45–60 s, sufficient to track the “first pass” of the contrast bolus through the intracranial vasculature without recirculation effects. Our current scanner (General Electric Lightspeed 16) offers 2 cm of coverage per bolus (two 10-mm-thick or four 5-mm-thick slices) [28, 38, 46]; however, the coverage volume of each acquisition depends greatly on the manufacturer and generation of the CT scanner and continues to increase with enlarging detector arrays and improving technology. The maximum degree of vertical coverage could potentially be doubled with each bolus using a “toggle table” technique, in which the scanner table moves back and forth, switching between two different cine views, albeit at a reduced temporal resolution of data acquisition [42]. Our current protocol employs two boluses to acquire two slabs of CTP data at different levels, increasing overall coverage [48]. Importantly, at least one imaged slice in each acquisition must include a major intracranial artery for CTP map reconstruction. Because the previously acquired CTA data are available prior to CTP acquisition, one can target the tissue of interest through the selection of an appropriate imaging plane for the CTP acquisition, which is particularly important given the relatively restricted CTP coverage obtained even with two CTP acquisitions. It has been our experience that a scan plane positioned parallel and superior to the orbital roof can provide sufficient sampling of the middle (both superior and inferior divisions), anterior, and posterior cerebral artery territories to assess perfusion in cases of large vessel anterior circulation stroke, and, when positioned parallel and inferior, in cases of large vessel posterior circulation stroke [15, 71, 72]. An important consideration in the design of an acute stroke protocol is the total contrast dose; in the sample protocol presented here, the contrast used for the CTA has been restricted in order to allow two 40-ml boluses during the CTP acquisitions.

Considerable variability exists in the protocols used for CTP scanning, because CTP imaging has only recently gained acceptance as a clinical tool, and because construction of perfusion maps is dependent on the specific mathematical model used to analyze the dynamic, contrast-enhanced datasets. Algorithm-dependent differences in contrast injection rates exist; for example, models that assume “no venous outflow” necessitate extremely high injection rates (which in practice can be difficult to achieve) in order to achieve peak arterial enhancement before venous opacification occurs [30]. Considerably slower injection rates can be used with the deconvolution-based models [73]. However, regardless of injection rate, as with MR perfusion imaging, higher contrast concentrations are likely to produce maps with improved signal-to-noise ratios [74].

One accepted deconvolution CTP imaging protocol calls for scanning at 80 kV, rather than at a more conventional 120–140 kV (Table 5.2). Theoretically, given a constant tube current, this tube voltage setting would not only reduce the administered radiation dose to the patient but would also increase the conspicuity of i.v. contrast, due, in part, to the greater importance of the photoelectric effect for 80 kV photons, which are closer to the “k-edge” of iodine [46]. Images are acquired in cine mode at a rate of approximately one image per second. Improved temporal resolution is possible with some scanners, with acquisition rates as fast as one image per half second, however the resulting moderate improvement in tissue-density curve noise may not justify the increased radiation dose.
Table 5.3. Advantages and disadvantages of CTP relative to MR perfusion-weighted imaging (PWI)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability and decreased cost of CT</td>
<td>Limited scan coverage</td>
</tr>
<tr>
<td>Speed of acquisition</td>
<td>Risks and complications of iodinated contrast</td>
</tr>
<tr>
<td>Ease of monitoring and intervention</td>
<td>Ionizing radiation</td>
</tr>
<tr>
<td>in an unstable clinical setting</td>
<td>More complex post-processing</td>
</tr>
<tr>
<td>Can be performed in patients with pacemakers</td>
<td></td>
</tr>
<tr>
<td>or other contraindications to MR,</td>
<td></td>
</tr>
<tr>
<td>or in patients who cannot be screened for MR</td>
<td></td>
</tr>
<tr>
<td>safety</td>
<td></td>
</tr>
<tr>
<td>Improved resolution</td>
<td></td>
</tr>
<tr>
<td>Quantitative perfusion information</td>
<td></td>
</tr>
</tbody>
</table>

5.3 Comparison with MR-PWI

5.3.1 Advantages

Quantitation and Resolution. While CTP and MR-PWI both attempt to evaluate the intricacies of capillary-level hemodynamics, the differences in technique create several important differences that should be considered (Table 5.3). While dynamic susceptibility contrast (DSC) MR-PWI techniques rely on the indirect T2* effect induced in adjacent tissues by high concentrations of intravenous gadolinium, CTP relies on direct visualization of the contrast material. The linear relationship between contrast concentration and attenuation in CT readily lends itself to quantitation, which is not possible with MR-PWI techniques. MR-PWI may also be more sensitive to “contamination” by large vascular structures and is also limited in some areas due to susceptibility effects from adjacent structures. In addition, CTP has greater spatial resolution than MR-PWI. These factors contribute to the possibility that visual evaluation of core/penumbra mismatch is more reliable with CTP than with MR-PWI [75,76].

