Whole-brain CTP in acute ischemic stroke

by

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PhD studying has never been an easy ride. Luckily, I have the most wonderful supervisors guiding me through ups and downs during the way. Therefore, I would like to pay my sincere thanks to my supervisors, Professor Mark Parsons and Professor Christopher Levi. Thank you, Mark, for sharing your precious time and knowledge with me. I have enjoyed very much our weekly meeting discussing new research ideas. Thank you, Chris, for helping me to stand on my own feet when I first came to Australia. For both my supervisors, your intelligence amazes me, your work ethic inspires me, and your charming personality makes it so easy to work for you.

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Finally, much love and thanks goes to my partner, Dante Dangelo-Kemp, who supports my PhD study not only mentally but also physically by waking me up early in the morning and driving me to work every weekday.
DECLARATION

I Longting Lin hereby declare that the thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968.

I Longting Lin hereby certify that this thesis is in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

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Peer reviewed publications included in this thesis:


- Lin L, Bivard A, Krishnamurthy V, Levi CR, Parsons MW. Whole-brain CT perfusion measures the acute infarct core and penumbra accurately and precisely (Submitted to Radiology, RAD-15-0319)

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Statement by co-authors for the paper:


As co-authors of the paper, we confirm that Longting Lin is the primary contributor to the publication. Longting Lin has made following contributions:

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ABSTRACT

Perfusion imaging technology not only enables stroke diagnosis by identifying the ischemic lesion earlier, but also helps the clinician to make treatment decisions by further classifying the ischemic lesion into salvageable tissue and non-salvageable tissue. The imaging of salvageable tissue, penumbra, provides a direct target for reperfusion treatment. However, the accuracy of penumbra measurement with perfusion imaging has been questioned, especially with CT perfusion (CTP). Perfusion images, acquired on earlier generation instruments such as the 16 or 64-detector scanners, have limited coverage of potentially ischemic brain, a factor recognised to reduce the accuracy of penumbra measurement. This limitation can be overcome by the advance in technology. The new generation “mega-detector” scanners, such as 320-detector Toshiba Aquilion One, provide whole brain coverage of 160mm from skull base to vertex. In this thesis, I presented a series of studies aiming to evaluate the utility of whole-brain CTP in acute ischemic stroke.

The first study was to derive the optimal penumbra measurement on whole-brain CTP with the reference of ischemic tissue outcome, and the second study was to test the penumbra measurement of whole-brain CTP in predicting clinical patient outcome. The two studies found that only with the threshold setting at Tmax>6s or DT>3s, did the whole-brain CTP achieve high accuracy (>99%) in delineating acute ischemic penumbra and good sensitivity (>80%) in predicting favourable clinical outcome. It was also confirmed that the accuracy of penumbra measurement was comprised when the brain coverage of CTP decreased from 160mm to 20mm.

Following two studies examined the utility of whole-brain CTP in the clinical setting. Firstly, CTP was compared to MRP, the perfusion modality that has already been well used in clinic. This work demonstrated that with whole brain coverage, CTP was as effective as MPR in
measuring the acute penumbra and in selecting patients for reperfusion treatment. Secondly, a case by case review was carried out to assist clinicians in the interpretation CTP output.

In conclusion, findings of this thesis support the usage of whole-brain CTP in acute ischemic stroke. Noticeably, the conclusion only applies to patients with anterior circulation stroke. Whole-brain CTP might also have advantage in detecting ischemic lesions in posterior circulation territory, which require studies to prove it in the future.
CHAPTER 1:

LITERATURE REVIEW

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1.1 Introduction of cerebral perfusion

Cerebral perfusion refers to the blood flowing into the capillary network of the brain, which is measured by the cerebral blood flow (CBF). Human brain is physiologically in high demand of energy to maintain its function and structure integrity. As an organ accounting for only 2% of the whole body weight, it consumes about 20% of the total oxygen supply at rest [1]. To match this high metabolic rate, a big proportion of blood perfuse to the brain tissues. The CBF, measuring the volume of blood passing through a given brain region per unit time, is around 45 ml/100g/min for health human adults [1-4].

To maintain stable and adequate CBF, cerebral autoregulation plays an important role. CBF is driven by the cerebral perfusion pressure (CPP) that is from the difference of arterial blood pressure and intracranial pressure [5]. When the CPP decreases, the autoregulation mechanism effects by dilating cerebral arterioles to maintain the pass of blood flow; vice versa. Therefore, the autoregulation mechanism maintains CBF at an appropriate level that protects the brain from edema damage when CVV is increased and from ischemia injury when CVV is decreased. However, according to previous study [6], the autoregulation of CBF is only effective within certain range of CVV. In the situation of ischemic stroke where CVV has a dramatic drop, the autoregulation mechanism fails to maintain CBF level or to protect brain from ischemic injury [7].

1.2 Technical knowledge of Perfusion imaging

The detection of cerebral perfusion requires a tracer (contrast agent) running through the brain and an imaging technique measuring radiographic signals stimulated by the tracer. The imaging technique is termed perfusion imaging and perfusion imaging, according to the previous review [8], can be classified into two types. The first type of perfusion imaging, including positron emission tomography (PET), single photon emission computed
tomography (SPECT), and Xenon-enhanced computed tomography (XeCT), uses a tracer that is highly diffusible to brain tissues. It measures CBF based on the Fick principle that is the tracer taken up by the brain tissues equals to the product of the CBF to the tissues and the arterial-venous concentration difference of the tracer. The second type of perfusion imaging uses none-diffusible tracer retaining in the vascular compartment. It calculates CB based on the central volume theorem that is the cerebral blood volume (CBV) equals to the CBF multiplied by the mean transit time (MTT). In other words, CBF is calculated as the ratio of CBV to MTT. This type of perfusion imaging technique includes computed tomography perfusion (CTP) and magnetic resonance perfusion (MRP). Comparing the two types of perfusion imaging, PET, SPECT, and XeCT are primarily research tools due to the limited availability in clinic, whereas CTP and MRP are widely applied in clinic [9, 10]. Therefore, CTP and MRP modalities are the focus of this literature review.

1.2.1 Perfusion imaging acquisition

The acquisition of CTP and MRP images involves four steps: firstly, a bolus of contrast is injected into antecubital vein; 5-7 seconds after the contrast injection, brain scanner starts to collect signal changes inside or around cerebral vessels when contrast flows through; the scanning repeats every 2-3 second and lasts for at least 60 seconds, resulting in a signal intensity-versus-time curve for each pixel (brain imaging unit); then, based on the relationship of contrast concentration and signal intensity, the signal intensity-versus-time curve is converted into contrast concentration-versus-time curve for the calculation of perfusion values of each pixel. Further detail of the imaging acquisition process can be found in these reviews [11-13].

1.2.1.1 CTP vs. MRP
The general principal of imaging acquisition is similar between CTP and MRP [14]. However, technical variation does exist between the two modalities. The main difference is the relationship between contrast concentration and signal intensity. CTP acquisition uses iodinated contrast that enhances the signal intensity in Hounsfield units (HU) inside vessels. Since the HU intensity has a linear relationship with iodinated contrast concentration, the intensity-versus-time curve can be easily converted into concentration-versus-time curve [12]. Conversely, MRP acquisition is based on the gadolinium contrast agent producing signal reduction (T2* effect) in the brain tissue around blood vessels. The relationship between gadolinium contrast agent concentration and signal intensity is more complicated, dependent on magnetic pulse sequence, the contrast-injection manner, and the patient’s circulatory system. Therefore, for MRP, the intensity-versus-time curve cannot be directly converted into concentration-versus-time curve [15]. This leads to the difficulty of quantifying absolute perfusion values on MRP and relative perfusion values are commonly generated on MRP.

