Sources of variability in computed tomography perfusion: implications for acute stroke management

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Object. Although dynamic, first-pass cerebral CT perfusion is used in the evaluation of acute ischemic stroke, a lack of standardization restricts the value of this imaging modality in clinical decision-making. The purpose of this study was to comprehensively review the reported sources of variability and error in cerebral CT perfusion results.

Methods. A systematic literature review was conducted, 120 articles were reviewed, and 23 published original research articles were included. Sources of variability and error were thematically categorized and presented within the context of the 3 stages of a typical CT perfusion study: data acquisition, postprocessing, and results interpretation.

Results. Seven factors that caused variability were identified and described in detail: 1) contrast media, the iodinated compound injected intravascularly to permit imaging of the cerebral vessels; 2) data acquisition rate, the number of images obtained by CT scan per unit time; 3) user inputs, the subjective selections that operators make; 4) observer variation, the failure of operators to repeatedly measure a perfusion parameter with precision; 5) software operational mode, manual, semiautomatic, or automatic; 6) software design, the mathematical algorithms used to perform postprocessing; and 7) value type, absolute versus relative values.

Conclusions. Standardization at all 3 stages of the CT perfusion study cycle is warranted. At present, caution should be exercised when interpreting CT perfusion results as these values may vary considerably depending on a variety of factors. Future research is needed to define the role of CT perfusion in clinical decision-making for acute stroke patients and to determine the clinically acceptable limits of variability in CT perfusion results.
(DOI: 10.3171/2011.3.FOCUS1136)

KEY WORDS • computed tomography perfusion • brain imaging • stroke • standardization

THERE are increasing therapeutic options for patients with acute ischemic stroke, including chemical and mechanical intraarterial thrombolysis.¹ Brain imaging is used to determine therapy eligibility by discriminating between patients who may benefit from therapy and patients who will not benefit or may even be further injured by therapy.

In the setting of acute stroke, the most practical initial imaging test is CT. Noncontrast CT rapidly and accurately identifies intracranial hemorrhage and helps discriminate nonvascular causes of neurological symptoms. Computed tomography angiography detects intra- and extracranial vessel abnormalities, and may guide treatment decisions for endovascular recanalization therapies. Dynamic CT perfusion generates quantitative measures

of cerebral perfusion and therefore has the unique potential to differentiate thresholds of reversible and irreversible ischemia.¹⁶

In conjunction with CT and CT angiography, CT perfusion has been shown to improve the diagnosis of acute stroke,⁷ but the usefulness of CT perfusion in making acute treatment decisions has not yet been established because CT perfusion imaging information about the degree of reversibility of ischemic injury has been limited by a lack of standardization.⁶ Patient selection for reperfusion therapies is not without significant risk because these drugs can cause life-threatening intracranial hemorrhage, and for CT perfusion results to be applied clinically, it is necessary to know that the data are accurate and reproducible. The purpose of this study was to systematically review the reported sources of variability in cerebral CT perfusion results and discuss the clinical implications for acute stroke management.

Abbreviations used in this paper: ASIST = Acute Stroke Imaging Standardization; CBF = cerebral blood flow; MCA = middle cerebral artery; STIR = Stroke Imaging Repository.

Methods

Data Acquisition

A systematic literature search was conducted. The following search key words were used in a variety of permutations: “CT,” “computed tomography,” “perfusion,” “blood flow,” “cerebral,” and “stroke.” Search limits included human species, English language, and publication dates from 1970 to 2010. The PubMed database was searched, which returned several hundred articles.

The abstracts of all articles were reviewed to identify reports that focused on cerebral CT perfusion, in which cerebral CT perfusion was defined as CT perfusion used in the context of brain imaging. One hundred twenty reports met this criterion. These reports and any relevant references listed within them were closely reviewed to identify original research articles that reported sources of real or potential variability and error in quantitative cerebral CT perfusion values. Twenty-three published original research articles fit these criteria. These studies were reviewed, and reported sources of real or potential variability and error in quantitative cerebral CT perfusion results were recorded (Table 1). In addition, non-peer-reviewed publications produced by the ASIST-Japan group (<http://asist.umin.jp/index-e.htm>) and the STIR consortium (<https://stir.ninds.nih.gov/html/index.html>) were reviewed. Non-peer-reviewed data included in this report are identified as such.

Data Organization

Sources of variability and error were thematically categorized to facilitate conceptualization.