Availability and Safety. CT also benefits from the practical availability and relative ease of scanning, particularly when dealing with critically ill patients and the attendant monitors or ventilators. CT may also be the only option for a subgroup of patients with an absolute contraindication to MR scanning, such as a pacemaker, and is a safe option when the patient cannot be screened for MR safety.

5.3.2 Disadvantages

Limited Coverage. A major disadvantage of current CTP techniques is the relatively limited coverage; while MR-PWI is capable of delivering information about the whole brain, the coverage afforded by CTP depends greatly on the available CT technology. Our current protocol (using a GE Lightspeed 16 scanner) provides four slices (5 mm each) derived from a 2-cm-thick slab of tissue for each contrast bolus. Even with two CTP cine acquisitions, the overall coverage necessitates a tailored approach that acquires perfusion data in areas of interest. Importantly, however, the limited coverage offered by current CTP techniques may be less of a problem with further advances in multidetector CT technology.

Ionizing Radiation. CTA/CTP also requires ionizing radiation and iodinated contrast. The safety issues involved are no different from those of any patient group receiving contrast-enhanced head CT scanning, and are discussed at length in multiple papers [15,77]. The CTP protocol, in particular, has been optimized to provide maximum perfusion signal with minimum dose [46]. Overall, each of the CTA and CTP components of our protocol delivers approximately the same low radiation dose to the head as a conventional CT.

Iodinated Contrast. Our current protocol employs two 40-ml boluses of iodinated contrast material for the CTP cine acquisitions, in addition to the contrast required for the CTA acquisition. This is a not insignificant dose of iodinated contrast, particularly in the relatively older population most at risk for stroke, and the dose may be of even higher concern if the pa-
Patient subsequently requires additional contrast for endovascular intervention. However, nonionic iodinated contrast has been shown not to worsen stroke outcome [78–80]. In patients with preexisting renal dysfunction (abnormally elevated creatinine) or insulin-dependent diabetes, our protocol calls for nonionic, iso-osmolar contrast administration, minimizing the chance of nephrotoxicity [81].

**Complex Post-Processing.** Post-processing of CTA and CTP images is more labor intensive than that of MRA and MRP images, although with training and quality control, 3D reconstructions of CTA datasets, as well as quantitative CTP maps, can be constructed rapidly and reliably [82–84].

### 5.4 CTP: General Principles

**Perfusion-weighted CT and MR techniques** – as opposed to those of MR and CT angiography which detect bulk vessel flow – are sensitive to capillary, tissue-level blood flow [85]. This evaluation of capillary-level hemodynamics extends the traditional anatomic role of imaging to provide insight into the delivery of blood to brain parenchyma. The idea of contrast-enhanced CT perfusion imaging emerged as early as 1976, when a computerized subtraction technique was used to measure regional cerebral blood volume (rCBV) using the EMI scanner. Sodium iothalamate was administered intravenously to increase x-ray absorption in the intracranial circulation, permitting regional differences in CBV to be measured [86]. More recently, prior to the advent of helical CT scanning, “time to peak” analysis of cerebral perfusion was proposed as a means of evaluating stroke patients. Patients with a prolonged (greater than 8 s) time to peak parenchymal enhancement had poor clinical outcomes. This dynamic CT study took 10–15 min longer to perform than a conventional CT exam. Therefore, given the absence of faster scanning or an approved treatment for acute stroke, this method never gained clinical acceptance [87].

The generic term “cerebral perfusion” refers to tissue-level blood flow in the brain. This flow can be described using a variety of parameters, which primarily include CBF, CBV, and MTT (Table 5.4). Understanding the dynamic relationships between these parameters as cerebral perfusion pressure drops in the setting of acute stroke is crucial to the accurate interpretation of perfusion maps. Definitions of these parameters are as follows:

- **Cerebral blood volume (CBV)** is defined as the total volume of blood in a given unit volume of the brain. This definition includes blood in the tissues, as well as blood in the large capacitance vessels such as arteries, arterioles, capillaries, venules, and veins. CBV has units of milliliters of blood per 100 g of brain tissue (ml · 100 g⁻¹).

- **Cerebral blood flow (CBF)** is defined as the volume of blood moving through a given unit volume of brain per unit time. CBF has units of ml of blood per 100 g of brain tissue per minute (ml · 100 g⁻¹ · min⁻¹).

- **Mean transit time (MTT)** is defined as the average of the transit time of blood through a given brain region. The transit time of blood through the brain parenchyma varies depending on the distance traveled between arterial inflow and venous outflow. Mathematically, MTT is related to both CBV and CBF according to the central volume principle, which states that MTT=CBV/CBF [88, 89].