Another technical difference between CTP and MRP is the brain coverage on the axial direction. While most MRP scanners cover the whole brain (over 100mm coverage), CTP scanners have the coverage varying from 20mm to 160mm.

1.2.2 Perfusion imaging post-processing algorithms

After acquisition, perfusion information needs to be processed to make it readable for human eyes. The post-processing of CTP and MRP data are similar, mainly involving the translation of the contrast concentration-versus-time curves into perfusion maps. The translation task can be completed either by deconvolution algorithm or by non-deconvolution algorithm. Comparison of the two mathematical models has been detailed in previous literature reviews [16-18]. In summary, the non-deconvolution algorithm depends on simplified assumptions which may produce less reliable perfusion values in some situations. Therefore, most imaging software’s nowadays are using deconvolution approach to generate perfusion maps.
A typical example of the deconvolution algorithm is the singular value decomposition (SVD). SVD algorithm calculates perfusion parameters from the impulse residue function of deconvolution. The impulse residual function refers to the fraction of contrast remains in a pixel after removing the effect of arterial input function (AIF, concentration-versus-time curve of the feeding artery to the pixel) on tissue concentration curve (concentration-versus-time curve of the pixel) [12, 18, 19]. Detail is shown in Figure 1.1. After post-processing, perfusion data are presented in following pixel-based colour-coded parametric maps.

- CBV-cerebral blood volume (ml/100g), the total volume of flowing blood through a given pixel, which is calculated from area under the residual function; MTT- mean transit time (seconds), the average time for blood transiting through a given pixel, which is calculated by the width of the residual function at half of its peak height;
- CBF- cerebral blood flow (ml/100g/min), the volume of blood passing through a given pixel per unit time, CBF=CBV/MTT;
- Tmax- time to the peak of the residual function (seconds), an index of the time from the beginning of contrast administration to the maximum enhancement of the residual function of a given pixel.
- DT-delay time to the peak of the residual function (seconds), alternative term for Tmax after delay correction.

1.2.2.1 Standard SVD vs. Delay-corrected SVD

According to previous studies [20, 21], the perfusion maps generated by SVD is subjected to delay effect. Delay effect refers to the delay time between the contrast bolus arriving at the feeding artery and arriving at the tissue pixel (Figure 1.1), which has been reported to cause the underestimation of CBF value and overestimation of MTT and Tmax value [20, 21]. Based on the finding, delay correction has been applied to SVD algorithm to post-process perfusion data [22-24]. The delay-corrected SVD (dSVD) incorporates the estimation of
delay time into the deconvolution algorithm (Figure 1.1). Compared to standard SVD (sSVD),
dSVD has been reported to generate higher CBF value and lower MTT value; the delay-
corrected Tmax (DT) has been reported to have lower value than the standard Tmax [22-24].

Although dSVD is superior to sSVD in theory (generating more accurate perfusion maps),
both sSVD and dSVD are functional in clinic, often one preferred over another in different
perfusion software. This variation of post-processing algorithm introduces a source of error in
perfusion studies, as the same raw data (i.e. the same scan of the same patient) might result in
different perfusion values with different SVD algorithms [25, 26]. This highlights the need
for studies assessing the variability of CTP results with heterogeneous deconvolution
algorithms (Chapter 3, Chapter 4, and Chapter 5).
Figure 1.1 Perfusion maps generated by algorithms with and without delay correlation.
1.3 Application of Perfusion imaging in stroke

From the brief introduction to perfusion technology above, we know that perfusion imaging provides new insight into the human brain with four-dimensional information. The next question is how are we going to use this information? Stroke is one major application. When ischemic stroke occurs, often the upstream occlusion leads to low blood supply in downstream brain tissues. The change is detected as hypoperfusion region on CTP, with at least one of the following changes (Figure 1.2):

- Low CBV;
- Low CBF;
- Prolonged MTT;
- Prolonged Tmax;
- Prolonged DT.
Figure 1.2 Acute brain imaging of ischemic stroke patient. 64 year old, male, presented with NIHSS 17 and received multi-model CT scanning (NCCT+CTA+CTP) 3.5 hours after stroke onset. NCCT looks normal. However, CTP shows low CBV, low CBF, prolonged MTT, and prolonged DT on the left MCA territory, which is consistent with the left MCA occlusion showed by CTA (blue arrow).
The usage of perfusion imaging has been and is being tested in various stroke trials, including DIAS and DIAS-2 (The Desmoteplase in Acute Ischemic Stroke) [27, 28], DEDAS (Dose Escalation of Desmoteplase for Acute Ischemic Stroke) [29], DEFFUSE and DEFFUSE-2 (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) [30, 31], EPITHET (Echo-planar Imaging Thrombolytic Evaluation Trial) [32], MR RESCUE [33], EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits) [34], EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy) [35], TASTE (Tenecteplase vs. Alteplase for Acute Ischemic Stroke) [36], and DUST (the Dutch Acute Stroke Trial) [37]. In these trials, perfusion imaging is applied in three aspects: diagnosing ischemic stroke, guiding the treatment with information of ischemic penumbra and infarct core, and judging the success of reperfusion treatment. The three aspects are reviewed separately below.

1.3.1 Diagnosis of ischemic stroke: CTP vs. NCCT vs. DWI

To diagnose ischemic stroke, evidence of an ischemic lesion is necessary. Traditionally, the evidence is provided by non-contrast-enhanced brain images, either by diffusion-weighted image (DWI) or by non-contrat CT (NCCT). Now, CTP is providing another option.

DWI and NCCT each has advantages and disadvantages in ischemic stroke diagnosis. DWI, according to the recommendation of American Academy of Neurology (Level A) [38], is the most accurate diagnosis tool for acute ischemic stroke. Studies showed that DWI had high sensitively (>90%) and specificity (>90%) in detecting ischemic lesion [39-42]. However, acquisition of DWI image is a relatively lengthy procedure, averaging 20-30 minutes [43, 44]. In comparison, acquisition time for NCCT are generally well within 10 minutes [43, 44]. Since time is critical for acute ischemic stroke management, NCCT is the preferred modality in most clinical setting. However, NCCT has the disadvantage of very low sensitivity in
detecting ischemic lesion, especially on early stage of acute stroke. That is because the changes caused by ischemia, including hypodensity and oedema of brain tissues, either are subtle or do not present at all on NCCT within three hours of stroke onset [45]. Previous studies of NCCT reported a range of sensitivity in ischemic stroke diagnosis, most of which below 60% [46, 47].

CTP shows greater speed of image acquisition compared to MRI and greatly improves the sensitivity of ischemic lesion detection compared to NCCT (Figure 1.2). Several studies compared the performance of CTP and NCCT and showed that CTP doubled the sensitivity, especially on early stage of stroke (within three hours of stroke onset) [48-50]. This is because ischemic changes appear on CTP minutes after stroke onset [51]. A recent systematic review [52] reported that CTP reaches the sensitivity of 80% in ischemic stroke diagnosis. The misdiagnoses that did occur, according to the review [52], were mainly caused by the location of ischemic lesions outside the coverage of CTP. This implies the sensitivity can be further improved with the extension of brain coverage, especially with whole-brain coverage CTP. Although research on whole-brain CTP is on its early stage [53, 54], current findings all indicate that whole-brain CTP improves diagnostic information with larger axial coverage [55-57]. Thus, with whole-brain coverage, CTP may be as sensitive as DWI in diagnosing acute ischemic stroke.