Results

Variability in Quantitative CT Perfusion Results

Contrast Media. Contrast media is the iodinated compound injected intravascularly to permit imaging of the cerebral vessels. Contrast media is injected intravenously during CT scanning. Kloska et al.¹⁰ compared 2 different contrast media concentrations (300 vs 370 mg iodine/ml) and found that they yielded equivalent CT perfusion source-image tissue enhancement in the caudate nucleus, thalamus, and frontal white matter of the nonischemic hemisphere, but significantly different CT perfusion source-image enhancement in the region of the superior sagittal sinus. Konig et al.¹² compared 300 versus 400 mg iodine/ml concentrations and found no significant difference between mean CT perfusion results derived from nonischemic frontal white matter. They did not assess the ischemic hemisphere. At a national stroke imaging meeting in 2007, participants recommended using 350–370 mg/ml concentrations,²⁸ but many institutions, including the authors', do not (we use 320 mg/ml).

Data Acquisition Rate. The data acquisition rate is the number of images obtained by the CT scanner per unit time. It is proportional to image resolution and radiation dose and therefore must be optimized to balance adequate image quality with radiation safety. The data acquisition rate

affects CT perfusion results, but the specific relationship is controversial. For example, Wintermark et al.³¹ found that sampling intervals > 1 second do not cause significant variability in CT perfusion results, while Kloska et al.¹¹ found that they do (for example, CBF values were increased [$p = 0.044$ – 0.001] with > 1 second intervals). Different studies recommend different data acquisition rates, ranging from 1 image/0.5 sec⁸ to 1 image/3 sec.²⁷

User Inputs. User inputs are the subjective selections that operators make during CT perfusion acquisition and postprocessing. For example, CT operators select the 2–4 cerebral slices that are scanned. Operators also select important inputs that are used to process image data. For instance, radiologists draw regions of interest on top of raw CT images to label 2 functions that are used to generate perfusion maps. These functions are called the arterial input function and the venous output function. Two studies^{3,30} found that varying placement of the arterial input function did not cause significant variability in CT perfusion results. Arterial input function placement distal to an arterial thrombus, however, undermines perfusion calculation assumptions, and causes significant variability in CT perfusion results.⁴ Two additional studies^{9,19} found that varying placement of the venous output function caused significant variability in CT perfusion results. Although the anterior cerebral artery is commonly selected for the arterial input function and the superior sagittal sinus is commonly selected for the venous output function, there is no standard recommendation for selecting these user inputs.

Observer Variation. Observer variation is the failure of operators to repeatedly measure CT perfusion values with precision. Observer variation may occur whenever user inputs are made. Two types of observer variation have been reported: interoperator (between operators), and intraoperator (reproducibility of 1 operator). Several authors have concluded that observer variation causes a minimal amount of variability in CT perfusion results.^{3,20,21,29} For example, Sanelli et al.²¹ found high inter- and intraoperator correlations ($r = 0.87$ – 0.99 and $r = 0.91$ – 0.99 , respectively) and low inter- and intraoperator coefficients of variability (2.5%–9.5% and 1.4%–6.5%, respectively) in CT perfusion results. Other studies^{5,23} report observer coefficients of variability > 30%, suggesting that observer variation causes a substantial amount of variability in CT perfusion results.

Software Operational Mode. The software operational mode refers to manual, semiautomatic, or automatic data processing. For example, many software applications allow manual, semiautomatic, or automatic selection of input functions (for example, arterial input function or venous output function). Two studies^{21,24} found that automated data processing caused more variability in CT perfusion results than manual mode data processing. In contrast, Soares et al.²³ found more consistent results.

Software Design. Software design is a broad category that refers to the mathematical algorithms used to process the image data. For example, CT perfusion software applications incorporate image data and operator inputs,

Variability in computed tomography perfusion

TABLE 1: Categorized list of original research articles included in this study*

Error Source	Authors & Year	No. of Patients	Patient Type
contrast media	Kloska et al., 2007 ¹⁰	90	suspected AIS
	Konig et al., 2007	21	suspected AIS
data acquisition rate	Kloska et al., 2010 ¹¹	32	suspected AIS
	Wiesmann et al., 2008	8	suspected AIS
	Kämenä et al., 2007	30	suspected AIS
	Wintermark et al., 2004 ³¹	60	AIS
user inputs	Ferreira et al., 2010	14	unilateral proximal MCA occlusion
	Wintermark et al., 2008 ³⁰	55	suspected AIS
	Bisdas et al., 2007	18	suspected AIS
	Kealey et al., 2004	40	AIS, CO, TIA, SAH
	Sanelli et al., 2004 ¹⁹	3	AIS
observer variation	Soares et al., 2009	30	suspected AIS
	Bisdas et al., 2007	18	suspected AIS
	Sanelli et al., 2007 ²⁰	20	suspected AIS, vasospasm, chronic cerebral ischemia
	Sanelli et al., 2007 ²¹	20	suspected AIS, vasospasm, chronic cerebral ischemia
	Wintermark et al., 2005 ²⁹	46	suspected AIS
	Fiorella et al., 2004	20	not specified
software operational mode	Soares et al., 2009	30	suspected AIS
	Sanelli et al., 2007 ²¹	20	suspected AIS, vasospasm, chronic cerebral ischemia
	Turk et al., 2007	33	CAS
software design	Ferreira et al., 2010	14	unilateral proximal MCA occlusion
	Kudo et al., 2010 ¹⁴	10	AIS
	Kudo et al., 2009 ¹³	6	healthy volunteers
	Sasaki et al., 2009	20	suspected AIS
	van der Schaaf et al., 2006	10	suspected aneurysms, suspected sinus thrombosis, SAH, intracerebral hematoma
	Kudo et al., 2003 ¹⁵	5	healthy volunteers
	Zussman et al., in press	11	suspected AIS
value type	Waaijer et al., 2007	20	CAS