### Table 5.4. Normal values for perfusion parameters in brain tissue (Adapted from [143])

<table>
<thead>
<tr>
<th></th>
<th>CBF (ml · 100 g⁻¹ · min⁻¹)</th>
<th>CBV (ml · 100 g⁻¹)</th>
<th>MTT (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray matter</td>
<td>60</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>White matter</td>
<td>25</td>
<td>2</td>
<td>4.8</td>
</tr>
</tbody>
</table>

### 5.5 CTP Theory and Modeling

Although easy to define in theory, the perfusion parameters of CBV, CBF, and MTT can be difficult to quantify in practice. The dynamic, first-pass approach to CT perfusion measurement involves the
dynamic i.v. administration of an intravascular contrast agent, which is tracked with serial imaging during its first-pass circulation through the brain tissue capillary bed. Depending on the assumptions regarding the arterial inflow and the venous outflow of the tracer, the perfusion parameters of CBV, CBF, and MTT can then be computed mathematically. Dynamic first-pass contrast-enhanced CTP models assume that the tracer (i.e., the contrast) used for perfusion measurement is non-diffusible, neither metabolized nor absorbed by the tissue bed through which it traverses. “Leakage” of contrast material outside of the intravascular space, which can occur in cases of blood–brain barrier (BBB) breakdown associated with tumor, infection, or inflammation, requires a different model to be used and therefore adds an additional layer of complexity to the calculations. Other means of assessing cerebral perfusion, including PET and xenon CT imaging for example, employ diffusible tracer models which generally involve fewer assumptions regarding steady-state CBF than do the dynamic, first-pass contrast-enhanced models used with MR and CT imaging. The two major types of mathematical models involved in performing these calculations are the deconvolution-based and nondeconvolution-based methods.

**Nondeconvolution Techniques.** Nondeconvolution-based perfusion methods rely on the application of the Fick principle to a given region of interest (ROI) within the brain parenchyma. This “conservation of flow” is expressed by the equation:

$$\frac{dC_t(t)}{dt} = CBF \cdot [C_a(t) - C_v(t)]$$

In the above formula, $C_t(t)$ is the tissue contrast concentration versus time curve (commonly referred to as the time density curve, TDC) measured within a given brain region. $C_a(t)$ is the TDC for the feeding artery (also known as the arterial input function, or AIF), and $C_v(t)$ is the TDC for the draining vein. In order to create “maps” of cerebral blood flow using cross-sectional imaging techniques, an independent TDC is obtained for each pixel. Because $C_t(t)$, $C_a(t)$, and $C_v(t)$ are known quantities, the equation can be solved, in principle, on a pixel-by-pixel basis, for CBF.

The ease of the mathematical solution to this differential equation, however, is highly dependent on the assumptions made regarding inflow and outflow to the region. One common model assumes no venous outflow, which simplifies the calculation at the cost of necessitating extremely high injection rates as described above.

CBV can be approximated as the area under the “fitted” (smoothed) tissue TDC, divided by the area under the fitted arterial TDC [66].

$$CBV = \int C_t(t) / \int C_a(t)$$

Note that when it is assumed that the contrast concentration in the arteries and capillaries is at a steady state, this equation forms the basis for the quantitative computation of CBV using the “whole brain perfused blood volume” method of Hunter and Hamberg [22, 29] described above. After soft tissue components have been removed by co-registration and subtraction of the pre-contrast scan, CBV then simply becomes a function of the density of tissue contrast, normalized by the density of arterial contrast.

**Deconvolution Techniques.** Direct calculation of CBF, applicable for even relatively slow injection rates, can be accomplished using deconvolution theory [73], which compensates for the inability to deliver a complete, instantaneous bolus of contrast into the artery supplying a given region of brain. In reality, a contrast bolus (particularly when administered in a peripheral vein) will undergo delay and dispersion before arriving in the cerebral vasculature; deconvolution attempts to correct for this reality, based on the following formula:

$$C_t(t) = CBF \cdot [C_a(t) \otimes R(t)]$$

Since the tissue and arterial TDCs [$C_t(t)$ and $C_a(t)$, respectively] can be determined directly from the CTP cine images, one can use deconvolution to solve for the product CBF-$R(t)$, the “scaled” residue function. CBF can then be obtained directly as proportional to the maximum height of this scaled residue function curve, whereas CBV is reflected as the area...
under the scaled residue function curve. Once CBF and CBV are known, MTT can be calculated using the central volume principle.