1.3.2 Quantification of hypoperfusion lesions

More importantly, perfusion imaging provides extra information that is not available on NCCT and DWI. It enables the differentiation of potentially salvageable tissue (penumbra) from unsalvageable tissues (infarct core) within the ischemic lesion. Penumbra measurement by perfusion imaging has been discussed intensively in previous published reviews [58-64]. The present review will focus on the following four questions: 1) what is penumbra and
infarct core; 2) how do we quantify penumbra and infarct core with perfusion imaging; 3) is there clinical significance to this information regarding the penumbra and infarct core; 4) how will penumbra imaging change the management of ischemic stroke in the future.

1.3.2.1 Concept of the penumbra and infarct core

Penumbra and infarct core are part of a continuum of pathophysiological changes in acute ischemic stroke. According to animal studies, the ischemia process can be divided into three stages. Firstly, cellular metabolism is affected [65, 66]. Protein synthesis is inhibited at CBF of 50 ml/100 g/ min and is completely suppressed below 35 ml/100 g/min; glucose utilization starts to decline at 25 ml/100 g/min; meanwhile, tissue acidosis occurs and lactate starts to accumulate. At CBF 26 ml/100 g/min, tissue ATP begins to decline. Secondly, the electrical failure of neurons occurs [67, 68]. The spontaneous and evoked electrical activities start to decline at 23-25 ml/100 g/min and disappear completely when CBF falls below 15-18 ml/100 g/min. Finally, ion homeostasis is disrupted. The extracellular K⁺ concentration starts to increase at CBF threshold around 10 ml/100 g/min [67], and Ca²⁺ is taken up by the cell [69], contributing to cell death. In summary, ischemic severity is divided by three thresholds corresponding to metabolism failure, electrical failure, and ion pump failure.

Accordingly, the ischemic area is divided into three regions: benign oligemia, penumbra, and infarct core [70, 71]. Benign oligemia is the mildest form of ischemia with metabolic compromise but no loss of electrical function; infarct core experiences the severest ischemia with ion pump failure followed rapidly by cell death. Between the two is penumbral tissue, with cells suffering from electrical failure but maintaining ion homeostasis.

Among the three regions, penumbra is the target for ischemic stroke treatment because of its reversibility. Penumbra was first detected in 1977 in ischemic baboon brains [67], and it was officially termed “penumbra” by Astrup et al in 1981 [71]. In analogy, penumbra refers to the
partly illuminated zone around the margin of a complete solar eclipse; in ischemic stroke, the penumbral tissue forms a ring surrounding the ischaemic core. According to Astrup et al [71], penumbra is potentially reversible if the cerebral blood supply can be rapidly restored. In a review of animal studies, Hakim et al [70] directly defined penumbra as “fundamentally reversible” ischemic tissue. The reversibility of penumbra, according to further animal studies [72-74], is time-dependent; as time elapses, penumbra is recruited into the infarct core. Overall, reversibility is the key feature of penumbra.

1.3.2.2 How to differentiate penumbra from infarct core by perfusion imaging

When considering penumbra detection in the ischemic human brain, the first step is to prove the existence of a region experiencing reversible ischaemic injury. On MR, Such a region is identified as the mismatch of the perfusion and diffusion lesion. According to the review by Markus [75], about 70% of patients had a MRP lesion greater than DWI lesion within 6 hours of stroke onset. The MRP-DWI mismatch region could progress to infarction as time elapses. This was demonstrated by the growth of the DWI lesion into the initially mismatch region in a study where patients had an initial MRP lesion exceeding the DWI lesion [76]. Another study [77] confirmed that the extent of DWI lesion growth depended on the initially mismatch region of MRP and DWI. However, in patients undergoing revascularization treatment, one study reported that the extent of DWI lesion growth was limited with successful revascularization [78] and several studies reported MRP lesion size reduction compared to baseline [79-81]. These studies indicated that the MRP-DWI mismatch region could be salvaged with restoration of blood flow. Further details of the MRP-DWI mismatch can be found in these reviews [82-86].

On CTP, quantification of penumbra relies on dual perfusion threshold setting, with the upper threshold differentiating penumbra from benign oligemia, and with the lower threshold
differentiating penumbra from infarct core (Figure 1.3). Mismatch regions of the two thresholds represents the penumbra volume [87, 88]. To determine the two thresholds, various studies have been performed in an approach using two conceptual groups of ischemic stroke patients [89-93]. The two groups are classified according to their revascularization status after ischemic stroke [94]. The approach is summarized as follows: 1) Group one has no effective revascularization, leading to the penumbral region completely developing to infarction; in this group, final infarction lesion should closely approximate the volume of acute infarct core plus penumbra. Using the final infarction lesion as reference, the upper threshold is derived in this group. 2) Group two has complete revascularization, resulting in the complete salvage of penumbra and no expansion of infarct core; thus, the final infarction lesion should be the same size to acute infarct core. In this group, the final infarction lesion is used as the reference to derive the lower threshold.

*Figure 1.3 Penumbra measured by dual threshold setting on CTP*
1.3.2.3 How penumbra and infarct core predicts clinical outcome

With perfusion imaging, either MRP-DWI mismatch or CTP dual-threshold mismatch, the penumbra is detectable in acute ischemic stroke patients. A following question is what is the clinical implication of penumbra measurement? According to the reviews [95-98], penumbral information is useful to select patients most likely to have a favourable response to reperfusion treatment. Reperfusion treatment, either using intra-venous (IV) thrombolytic drug or intra-arterial (IA) strategies, is the only effective treatment for acute ischemic stroke. The treatment aims to revascularize ischemic tissues, yet the randomised trials of reperfusion therapies demonstrate that the successful revascularization does not always result in clinical improvement in all ischemic stroke patients. Evidence is now emerging that the effectiveness of thrombolytic treatment depends on the two key factors: the existence of salvageable tissues (penumbra) and the lack of a “malignant profile” (large infarct core).

The clinical significance of penumbra was tested in MR and CTP studies separately. 1) For MR modality, MRP-DWI mismatch relates to the benefit of revascularisation treatment. This was first observed in a pilot study [80] and then validated by three clinical trials- DEFFUSE, EPITHET, and DEFFUSE-2. In DEFFUSE [30], MRP-DWI mismatch was detected in 54% of patients and those with mismatch had favourable clinical outcome (clinical outcome was measured by modified Rankin Score three months after stroke onset, see appendix table 1). In EPITHET [32 99], MRP-DWI mismatch existed in 86% of the patients; in the mismatch group, good clinical outcome was observed with revascularisation. In the above two trials, revascularization was achieved by IV thrombolysis. In DEFFUSE-2[31], patients were treated with IA revascularization; IA revascularisation was associated with good clinical outcome in patients with mismatch, but not in those without mismatch. 2) Similar result was found when penumbra was defined by CTP mismatch, i.e. mismatch of the dual perfusion thresholds. Two CTP studies reported that a larger penumbra size was correlated with greater
odds of a good clinical outcome [100, 101]. In ischemic stroke patients treated by IA or IV thrombolysis, CTP mismatch was reported to be the main predictor of good clinical outcome [102, 103]. Result of Campbell’s recent study suggested that CTP mismatch has similar performance to MRP-DWI mismatch [104]. The positive role of CTP mismatch is being further tested in an on-going trial--DUST [37]. Of notice, there is one trial, MR-RESCUE, showing no correlation of clinical outcome and the existence of penumbra [33]. This conflicted finding might due to biased selection of patients with big infarct core.