* AIS = acute ischemic stroke; CAS = carotid artery stenosis; CO = carotid occlusion; SAH = subarachnoid hemorrhage; TIA = transient ischemic attack.

and perform multistep mathematical operations to generate perfusion results. Different algorithms, such as the maximum slope algorithm and the deconvolution family of algorithms, generate significantly different CT perfusion results for identical source data.¹⁴ Similarly, different software applications using different corrective functions for tracer delay (an effect that occurs when contrast media reaches tissues of interest more slowly than predicted) yield significantly different CT perfusion results.^{4,13,14,22} Different corrective functions for partial-volume effects (inaccurate measurements of contrast media concentration that occur due to the small size or location of cerebral vessels) cause significantly different CT perfusion results.²⁵ Computed tomography perfusion software that uses a corrective technique called vascular pixel elimination was found to more closely correlate with PET results than software that does not incorporate this technique.¹⁵ As a result, different commercial CT perfusion software postprocessing applications have been shown to produce significantly different CT perfusion results for identical source data.^{14,32} Because there is no industry standard for

software design, calibration, or validation, quantitative assessment is not comparable across platforms (Fig. 1).

Value Type. The value type refers to absolute versus relative CT perfusion values. For example, when perfusion values for a given region of tissue are directly reported, they are called absolute values. A given region of tissue can also be compared with the corresponding region of tissue on the contralateral cerebral hemisphere, creating a ratio between the 2 hemispheres. When reported, these ratios are called relative values. Waaijer et al.²⁶ compared absolute and relative values and found that relative values caused less variability in CT perfusion results than absolute values. This suggests that absolute values of CT perfusion are less reliable and reproducible than relative values and should not be used as a basis for decision-making.

Non–Peer-Reviewed Factors. Additional factors have been shown to affect raw CT image data including tube current and voltage, scan mode (cine vs intermittent), scan timing, and the tomographic reconstruction process,

FIG. 1. Different commercial CT perfusion software applications produce significantly different quantitative results for identical source data. The figure shows CBF perfusion color-maps for the same patient data that were reproduced at our institution using 2 different software applications, Vendor 1 (left) and Vendor 2 (right). The maps reveal severe ischemia in the region of the right MCA territory. Regions-of-interest (numbered ovals 1–4) were drawn on the perfusion maps, and software platforms returned perfusion results for the tissue enclosed within each oval. Note that quantitative perfusion results for the ischemic tissue (r1 and r3), as well as for the normal contralateral hemisphere (r2 and r4) differed considerably by vendor, although the general trend of decreased CBF in the ischemic tissue was consistent for both vendors. There is no industry standard for software design.

all of which affect CT perfusion results (K. Kudo, unpublished data, 2004). Consensus-based expert recommendations for a CT perfusion image acquisition protocol were recently published,²⁸ but many institutions have not adopted them.

Additional software design considerations that have been shown to affect CT perfusion results include the presence and type of preprocessing denoising filter, image matrix size, and deconvolution method (K. Kudo, unpublished data, 2004).

Variability in Qualitative CT Perfusion Results

In addition to being quantitative, CT perfusion results are also qualitative. For example, perfusion para-

metric maps display quantitative CT perfusion values in a color-map overlay that allows qualitative, contextual visualization of an entire brain slice. Computed tomography perfusion color-maps are not standardized and vary by manufacturer, meaning that a given quantitative value will be translated into different colors by different CT perfusion software applications. These parametric color maps are used to qualitatively assess relative variations in CT perfusion metrics. The color scale is not fixed and is operator-adjustable (Fig. 2). Although there is a suggested CT perfusion color scale standard (<http://asist.umin.jp/index-e.htm>), it is not in general use and has not been incorporated into commercial software.