Mathematically, deconvolution of the arterial (AIF) and tissue curves can be accomplished using a variety of techniques, including the Fourier transform and the singular value decomposition methods. These methods vary in their sensitivity to such factors as: (1) the precise vascular anatomy of the underlying tissue bed being studied, and (2) the degree of delay, or dispersal, of the contrast bolus between the measured arterial and tissue TDCs [90]. In current clinical software, the singular value decomposition method, which is more sensitive to contrast dispersal factors than to specific local arterial anatomy, is the more commonly employed.

The creation of accurate, quantitative maps of CBV, CBF, and MTT using the deconvolution method has been validated in a number of studies [28, 37–39, 47, 90–93]. Specifically, validation has been accomplished by comparison with xenon [47, 94], PET [95], and MRP [96–98] in humans, as well as with microspheres in animals [28, 37, 38].

5.6 CTP Post-Processing

In urgent clinical cases, perfusion changes can often be observed immediately following scanning by direct visual inspection of the axial source images at the CT scanner console. Soft copy review at a workstation using “movie” or “cine” mode can reveal relative perfusion changes over time, although advanced post-processing is required to appreciate subtle changes, and to obtain quantification.

Axial source images acquired from a cine CT perfusion study are networked to a freestanding workstation for detailed analysis, including construction of CBF, CBV, and MTT maps. Prior to loading these data into the available software package, the source images should be visually inspected for motion artifact. Images showing significant misregistration with the remaining dataset can be deleted or corrected, depending on the sophistication of the existing software.

The computation of quantitative first-pass cine cerebral perfusion maps typically requires some combination of the following user inputs (Fig. 5.1):

- **Arterial input ROI**: A small ROI (typically 2 × 2 to 4 × 4 pixels in area) is placed over the central portion of a large intracranial artery, preferably an artery orthogonal to the imaging plane in order to minimize “dilutional” effects from volume averaging. An attempt should be made to select an arterial ROI with maximal peak contrast intensity.

- **Venous outflow ROI**: A small venous ROI with similar attributes is selected, most commonly at the superior sagittal sinus. With some software packages, selection of an appropriate venous ROI is critical in producing quantitatively accurate perfusion maps, while others are less sensitive to this selection [84].

- **Baseline**: The baseline is the “flat” portion of the arterial TDC, prior to the upward sloping of the curve caused by contrast enhancement. The baseline typically begins to rise after 4–6 s.

- **Post-enhancement cutoff**: This refers to the “tail” portion of the TDC, which may slope upwards towards a second peak value if recirculation effects are present. When such upward sloping at the “tail” of the TDC is noted, the data should be truncated to avoid including the recirculation of contrast. The perfusion analysis program will subsequently ignore data from slices beyond the cutoff.

Other user-defined inputs, such as “threshold” or “resolution” values, are dependent on the specific software package used for image reconstruction. It is worth noting that major variations in the input values described above may not only result in perfusion maps of differing image quality, but, potentially, in perfusion maps with variation in their quantitative values for CBF, CBV, and MTT. As previously noted, special care must often be taken in choosing an optimal venous outflow ROI, because that ROI value may be used to normalize the quantitative parameters.

Although the precise choice of CTP scanning level is dependent on both the clinical question being asked and other available imaging findings, an essential caveat in selecting a CTP slice is that the imaged
level must contain a major intracranial artery. This is necessary in order to assure the availability of an AIF, to be used for the computation of perfusion maps using the deconvolution software.

In the construction of perfusion maps from either CT or MR datasets, voxels comprising the AIF can be selected in a semi-automated manner. In general, deconvolution is also less sensitive to variations in underlying vascular anatomy than are the nondeconvolution-based methods. This is because, for simplicity, the fundamental assumption of most nondeconvolution cerebral perfusion models is that a single feeding artery and a single draining vein support all blood flow to and from a given tissue bed, and that the precise arterial, venous, and tissue TDCs can be uniquely identified by imaging. This assumption is clearly an oversimplification. While MR-PWI maps (CBF and MTT) have been shown to have increased accuracy with a bolus delay-corrected technique (BDC) [99], a delay correction is built into most available CTP processing software, so this is less of a concern in CTP.

Potential imaging pitfalls (Table 5.5) in the computation of CBF using the deconvolution method include both patient motion and partial volume averaging, which can cause the AIF to be underestimated. The effects of these pitfalls can be minimized by the use of image coregistration software to correct for patient motion, as well as by careful choice of ROIs for the AIF. In addition, comparison with the contralateral (normal) side to establish a percentage change from normal is a useful interpretive technique, since the reliability of quantitative data is in the range of 20–25% variation and the robustness of the quantitative data has not been established in large clinical trials.
5.7 Clinical Applications of CTP