A large infarct core predicts poor clinical outcome of ischemic stroke patients, even those with successful revascularisation treatment. The hypothesis was tested in the DEFFUSE trial by defining infarct core>100ml as malignant profile [30]. The results of DEFUSE indicated that patients with the malignant profile had lower rate of good clinical outcome and higher rate of haemorrhagic transformation (a known risk of from revascularization treatment). This was confirmed in a later study [105] showing a 5.8 fold increase in the risk of symptomatic intracerebral haemorrhage in patients with large-volume infarct core (>100 mL) compared to small (<10 mL) and moderate core (10–100 mL). A different malignant profile, infarct core size around 70 ml, was noticed by EPITHET investigators when they post-hoc analysed the group of patients with poor clinical outcome [106]. This finding agreed with a study showing that infarct core>70ml resulted in poor clinical outcome despite successful revascularization treatment [107]. In these studies, the malignant profile was validated with DWI measurement [108]. With CTP measurement, the malignant profile is also being assessed [104, 109]. A recent study reported that the best CTP measurement to identify patients with poor outcome was a CBF-based infarct core >53 ml [110].

1.3.2.4 From “Time is brain” to “Imaging is brain”
In summary, penumbra information helps predicting the benefit of reperfusion treatment, while the infarct core information helps predicting the risk of haemorrhagic transformation with reperfusion treatment. Combing the information of penumbra and infarct core enables clinicians to select ischemic stroke patients who would have high benefit-to-risk ratio from reperfusion treatment. Such patient selection is now possible with perfusion imaging. The image-based patient selection has been applied in following trials: DEDAS (Phase II) [29], DIAS (Phase II) [27], DIAS-2 (Phase III) [28], EXTEND (Phase III) [34], EXTEND-IA (Phase II) [35], and TNK vs rtPA (Phase II) [36]. In these trials, patients with big penumbra and small infarct core are recruited. To be more specific, two imaging criteria are used to recruited patients: 1) mismatch ratio>1.8, penumbra volume>15ml and infarct core<100ml; 2) mismatch ratio>1.2, penumbra volume>10ml and infarct core <70ml. Primary results of these trials confirm the role of perfusion imaging in patient selection, which could change the mantra of acute ischemic stroke management from “time is brain” to “imaging is brain” [111-113].

Currently, time is the main criteria used to select patients for revascularization treatment. According to the recommendation of the American Stroke Association [114], 4.5 hours is the time window for Intravenous thrombolytic treatment with Alteplase. That means patients would not be treated if they arrived at hospital beyond 4.5 hours after stroke onset. The 4.5-hour time window is based on the results of two large randomised clinical trials- National Institute of Neurological Disorders and Stroke 2 (NINDS-2) and the European Cooperative Acute Stroke Study III (ECASS III). In 1995, the NINDS research group reported the higher ratio of favourable clinical outcome in patients treated by Alteplase within 3 hours of stroke onset [115]. The time window was extended to 4.5 hours by ECASS III in 2008[116]. The finding was further supported in a later study pooling up data from 6 clinical trials [117], including NINDS and ECAS III. The pooled data showed that haemorrhagic risk increased
and benefit decreased as the time from stroke onset to treatment delayed; beyond 4.5 hours, risk outweighed benefit from thrombolytic treatment. Noticeably, the benefit-to-risk ratio was derived at the population level without taking individual difference into consideration.

For individual patients, the rigid time window is not an ideal guide to treatment. This statement is supported by two aspects of previous findings. On one hand, some patients can still benefit from revascularization treatment beyond 4.5 hours. From the study combing data of DEFFUSE and EPITHEPT [118], the benefit was found up to 6 hours in patients with penumbra. Since penumbra was reported to be present as late as 24 hours or even up to 48 hours after stroke onset [119-122], in theory, patients could still be treated with thrombolytic agents up to 2 days after stroke onset. This was verified in a recent study [123], showing the success of penumbra salvage up to 48 hours with thrombolysis and the salvage of penumbra resulting in a favourable clinical outcome. One the other hand, some patients cannot benefit or even suffer harm from thrombolysis within the 4.5-hour time window. Studies are limited on this group of patients; however, the lack of penumbra or the existence of large infarct core would explain the poor clinical outcome despite successful revascularization within the recommended time window [124-126].

Perfusion imaging provides a new direction for treatment guidance. It has following two advantages. Firstly, imaging-based guidance breaks the limitation of the current time window. This is of particularly use to patients with unknown stroke onset time, such the wake-up ischemic stroke [127]. In EXTEND and EXTEND-IA trials, patients with wake-up ischemic stroke were recruited, which would not be possible with time-window-based patient selection [34, 35]. Secondly, imaging-based patient selection provides a better target for new thrombolytic agents. In DEDAS, DIAS, and DIAS-2 trial, the new agent Desmotelase was compared to placebo in patients with mismatch penumbra [28, 29, 128]; in TASTE trial, another new agent Tenecteplase was compared to Alteplase in patients with mismatch
penumbra [36]. Results of DEDAS and DIAS supported the use of MRP-DWI mismatch for patient selection, and results of TASTE supported the use of CTP mismatch. However, DIAS-2 had negative finding regarding the efficacy of the new drug. Researchers suspected patients were not well selected in DIAS-2, with CTP and MR both used as imaging criteria. The agreement of CTP and MRP in patient selection needs further validation (Chapter 5).

1.3.3 Quantification of Reperfusion

Perfusion imaging not only provides guidance for thrombolytic treatment, it also helps to assess success of the treatment. That is the reperfusion. To discuss the significance of reperfusion, its definition needs to be clarified first. The term “reperfusion” has been used interchangeably with “recanalization” and “revascularization” in previous studies. This terminology confusion has been discussed in the reviews [129, 130], and the reviewers recommend the following definitions. Revascularization is a larger concept including two aspects--recanalization and reperfusion; recanalization refers to the re-open of vessel and restoration of blood flow in the downstream arterial branches; reperfusion refers to the restoration of blood flow in capillary network. According to the reviews [129-131], recanalization does not necessary lead to reperfusion, leading to the existence of the “no-flow” phenomenon; on the other hand, reperfusion may occur without recanalization, as the restoration of blood flow from collateral flow. Therefore, the meanings of reperfusion and recanalization are different.