Discussion

Computed tomography perfusion imaging measures cerebral perfusion and calculates quantitative perfusion results. The typical CT perfusion study has 3 stages: data acquisition, postprocessing, and results interpretation. In the data acquisition stage, the patient is scanned and a contrast agent is injected. Image data gathered during this stage is then transferred to a proprietary vendor workstation for postprocessing. In the postprocessing stage, radiologists use software applications to generate quantitative CT perfusion results. These results are then displayed as quantitative values and qualitative, parametric color-maps for results interpretation. In the results interpretation stage clinicians evaluate CT perfusion values and maps and reformat them to their liking, to aid in clinical decision-making. Sources of variability in CT perfusion are introduced at different stages of a CT perfusion study, and Figure 3 shows the sources of variability identified by this study within the context of the 3 CT perfusion stages.

Several recent studies underscore CT perfusion's clinical potential, but also indirectly highlight the great challenges facing CT perfusion. For example, Murphy et al.¹⁷ studied 30 stroke patients and compared CT perfusion studies (performed at admission) to noncontrast CT studies (performed 5–7 days poststroke). They identified a highly sensitive (95%) and specific (94%) CT perfusion threshold for differentiating between ischemic white matter that ultimately infarcted and ischemic white matter that recovered. Aviv et al.² studied 40 stroke patients by comparing admission CT perfusion studies to MR and

FIG. 2. Different or adjustable color scales mean that identical source data can look very different, depending on the scale chosen. The figure shows mean transit time perfusion color-maps for the same patient data that were reproduced at our institution using different color scale settings. Intervendor color differences are shown: image A was generated using vendor 1 software, image B with vendor 2 software, and images C–E with vendor 3 software. Intravendor color differences are also shown: images C–E were generated using 3 different color scales available on the same software platform.

Fig. 3. Illustration of the sources of variability at different stages of a CT perfusion (CTP) study.

CT studies performed at poststroke follow-up. They identified a highly sensitive (77%) and specific (94%) CT perfusion threshold for predicting hemorrhagic transformation in acute stroke patients. These and other studies underscore CT perfusion's great potential because they offer a glimpse of how quantitative cerebral perfusion data might influence decision-making in the context of cerebrovascular disease.

While these studies underscore the potential clinical value of CT perfusion, they also highlight a major limitation of this technique, namely variability and error caused by a lack of standardization. For example, the data of Murphy et al.¹⁷ were analyzed using a single vendor's postprocessing platform, which raises the question of whether the authors would have identified the same results and reached the identical conclusion had a different vendor been chosen for this study. This question may be especially relevant in stroke centers that use multiple ven-

dor acquisition devices and postprocessing platforms to determine whether to administer thrombolytics. Simply put, it is questionable whether CT perfusion results generated by one protocol can be meaningfully compared with CT perfusion results derived using a different protocol.

The clinical significance of the widespread variability in CT perfusion results is difficult to estimate. Few studies have directly examined how CT perfusion affects clinical decision-making or influences patient outcomes,¹⁸ and the clinically acceptable limits of variability in CT perfusion results are unknown. These gaps in the medical literature call attention to the need for future studies to define the role of CT perfusion in acute stroke management. Future studies should take into consideration the widespread variability in CT perfusion results.

For quantitative CT perfusion results, standardization at all 3 stages of CT perfusion studies is warranted, and progress is being made. For example, in 2007, data acqui-

sition (Stage 1) protocols were drafted at an international symposium of stroke imaging experts.²⁸ Furthermore, the calibration of postprocessing software applications (Stage 2) against a digital, universal standard is increasingly likely, thanks to recent work of the ASIST-Japan group and the STIR consortium (Kudo et al., unpublished data, 2010). It is worth noting that although numerous factors cause variability in CT perfusion results, software design is a large factor, relative to other factors,³² which makes software standardization especially relevant. For qualitative CT perfusion results, standardized parametric-map representations of perfusion metrics are needed.

This study has several implications for current practice. First, caution should be exercised when interpreting CT perfusion results because they may vary considerably, depending upon a variety of factors. It remains unknown if, and to what extent, this variability may affect clinical decision-making or influence patient outcomes. Second, future studies evaluating CT perfusion should consider the finding that CT perfusion results generated by different techniques are not necessarily interchangeable. Third, standardization efforts at all 3 stages of the CT perfusion study cycle should be pursued.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Zussman. Acquisition of data: Zussman, Talekar. Analysis and interpretation of data: Zussman, Talekar, Flanders. Drafting the article: Zussman, Flanders. Critically revising the article: all authors. Approved the final version of the paper on behalf of all authors: Jabbour. Administrative/technical/material support: Talekar. Study supervision: Flanders.

Acknowledgment

The authors are grateful to Dr. K. Kudo, ASIST-Japan group, for kindly sharing the copies of 2 presentations on CT perfusion standardization.

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Manuscript submitted February 9, 2011.

Accepted March 7, 2011.

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