Indications (and potential indications) for advanced “functional” imaging of stroke in the first 12 h include the following: (1) exclusion of patients most likely to hemorrhage and inclusion of patients most likely to benefit from thrombolysis; (2) extension of the time window beyond 3 h for i.v. and 6 h for anterior circulation i.a. thrombolysis; (3) triage to other available therapies, such as hypertension or hyperoxia administration; (4) disposition decisions regarding neurological intensive care unit (NICU) admission or emergency department discharge; and (5) rational management of “wake up” strokes, for which precise time of onset is unknown [100]. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS) suggests that the i.v. use of desmoteplase can be extended to a therapeutic window of 3–9 h post-ictus, with significantly improved reperfusion rates and clinical outcomes achieved in patients with a diffusion–perfusion mismatch on MR [101]. Methods that accurately distinguish salvageable from nonsalvageable brain tissue are being increasingly promoted as a means to select patients for thrombolysis beyond the 3-h window for i.v. therapy.

5.8 CTP Interpretation: Infarct Detection with CTA-SI

A number of groups have suggested that CTA source images, similar to DWI, can sensitively detect tissue destined to infarct despite successful recanalization [26, 36, 105]. Theoretical modeling indicates that CTA-SI, assuming an approximately steady state of contrast in the brain arteries and parenchyma during image acquisition, are weighted predominantly by blood volume, rather than blood flow, although this has yet to be validated empirically in a large series [22, 29, 66, 98]. An early report from our group indicated that CTA-SI typically defines minimal final infarct size and, hence, like DWI and CBV, can be used to identify “infarct core” in the acute setting [36] (Fig. 5.2). Co-registration and subtraction of the conventional, unenhanced CT brain images from the axial, post-contrast CTA source images should result in quantitative blood volume maps of the entire brain (Fig. 5.3) [15, 22, 29]. CTA-SI subtraction maps, obtained by co-registration and subtraction of the unenhanced head CT from the CTA source images, are particularly appealing for clinical use because – unlike quantitative first-pass CT perfusion maps – they provide whole brain coverage. Rapid, convenient co-registration/subtraction software is now commercially available on multiple platforms, allowing generation of these maps outside of the research arena [106, 107]. Subtraction maps, despite the improved conspicuity of blood volume lesions, may be limited by increased image noise [27]. A pilot study from our group of 20 consecutive patients with MCA stem occlusion who underwent i.a. thrombolysis following imaging demonstrated that CTA-SI and CTA-SI subtraction maps improve infarct conspicu-
CT Perfusion (CTP)

Chapter 5

Figure 5.2

An infarct in the left middle cerebral artery (MCA) distribution is more conspicuous on the CT angiography source image (CTA-SI) (top right, arrows) than the unenhanced CT (top left) performed in the acute setting. Subsequent diffusion-weighted image (DWI, bottom left) and unenhanced CT (bottom right) confirm the territory of infarction seen on CTA-SI.

In another study, CTA-SI preceding DWI imaging was performed in 48 consecutive patients with clinically suspected stroke, presenting within 12 h of symptom onset (42 patients within 6 h) [26]. CTA-SI and DWI lesion volumes were independent predictors of final infarct volume, and overall sensitivity and specificity for parenchymal stroke detection were 76% and 90% for CTA-SI, and 100% and 100% for DWI, respectively. When cases with an initial DWI lesion volume <15 ml (small lacunar and distal infarctions) were excluded from analysis, CTA-SI sensitivity and specificity increased to 95% and 100%, respectively. Although DWI is more sensitive than CTA-SI for parenchymal stroke detection of small lesions (Fig. 5.4), both DWI and CTA-SI are highly accurate predictors of final infarct volume. DWI tends to underestimate final infarct size, whereas...
CTA-SI more closely approximates final infarct size, despite the bias towards DWI being obtained after the CTA-SI in this cohort of patients with unknown recanalization status.

Finally, it is noteworthy that, as with DWI, not every acute CTA-SI hypodense ischemic lesion is destined to infarct [108, 109]. In the presence of early complete recanalization, sometimes dramatic sparing of regions with reduced blood pool on CTA-SI can occur (Fig. 5.5). This suggests that, as with CBV, CBF, and DWI, time-dependent thresholds exist for distinguishing viable from nonviable CTA-SI (or CTA-SI subtraction) ischemia. Hunter et al. [110] studied the normalized blood volume on CTA-SI from 28 acute stroke patients at the very thin boundary between infarcted and spared tissue. They found that the probability of infarction in the core, inner boundary, and outer boundary were 0.99, 0.96, and 0.11 respectively, supporting the concept that CTA-SI thresholds predictive of tissue outcome exist [110].
**Figure 5.4**
A “false-negative” CTA-SI due to early imaging of a small infarct, retrospectively seen to be present on both the unenhanced CT and CTA-SI. It is noteworthy that the DWI lesion, although clearly more conspicuous, was imaged at a much later time point. Top row: unenhanced CT and CTA-SI at 3.5 h. Bottom row: DWI at 11 h and follow-up unenhanced CT at 33 h.