In the clinical settings, reperfusion and recanalization are measured with different imaging modalities. Recanalization is measured by angiography and quantified by either TIMI (Thrombolysis in Myocardial Infarction) scale or TICI (Thrombolysis in Cerebral Infarction) scale; TIMI>=2 or TICI>=2b is considered successful recanalization. Details of the two scales are seen table 1.2, and comparison of the two scales can be found in these papers [132-
On the other hand, reperfusion status is measured by perfusion imaging; it is quantified by the reperfusion index as the change in perfusion abnormality pre- and post-treatment; reperfusion index over certain percentage (varying from 30% to 90% among studies [129]) is considered as successful reperfusion. The equation for reperfusion calculation is as follows:

\[ \text{Reperfusion index} = \frac{(\text{acute hypoperfusion region}) - (\text{follow-up hypoperfusion region})}{(\text{acute hypoperfusion region})} \times 100 \]

Table 1.1 Recanalization measurements by TIMI or TICI score

<table>
<thead>
<tr>
<th></th>
<th>TIMI (Thrombolysis in Myocardial Infarction) scale</th>
<th>TICI (Thrombolysis in Cerebral Infarction) scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absence of any antegrade flow beyond occlusion</td>
<td>No reperfusion</td>
</tr>
<tr>
<td>1</td>
<td>Faint antegrade flow beyond the occlusion with incomplete filling of the distal territory</td>
<td>Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion</td>
</tr>
<tr>
<td>2</td>
<td>Delayed or sluggish antegrade flow with complete filling of the distal territory</td>
<td>2a Perfusion of&lt;50% of the vascular distribution of the occluded artery</td>
</tr>
<tr>
<td>3</td>
<td>Normal flow which fills the distal territory completely</td>
<td>2b Perfusion of &gt;50% of the vascular distribution of the occluded artery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 Full perfusion with filling of all distal branches</td>
</tr>
</tbody>
</table>

Either reperfusion or recanalization has been reported to predict good clinical outcome of ischemic stroke patients. Reperfusion has been used as the imaging surrogate for successful thrombolytic treatment in clinical trials, including DEDAS [29], DIAS [27], DEFUSE [135], DEFUSE-2 [31], EPITHET [32], EXTEND [34], and TASTE [36]. According to the published results of these trials, reperfusion predicts good clinical outcome at three months (the definition of good clinical outcome is found in table 1.2). Successful reperfusion increased the odds of having good clinical outcome by almost 3.4 fold in the DIAS trial, by
9.6 fold in DEDAS, by 5.4 fold in DEFUSE, and by 7.2 fold in EPITHET. Overall, according to a meta-analysis of these four studies [136], the odds ratio was 5.2 for patients who had successful reperfusion compared to those who did not. This odds ratio looks higher than the finding of recanalization studies. According to a meta-analysis of recanalization [137], the odds ratio was 4.43 comparing patients with successful recanalization to those without it in terms of predicting good clinical outcome at three months. Better performance of reperfusion is confirmed in recent three studies [138-140]. The three studies had similar findings in that recanalization was a significant factor in the prediction of clinical outcome and tissue outcome in a univariate analysis; however, when reperfusion was introduced as covariate in a multivariate analysis, recanalization lost its significance. Reperfusion, on the other hand, was associated with improved clinical outcome independent of whether or not recanalization occurred. These studies suggested that that the impact of recanalization on clinical outcomes might be attributable to reperfusion.

Table 1.2 modified Rankin score (mRS). Ischemic stroke patients with mRS 0-2 at three month are considered having good clinical outcome.

<table>
<thead>
<tr>
<th>mRS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms.</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability. Able to carry out all usual activities, despite some symptoms.</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability. Requires some help, but able to walk unassisted.</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability. Requires constant nursing care and attention, bedridden, incontinent.</td>
</tr>
<tr>
<td>6</td>
<td>Dead.</td>
</tr>
</tbody>
</table>

1.4 Limitations of CT perfusion in ischemic stroke application
Perfusion imaging has the potential to provide information of ischemic stroke patients that allows more informed treatment decision making by neurologists. However, the importance of perfusion imaging has not been well acknowledged in clinical setting. In the Canadian best practice recommendations for stroke care 2008 [141], it is not recommended as the first line imaging strategy. In the UK national guidelines 2008 [142], no definitive recommendation is made for the usage of perfusion imaging, leaving the decision to local clinical judgement. A low level recommendation is included in the guideline of the European Federation of Neurological Societies (Class IV, Level GCPP) [143]. In the most recent guideline of the American Stroke Association [114], although the importance of perfusion imaging is recognized, the recommendation of using this technology in clinical practice is on low evidence level (Class IIb; Level of Evidence B). Therefore, further efforts are required to promote the use of perfusion imaging in routine practice of ischemic stroke patients. To achieve the goal, the first approach is to gain stronger evidence from large stroke trials, and the second approach is to address the technical limitations of perfusion imaging technology which is the interest of this thesis. Extra studies are especially needed for CT perfusion [144, 145]. Between the two perfusion modalities, MRP was developed earlier and has reached certain level of consensus among different research groups in terms of the imaging acquisition, imaging post-processing and penumbra definition. CTP, on the other end, is relatively new and still considered debatable. The debate focuses on the following two issues: 1) limited brain coverage, and 2) variation in the approach to quantifying ischemic lesions

1.4.1 Limited brain coverage of CTP

Limitation on the brain coverage has long been an issue for CTP, and the issue is now solvable with the latest generation of CT scanners [146, 147]. In the early 2000’s, perfusion imaging was acquired on 16-detector and 64-detector CT scanners, with axial brain coverage of 20mm and 40mm respectively. In these scanners, the CT slab centred on basal ganglion
level, missing partial cerebral information, e.g. the superior cerebrum (Figure 1.4).

Researchers back then realized the limited brain coverage and tried to extend it using two approaches: the shuttle-mode acquisition [148] and the two-slab acquisition [149]. Both methods doubled the brain coverage at the expense of other features of CTP. In shuttle mode, two sections of the brain were scanned in succession by moving the CT table back and forth along the axial direction of the patient’s brain; the temporal interval for the shuttle movement was 4-5 seconds, which, according to later studies [150], compromised the temporal resolution of CTP and could potentially underestimate cerebral perfusion values.

Alternatively, two slabs of CTP data (on different brain axial levels) were generated by the injection of two boluses; however, this required twice the contrast and exposed the patient to twice the radiation dose. Therefore, researchers and technicians didn’t stop searching for an ideal approach to extend the brain coverage of CTP. After 2005, the CTP research finally embraced a breakthrough with the introducing of 256-detector helical scanner and 128-detector spiral scanner, covering the axial direction of 80mm and 100mm respectively with one bolus of contrast [56, 151]. More recently, the brain coverage of CTP was further extended to 160mm with 320-detector CTP [53, 55, 152-154]. These “mega-detector” CT scanners enable perfusion images cover the whole brain (Figure 1.4).
Figure 1.4 Brain coverage of CTP. X, Y, Z axis refer to coronal direction, sagittal direction, and axial direction respectively. 16-detector has limited brain coverage, while 320-detector CTP covers the whole brain.

However, studies on whole-brain CTP are in their very early stages. They can be classified on three aspects. The first type of studies focuses on the feasibility of whole-brain CTP. According to preliminary clinical experiences [154, 155], acquisition and post-processing of the whole-brain perfusion data was reasonably fast, requiring 5 minutes and 10 minutes respectively. Compared to limited-slice CTP, whole-brain CTP was compromised in the imaging quality [153]; however, the imaging quality was still good enough to result in reliable measurement of perfusion values. The second type of studies examines the safety of whole-brain CTP, since radiation dose has always been a concern for CT scanning. While the radiation dose was reported to be 7.5-11.4 mSv for limited-coverage CTP, it was 4.3-11.2 mSv for whole-brain CTP [53]. Therefore, patients are not exposed to higher dose with extended-brain-coverage scanning. The last type of studies assesses the advantage of whole-brain CTP on ischemic stroke diagnosis. Dorn et al [56] compared the performance of 256-
detector CTP and simulated 16-detector CTP and found that three lesions were missed by 16-detector CTP but detected by 256-detector CTP. Morhard et al [57] found that 128-detector spiral CTP detected extra pathologic changes in 24.1% of 54 patients, which would be missed on 16-detector CTP; the extended brain coverage resulted in a different diagnosis in 34.7% of patients. Page et al [55] compared 320-detector CTP and simulated 64-detector CTP and observed an increase of diagnosis accuracy by 320-detector CTP in 78% of patients. In summary, whole-brain CTP has been proven to be feasible and safe with advantages in ischemic stroke diagnosis. However, no study has validated the superiority of whole-brain CTP on quantifying penumbra and infarct core (Chapter 3).

1.4.2 Variation in perfusion threshold setting on CTP

To quantify penumbra and infarct core on CTP, dual threshold is the common method. However, so far, no consensus has been reached regarding the optimal threshold setting. Different maps and various thresholds have been used for overall ischemic lesion, for infarct core, and for penumbra (Figure 1.5).

- The entire ischaemic lesion has been defined by time-domain parameters, varying from MTT, TTP, DT, to Tmax. Studies by Wintermark [89] found that relative MTT>145% has high sensitivity and specificity in separating ischemic tissue from tissue experiencing benign oligemia. However, later studies by Bivard [90, 91] found that DT>2s outperformed MTT in the role with higher sensitivity. According to the findings of another research group [104], Tmax>6s was also - adequately when used as a threshold to delineate the ischemic - region on acute CTP.

- To define infarct core, CBF and CBV have been the two main candidates. Early studies showed the superiority of CBV over CBF. Koenig [156] found that infarct core was best defined by relative CBV<60% and relative CBF<48%, but CBV had
slightly better sensitivity, specificity and efficiency; similarly, CBV < 2 ml/100g was
found to be the optimal threshold in discriminating between areas of infarction and
non-infarction [89]. On the contrary, recent studies showed the better performance of
CBF over CBV. Study of Campbell et al [93] found that CBF corresponded with the
acute DWI lesion better than CBV, the optimal threshold for infarct core was relative
CBF < 30%; Study of Bivard et al [90, 91] reported that relative CBF < 40% rather
than CBV threshold (within the DT > 2 s perfusion lesion) was the most accurate CTP
threshold at defining infarct core.

- To define penumbra on CTP, four types of mismatch have been proposed. These were
  DT > 2 s/CBF < 40% mismatch [90, 91], Tmax > 6 s/CBF < 30% mismatch [104],
  MTT > 145% /CBV < 2 ml/100g [89], and MTT > 150% /CBV < 56% [157]. Notably,
  different post-processing algorithms and CT scanners were used in each of the above
  studies. Thus, optimal thresholds might change with the post-processing algorithm
  and the brain coverage of CTP (Chapter 3).

Due to the variance in threshold setting for the ischemic lesion, reperfusion of the lesion has
been quantified by various approaches. In early clinical trials, including EPITHET and
DEFFUSE [32, 135], reperfusion was measured by the restoration of the ischemic region
defined by Tmax > 2 s; however, later study found that Tmax > 2 s was less ideal since it not
only assessed the reperfusion of ischemic lesion, but also included the reperfusion
information of benign oligemia [158]. From the study, a better threshold Tmax > 6 s was
proposed and later used in DEFFUSE-2 and EXTEND trial to define reperfusion [31, 34].
According to the study of Eilaghi et al [140], reperfusion of the ischemic region defined
Tmax > 6 s had high sensitivity and specificity in predicting good clinical outcome. The recent
TASTE study used a different measurement for reperfusion MTT > 145% [36, 159].
Reperfusion of the ischemic region measured by MTT > 145%, according to the study of
Soares et al [139], had high sensitivity and specificity in predicting final infarct volume. In summary, reperfusion can be quantified by the restoration of the ischemic region defined either by Tmax>6s or by MTT>145%. No studies have compared the performance of the two different reperfusion measurements in predicting outcome of ischemic stroke (Chapter 4).

*Figure 1.5 Various thresholds setting for penumbra and infarct core*
1.5 Summary of the literature review

CTP and MRP are the two main perfusion technologies. Between the two perfusion modalities, MRP was developed earlier and has reached certain level of consensus among different research groups in terms of its important role in ischemic stroke. CTP, on the other end, is relatively new and still considered debatable. The main concern of CTP is its inaccuracy in quantifying acute ischemic lesion which might provide wrong guidance for reperfusion treatment or wrong estimation of the success of reperfusion.

The inaccuracy can be caused by limited brain coverage of CTP. Although limitation on brain coverage has been addressed by new mega detector CT scanner and early study shows whole-brain CTP scanning is feasible and safe, no literature is available regarding to the accuracy of whole-brain CTP in ischemic lesion quantification. Besides brain coverage, threshold setting is another factor that might contribute to inaccurate measurement by CTP. In literatures, various thresholds have been used to define ischemic penumbra as well as to calculate reperfusion status. One threshold was proven to be accurate in one research report but no so in another. These factors that cause inaccuracy in CTP measurement need to be addressed to promote the application of CTP in ischemic stroke.
1.6 Reference


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CHAPTER 2:

RESEARCH AIMS AND HYPOTHESIS
2.1 Aims

CTP is being increasingly used in acute stroke given its availability and accessibility. However, one disadvantage of CTP has been its limited brain coverage. The new generation of CTP overcomes this limitation, but its usage in stroke has not been well validated.

- The primary aim of this thesis is to validate the usage of whole-brain CTP in ischemic stroke.

The application of whole-brain CTP involves in two aspects: delineating acute ischemic region (including penumbra and infarct core) and quantifying reperfusion of the ischemic region, both of which requires setting threshold to perfusion maps.

- The second aim of this thesis is to derive the perfusion threshold on whole-brain CTP that quantify the acute ischemic lesion and its reperfusion status accurately.

2.2 Hypothesis

- Hypothesis One: Whole-brain CTP has high accuracy in delineating the acute ischemic region and in differentiating acute penumbra and infarct core within the ischemic region; reperfusion of the ischemic lesion on whole-brain CTP predicts good clinical outcome of ischemic stroke patients (Chapter 3 & 4).

- Hypothesis Two: Whole-brain CTP is more accurate than limited-coverage CTP in quantifying ischemic region (Chapter 3).

- Hypothesis Three: Whole-brain CTP is as good as MRP in quantifying ischemic region and providing treatment guidance (Chapter 5).

- Hypothesis Four: Accuracy of whole-brain CTP measurement depends on proper threshold setting; among perfusion maps, Tmax has the threshold that best delineates ischemic lesion and best predicts clinical outcome of ischemic stroke (Chapter 3, 4 & 5).
2.3 Chapter overview

The studies incorporated in each chapter are summarized in Figure 2.1.

- In Chapter 3, two steps were performed. Firstly, 24-hour DWI was used as the reference for infarct core and penumbra, from which were derived the penumbra and core threshold on 320-detector CTP (Hypothesis One and Four). Then, the brain coverage of 320-detector CTP was gradually reduced to simulate limited-coverage CTP, measuring how the accuracy of lesion detection changed as the brain coverage decreased (Hypothesis Two).