**Figure 5.5**
Reversal of CTA-SI abnormality. A patient with a right M1 thrombus who had complete recanalization after 90 min following intraarterial (i.a.) thrombolysis. There is a large MCA territory blood pool deficit on the CTA-SI (left, arrows), but only a small deep gray lenticular hypodensity on the post-lysis unenhanced CT (right). Late follow-up showed lenticular infarct with minimal, patchy, incomplete infarction in other portions of the MCA territory. (Courtesy of Jeffrey Farkas, MD)
5.9 CTP Interpretation: Ischemic Penumbra and Infarct Core

An important goal of advanced stroke imaging is to provide an assessment of ischemic tissue viability that transcends an arbitrary “clock-time” [111–113]. The original theory of penumbra stems from experimental studies in which two thresholds were characterized [114]. One threshold identified a CBF value below which there was cessation of cortical function, without an increase in extracellular potassium or reduction in pH. A second, lower threshold identified a CBF value below which there was disruption of cellular integrity. With the advent of advanced neuroimaging and modern stroke therapy, a more clinically relevant “operationally defined penumbra” -- that identifies hypoperfused but potentially salvageable tissue -- has gained acceptance [111, 115–117].

**Ischemic Penumbra.** Cine single-slab CT perfusion imaging, which can provide quantitative maps of CBF, CBV, and MTT, has the potential to describe regions of “ischemic penumbra” -- ischemic but still viable tissue. In the simplest terms, the “operationally defined penumbra” is the volume of tissue contained within the region of CBF–CBV mismatch on CTP maps, where the region of CBV abnormality represents the “core” of infarcted tissue and the CBF–CBV mismatch represents the surrounding region of tissue that is hypoperfused but salvageable (Figs. 5.6–5.8). The few papers that have investigated the role of CTP in acute stroke triage have typically
assumed predefined threshold values for “core” and “penumbra” based on human and animal studies from the PET, MR, SPECT, or xenon literature, and determined the accuracy of these in predicting outcome [48]. By assuming cutoff values of ≥34% reduction from baseline CT-CBF for penumbra and ≤2.5 ml/100 g CT-CBV for core, Wintermark et al. [48] found good correlation between DWI and CT-CBV infarct core ($r=0.698$) and the MR-MTT and CT-CBF ischemic penumbra ($r=0.946$). Of note, the CT-CBV maps suffer from decreased signal-to-noise relative to CT-CBF maps, suggesting that the interpretation of CBV maps may benefit from a semiautomated thresholding approach to segmentation to more accurately gauge the size of infarct [76]. The interpretation of CTP in the setting of acute stroke is summarized in Table 5.6.

CT-CBF–CBV mismatch correlates significantly with lesion enlargement. Untreated or unsuccessfully treated patients with large CBF–CBV mismatch exhibit substantial lesion growth on follow-up, whereas those patients without significant mismatch – or those with early, complete recanalization – do not exhibit lesion progression of their admission CTA-SI lesion volume (Figs. 5.6–5.8). CTP-defined mismatch might therefore serve as a marker of salvageable tissue, and thus prove useful in patient triage for thrombolysis [118]. This result clearly has implications for the utility of a CTP-based model for predicting outcome in patients without robust recanalization. Sim-
Similarly, in an earlier pilot study of CTP imaging, ultimate infarct size was most strongly correlated with CT-CBF lesion size in 14 embolic stroke patients without robust recanalization [119], again demonstrating the importance of this mismatch region as tissue at risk for infarction.

Several studies of MR-PWI suggest that CBF maps are superior to MTT maps for distinguishing viable from nonviable penumbra [120–122]. The reason for this relates to the fact that MTT maps display circulatory derangements that do not necessarily reflect ischemic change, including large vessel occlusions with compensatory collateralization (Fig. 5.9) and reperfusion hyperemia following revascularization (Fig. 5.10).

Refinements of the Traditional Penumbra Model.
The “operationally defined penumbra,” however, oversimplifies reality, as not all tissue contained within the operationally defined penumbra is destined to infarct. There is a region of “benign oligemia” contained within the region of the CBV–CBF mismatch that is not expected to infarct even in the absence of reperfusion. This refinement of the traditional model has important clinical implications, since treatment regimens that are based on an overestimated volume of tissue at risk will likely be too aggressive, exposing the patient to the risks and complications of treatment for tissue that would not likely have proceeded to infarct even without intervention. Few studies have reported specific CBF thresholds for distinguishing penumbra likely to infarct in the absence of early recanalization (nonviable penumbra) from penumbra likely to survive despite persistent vascular occlusion (viable penumbra) [120, 122].