- In Chapter 4, acute CTP and 24-hour CTP of the same patients were compared to derive a reperfusion index. The sensitivity and specificity of the reperfusion index in predicting good clinical outcome (mRS≤2) was assessed, from which was derived the cut-off value to define successful reperfusion (Hypothesis One and Hypothesis Four).

- In Chapter 5, acute CTP and acute MRP were compared to derive the perfusion measure with the highest agreement between the two imaging modalities in measuring penumbra (Hypothesis Three and Four). Then, acute CTP and acute MRP were further compared in selecting patients for thrombolytic treatment (Hypothesis Three). Acute CTP and 24-hour MRP were also compared to calculate the cross-modality reperfusion index.

Analysis in above three chapters was limited to patients with acute anterior circulation stroke. Cases excluded from the published analyses, such as posterior circulation stroke, were presented in Chapter 6.
Figure 2.1 Chapter overview of the thesis
CHAPTER 3:

VALIDATION WHOLE-BRAIN CTP MEASUREMENT FOR PENUMBRA AND INFARCT CORE

Introduction: This chapter tests the hypothesis that whole-brain is accurate in delineating acute ischemic region and in differentiating acute penumbra to infarct core within the ischemic region. The chapter also tests the hypothesis that whole-brain CTP is more accurate than limited-coverage CTP in quantifying the ischemic region. The aim of this chapter is to derive the perfusion threshold that defines the penumbra and infarct core with the highest accuracy.

Results of this paper have been submitted to the Radiology Journal and it has been accepted for publication (25 March 2015) pending appropriate revision to reviewers’ comments.

ABSTRACT

Purpose: Due to the concerns about its accuracy in measuring ischemic lesions, the routine use of CT perfusion (CTP) in acute stroke imaging protocols has been limited. Now that CTP with whole-brain coverage is achievable, we aimed to assess its performance in measuring acute hemispheric ischemia in comparison to limited-coverage CTP. Materials and Methods: 266 consecutive patients who underwent CTP within 6 hours of ischaemic stroke onset were studied. CTP data were acquired on a 320-detector scanner with brain coverage of 160mm. Other commonly-used CTP coverage ranges were simulated on the same patient data by progressively limiting the slice coverage to 100mm, 80mm, 40mm, and to 20mm. The ability of different slice coverage CTP to measure the infarct core and penumbra was assessed by comparison to the reference standard of MR diffusion weighted imaging (DWI). Volumetric agreement was assessed by accuracy and precision measures (Lin’s concordance correlation coefficient), and pixel agreement was measured by sensitivity and specificity (Receiver Operating Curve analysis). Results: Whole-brain CTP had excellent accuracy (>99%) and precision (>95%), very good specificity (>91%), and good sensitivity (>78 %) in the identification of both infarct core and penumbra. Limiting the brain coverage to 100mm or 80mm resulted in a loss of sensitivity but CTP retained overall good performance. Limiting the coverage to 40mm and 20mm, however, resulted in significant underestimation of ischemic lesions (p<0.05) and a dramatic drop in accuracy (<86%) and sensitivity (<50%). Conclusion: Whole-brain CTP can measure the acute infarct core and penumbra with very high accuracy.
INTRODUCTION

Perfusion imaging is being used in stroke trials to triage patients for reperfusion treatment, based on quantifying volumes of salvageable tissue (penumbra) and non-salvageable tissue (infarct core) using perfusion thresholds [1-5]. Magnetic resonance imaging (MRI) perfusion has been available for over two decades; however, computed topography (CT) perfusion has advantages of more rapid acquisition and greater accessibility, both essential for efficient and effective acute stroke management [6].

CT perfusion (CTP) has mostly been limited to 16-detector and 64-detector scanners, covering 20-40mm in the axial direction [7]. This spatial limitation leads to underestimation of the ischemic lesion [8], which, combined with doubts about the overall accuracy of CTP in measuring infarct core and penumbra, is a key reason why CTP has not been widely used in the routine work-up of acute stroke patients prior to acute reperfusion therapy. Approaches to improve spatial coverage have included the usage of a ‘jog’ or ‘shuttle’ acquisition on traditional CT scanners with limited slice coverage [9, 10], but this compromises temporal resolution[11] and has been poorly validated in terms of its accuracy in measuring core and penumbra.

The advent of newer ‘mega-detector’ CT scanners (particularly the 320-detector scanner providing 160 mm of axial coverage), overcomes the spatial limitation by extending scanning range to cover the whole brain [8]. This whole-brain coverage is a technical breakthrough for CTP. As the International Organization for Standardization (ISO) and Food and Drug Administration (FDA) recommend [12-14], with major technical modifications such as whole-brain CTP, further validation is needed. In this study we aimed to validate whole-brain CTP measurements for ischemic penumbra and infarct core in terms of accuracy, precision, sensitivity, and specificity and compare these results with limited slice coverage CTP data.
MATERIALS AND METHODS

Patients

Consecutive patients, who were imaged with multi-modal CT within six hours of ischemic stroke onset from June 2011 to January 2014, were studied. These patients routinely had MRI scanning at 24-48 hours; a subset of these patients also had MRI performed immediately after CT. We included only patients with complete occlusion on middle cerebral artery (MCA) or internal carotid artery (ICA) at baseline (as we needed to assess recanalization as part of the study). We excluded patients with parenchymal hematoma on follow-up imaging (as accurate infarct measurement is not possible) or patients with severe motion artefact on acute CTP. If eligible, patients were treated with intravenous thrombolysis according to standard guidelines. The study was approved by the institutional ethics committee.

Image acquisition

CT images were acquired on 320-detector Toshiba scanner (Toshiba Aquilion ONE; Toshiba Medical Imaging, Tokyo, Japan). The standard acute stroke multimodal CT protocol included non-contrast CT (NCCT), CT angiography (CTA), and CT perfusion (CTP). The intracranial CTA and CTP were acquired from the same acquisition (detail of the acquisition in Appendix 1). Temporary, 19 time frames were obtained commencing seven seconds after non-ionic iodinated contrast injection into an antecubital vein (40 ml, 6ml/s; Bayer HealthCare, Berlin, Germany). The acquisition duration was 65 seconds, and was divided into three phases: phase one, 1 frame was generated (80kV, 310mA) as a baseline; phase two, 13 frames were generated at rate of one frame per two seconds (80kV, 150/300mA); phase three, 5 frames were generated at rate of one frame per five seconds (80kV, 150mA). FOV was 220×220mm,
and Matrix was 512×512. Spatially, one gantry rotation resulted in 320 slices with the thickness of 0.5mm, which covered 160mm on z-axis. To simplify following analysis, we merged the 320 thin-slice CTP data into 32 slices with thickness of 5mm.

MRI was performed on a 3-Tesla scanner (Siemens Verio, Erlangen, Germany). It included diffusion-weighted imaging (DWI), and time of flight angiography (MRA). DWI was acquired in 25 axial slices with slice thickness of 5mm and a slice gap of 1.5mm. The acquisition parameters were as follows: TR 3200 msec, TE 100 msec, Flip 90, FOV 240mm×240mm, and Matrix 128×128.