In a pilot study of CTP thresholds for infarction, we found that normalized, or relative CBF is the most robust parameter for distinguishing viable from nonviable penumbra. All regions with a less than 56% reduction in mean CBF survived whereas all regions with a greater than 68% reduction in mean CBF infarcted. In rough approximation, therefore, CT-CBF penumbra with less than one-half reduction from baseline values has a high probability of survival, whereas penumbra with a greater than two-thirds reduction from baseline values has a high probability of infarction. No region with a mean relative CBV less than 0.68, absolute CBF less than 12.7 ml · 100 g⁻¹ · min⁻¹, or absolute CBV less than 2.2 ml · 100 g⁻¹ survived. The latter compares well with the CBV threshold of 2.5 ml · 100 g⁻¹ selected by Wintermark et al. [48] to define “core.” Because of differences in CBV and CBF between gray and white matter (Table 5.4), it is essential for the contralateral ROI used for normalization to have the same gray matter/white matter ratio as the ipsilateral ischemic region under study. Moreover, a number of studies suggest that, due to different cellular populations, gray and white matter may respond differently to ischemic injury.

There is little literature addressing perfusion thresholds in patients undergoing i.a. recanalization procedures [124]. Our results of mean relative CBF thresholds of 0.19 for core, 0.34 for nonviable penumbra, and 0.46 for viable penumbra are in general agreement with those of a SPECT study of patients with complete recanalization following i.a. thrombolysis. Pre-treatment SPECT showed CBF>55% of cerebellar flow in viable penumbra, even with treatment initiated 6 h after symptom onset [125]. Ischemic tissue with CBF >35% of cerebellar flow may remain salvageable if recanalization is achieved in under 5 h. Our results for mean relative CBF thresholds are also in agreement with SPECT and MR studies performed in patients who received other stroke therapies [120, 126–128].

<table>
<thead>
<tr>
<th>CBV, CBF match</th>
<th>No treatment regardless of lesion size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large CBV, larger CBF</td>
<td>Possible treatment based on time post ictus, size</td>
</tr>
<tr>
<td></td>
<td>Consider no treatment if CBV &gt;100 ml</td>
</tr>
<tr>
<td>Small CBV, larger CBF</td>
<td>Typically a good candidate for treatment</td>
</tr>
<tr>
<td></td>
<td>Consider no treatment if prolonged time-post-ictus</td>
</tr>
</tbody>
</table>

Table 5.6. Summary of CTP interpretation
Figure 5.8
A 77-year-old bartender presenting with a left facial droop. Subtle changes of the insula and right lentiform nucleus were seen on initial unenhanced CT, and CTA revealed acute occlusion of the right M1 segment. The infarct is more conspicuous on CTA-SI, and CTP demonstrates an ischemic penumbra involving the entire right MCA territory, consistent with a large territory at risk for subsequent infarction. Successful i.a. thrombolysis at 3 h was performed. Follow-up DWI showed an infarct limited to the initial CTA-SI abnormality. Top row: initial unenhanced CT and CTA. Second row: CTA-SI. Third row: CTP (CBV/CBF/MTT).
Figure 5.8 (continued)

Fourth row: follow-up DWI at 36 h

Figure 5.9

Perfusion abnormalities associated with a left internal carotid artery (ICA) dissection at the skull base. Despite the MTT abnormality that might have been mistaken for ischemic penumbra, follow-up unenhanced CT shows no evidence of infarction. The prolonged MTT was related to collateral flow necessitated by the ICA dissection. Top row: CBV, CBF, and MTT reveals prolonged MTT in the left hemisphere (arrows). Bottom row: curved reformat from a CTA shows the site of dissection (arrow).
Figure 5.10

CTP was performed 3 h following left carotid endarterectomy (CEA) showing reperfusion hyperemia. *Top row:* CTA shows preserved flow in the left carotid artery at the site of CEA. *Bottom row:* CBV/CBF/MTT shows increased CBF and shortened MTT on the left, consistent with reperfusion hyperemia.
5.10 Imaging Predictors of Clinical Outcome

Predicting outcome is perilous. The penumbra is dynamic, and several factors influence its fate, including time post-ictus, residual and collateral blood flow, admission glucose, temperature, hematocrit, systolic blood pressure, and treatment, including hyperoxia [129]. As already mentioned, CTA/CTP has the potential to serve as a surrogate marker of stroke severity, likely exceeding the NIHSS score or ASPECTS as a predictor of outcome [26, 50–57].

Infarct Core and Clinical Outcome. As noted earlier, measuring the penumbra is technically challenging. Flow thresholds for various states of tissue perfusion vary considerably among studies and techniques applied [130]. Despite this, a number of consistent messages emerge from a review of the literature regarding imaging outcome prediction in acute ischemic stroke. The most important of these messages is that “core” is crucial. Multiple studies, examining heterogeneous cohorts of patients receiving varied treatments, consistently find that ultimate clinical outcome is strongly correlated with admission “core” lesion volume – be it measured by DWI, CT-CBV, subthreshold xenon CT-CBF, or unenhanced CT [131–135]. One of these studies is especially noteworthy, because results were stratified by degree of recanalization at 24 h. This study revealed “that 2 factors mainly influenced clinical outcome: (1) recanalization (P=0.0001) and (2) day-0 DWI lesion volume (P=0.03)” [136]. In a study of CTP in patients with MCA stem occlusions, patients with admission whole-brain CT perfusion lesions volumes >100 ml (equal to approximately one-third the volume of the MCA territory) had poor clinical outcomes, regardless of recanalization status. Moreover, in those patients from the same cohort who had early complete MCA recanalization, final infarct volume was closely approximated by the size of the initial whole-brain CT perfusion lesion [36].

Risk of Hemorrhage. The degree of early CBF reduction in acute stroke may also help predict hemorrhagic risk. Preliminary results from our group suggest that severe hypoattenuation, relative to normal tissue, on whole-brain CTP images, may also identify ischemic regions more likely to bleed following i.a. thrombolysis [45]. In a SPECT study of 30 patients who had complete recanalization within 12 h of stroke onset, those with less than 35% of normal cerebellar flow at infarct core were at a significantly higher risk for hemorrhage [125]. Indeed, multiple studies have suggested that severely ischemic regions with early reperfusion are at the highest risk for hemorrhagic transformation [133, 137]. Of note, there is a suggestion that the presence of punctate microhemorrhage is correlated with the risk of hemorrhagic transformation; these small foci of hemorrhage are seen on gradient echo (susceptibility-weighted) MR sequences and are not visible on unenhanced CT [138]. It remains to be seen, however, whether these microbleeds will serve as a contraindication to thrombolytic therapy.

5.11 Experimental Applications of CTP in Stroke

The additional information about capillary-level hemodynamics afforded by CTP could be particularly important in future clinical trials of acute stroke therapy, in which CTP could refine the selection of subjects to include only those patients most likely to benefit from treatment; this imaging-guided patient selection may help to demonstrate beneficial effects that would be obscured if patients without salvageable tissue were included. CTA combined with CTP could be used to identify patients with proximal large vessel occlusive thrombus, who are the most appropriate candidates for i.a. treatment [14, 29, 139]. The ability of perfusion imaging to quantitatively determine ischemic brain regions that are viable but at risk for infarction if blood flow is not quickly restored – so called ischemic penumbra – might provide a more rational basis for establishing the maximum safe time window for administering thrombolytic agents than the current, arbitrary cutoffs of 3 h post-ictus for i.v. and 6 h post-ictus for i.a. thrombolysis [50, 140] (Table 5.6). MRP has already been used to support extending the therapeutic time window in a subset
of patients with a DWI–MR-PWI mismatch: the DIAS trial of patients with an NIHSS of 4–20 and an MR diffusion–perfusion mismatch (where the perfusion abnormality was defined using MTT) showed significantly improved rates of reperfusion and clinical outcome when i.v. desmoteplase was administered between 3 and 9 h of ictus onset in an escalating dose range of 62–125 μg/kg [101]. CTP could serve a similar role in rationally extending the therapeutic time window for stroke intervention.

Despite a multitude of animal studies that have demonstrated a benefit from neuroprotective agents, the only therapy proven in humans to improve outcome has been thrombolysis (both i.v. and i.a.) [2, 3, 140]. There is growing literature positing that ischemic, potentially salvageable “penumbral” tissue is an ideal target for neuroprotective agents [55, 111, 141], suggesting that CTP or other perfusion techniques may be suited to selection of patients in trials of these agents. Kidwell and Warach [142] argue that enrollment in clinical trials should require a definitive diagnosis of stroke, confirmed by imaging and lab studies.

5.12 Conclusion

As new treatments are developed for stroke, the potential clinical applications of CTP imaging in the diagnosis, triage, and therapeutic monitoring of these diseases are certain to increase.

Technical advances in scanner hardware and software will no doubt continue to increase the speed, coverage, and resolution of CTP imaging. CTP offers the promise of efficient utilization of imaging resources, and, potentially, of decreased morbidity. Most importantly, current CT technology already permits the incorporation of CTP as part of an all-in-one acute stroke examination to quickly and accurately answer the four fundamental questions of stroke triage, further increasing the contribution of imaging to the diagnosis and treatment of acute stroke.

References


Chapter 5

CT Perfusion (CTP)