**Threshold analysis on 320-detector CTP**

CTP data was processed by commercial software MIStar (Apollo Medical Imaging Technology, Melbourne, VIC., Australia) [15, 16], with singular value decomposition (SVD) algorithm[17]. Two types of SVD, standard SVD (sSVD) and delay-corrected SVD (dSVD), were applied to generate perfusion maps. sSVD generated cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak of the residual function (Tmax). dSVD generated delay-corrected CBF, delay-corrected CBV, delay-corrected MTT, and delay time to peak of the residual function (DT).

On CTP maps, dual threshold setting is commonly used in ischemic stroke, with the upper threshold (penumbra threshold) differentiating normal tissue from penumbra and with the lower threshold (infarct core threshold) differentiating infarct core from penumbra. For the two thresholds, several candidates have been proposed by previous studies on limited-coverage CTP [18]. Therefore, in this study, we first tested the accuracy of those previously validated thresholds on 320-detector CTP. If proven inaccurate, then, a wider range of thresholds were assessed to derive new measures for penumbra and infarct core on whole-brain CTP.
The following threshold ranges were covered: For CBF and CBV, the threshold ranged from 100% to 0%, with 5% decrements; on MTT, the threshold range was from 100% to 300%, with 5% increment; on DT and Tmax, it was from 0 seconds to 20 seconds with increment of 0.5 seconds. The threshold level was relative to the mean tissue perfusion value of the unaffected hemisphere. Each threshold delineated an individual ischemic volume in each slice; by adding the volume of 32 axial slices, the overall lesion volume was calculated for each patient.

**Coverage analysis across CTP scanners**

With the optimal threshold setting, the lesion volume of each slice was then plotted against slice level of 320-detector CTP (Figure 3.1). From the plot, we observed the distribution pattern of lesion on axial direction, and calculated the slice range that covered 95% of lesion volume. Guided by the lesion distribution pattern on 320-detector CTP, we then simulated brain coverage ranging from 20mm to 100mm (Figure 3.1). Performance of the various slice coverage was compared in terms of measuring penumbra and infarct core.
Figure 3.1 Simulation of limited-coverage CTP from 320-detector CTP data. To simulate the coverage of 16-detector scanner, slice of 18-21 (20mm) is used; for simulation of 64-detector scanner, slice of 16-23 (40mm) is applied; for simulation of 256-detector scanner, slice 12-27 (80mm) is applied; for simulation of 128-detector spiral scanner, slice 10-29 (100mm) is applied.
**Reference for ‘true’ ischemic lesion**

The 24-hour DWI lesion was used as the main reference standard for ischemic lesions [19]. For patients with no recanalization, follow-up DWI lesion was used to validate the penumbra threshold of CTP; for patients with complete recanalization, it was used to validate the infarct core threshold of CTP. The underlining principle is as follows: without recanalization of occluded vessel, acute infarct core progresses into penumbra and the final infarction volume on follow-up DWI is assumed to be the sum of acute infarct core and acute penumbra; with recanalization, no expansion of infarct core happens and the final infarction size is supposed to be the same to acute infarct core. This approach has been well applied previously to validate CTP measurements for infarct core and penumbra [15, 16, 20].

In a subgroup of patients who had acute DWI and CTP performed concurrently, the acute DWI lesion was used the secondary reference for infarct core. DWI lesion was measured by MIStar software with a semi-automatic method setting an individual signal intensity threshold for each patient to best separate ischemic tissue (increased signal intensity) and normal tissue [21]. The threshold setting was done by LL.

Recanalization status was graded on follow-up MRA by evaluating the restoration of patency of the previously occluded vessel with modified Thrombolysis in Myocardial Infarction (mTIMI) scoring system [22]. An mTIMI score of 0 was considered as no recanalization, score of 1-2 was considered as partial recanalization, and score of 3 was complete recanalization.

**Statistical analysis**

The volume of the ischemic lesion was summarized by mean and standard deviation. Volumetric difference of ischemic lesion between CTP and reference imaging modality was
assessed with paired t-test (paired by patient ID), at a significance level of 0.05. For thresholds that resulted in a non-significant difference between CTP and DWI, two further analyses were carried out (below).

In volumetric analysis, Lin’s concordance correlation coefficient (CCC) assessed the agreement of CTP and DWI on quantifying ischemic lesion volume. CCC measures both precision and accuracy to determine whether the observed data deviate significantly from the line of perfect concordance (i.e., the line at 45°, Figure 3.2a). It can be expressed as the product of the Pearson correlation coefficient \( \rho \) (the measure of precision) and the bias-correction factor \( C_b \) (the measure of accuracy) [23].

In pixel analysis, DWI and CTP image were co-registered and reformatted to the same pixel size by MIStar software (FOV=205mm×205mm, Matrix=256×256, slice thickness=5mm). For both DWI and CTP, pixels within the lesion were marked as “1”, and pixel within the normal tissue were marked as “0” (Figure 3.2b). Then, receiver operating characteristic (ROC) curve was used to assess the sensitivity and specificity of CTP in predicting the DWI binary outcome (Figure 3.2c). All Statistical analyses were done on STATA 13.0.
Figure 3.2 Performance of CTP on measuring penumbra with 3 seconds threshold setting on DT map. (A) DT>3s has 99.90% accuracy and 95.90% precision on measuring penumbral volume, which is calculated from the concordance of CTP and 24-hour DWI lesion volume in no recanalization group. Accuracy is the reduced major axis, and precision is the tightness of the data about the reduced major axis. (B, C) DT>3S has 78.59% sensitivity and 91.04% specificity in predicting penumbral pixel. Sensitivity and specificity are derived from pixel analysis. Pixels where the DWI lesion and CTP lesion overlaps are considered “true positive” (TP). Overlapped pixels between the DWI normal region and CTP normal region are considered “true negative” (TN). Pixels within the CTP lesion but not within the DWI lesion are assigned ‘false positive’ (FP), and pixels within the DWI lesion but not within the CTP lesion are assigned ‘false negative’ (FN). Specificity=TN/(TN + FP), and sensitivity=TP/(TP + FN).
RESULTS

Patients

From 5th June 2011 to 30th January 2014, 266 consecutive ischemic stroke patients were scanned by acute CTP and 24-hour MRI. Of the 266 patients, 27 were excluded due to PCA/basilar occlusion, 67 were excluded due to no baseline occlusion, 16 were excluded due to partial baseline occlusion with antegrade flow, 24 were excluded due to subsequent haemorrhage transformation, and 10 patients were excluded due to severe motion artefact on CTP. Therefore, 122 patients were used for further imaging analysis. Among the 122 patients, 40 patients had no recanalization, 44 patients had complete recanalization, and 38 patients had partial recanalization. Of the 122 patients, 25 had acute DWI data. Characteristics of these patients could be found in Table 3.1.

Table 3.1 the characteristics of patients (N=122)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR), y</td>
<td>74 (18)</td>
</tr>
<tr>
<td>Median NIHSS at baseline (IQR)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Median mRS at 90 days (IQR)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Median time to acute CT (IQR), min</td>
<td>159 (120)</td>
</tr>
<tr>
<td>Acute MRI</td>
<td></td>
</tr>
<tr>
<td>Cases with acute MRI (N), %</td>
<td>20.49 (25)</td>
</tr>
<tr>
<td>Median time from acute CT to acute MRI (IQR), min</td>
<td>80 (35)</td>
</tr>
<tr>
<td>Recanalization status on follow-up MRA</td>
<td></td>
</tr>
<tr>
<td>No recanalization (N), %</td>
<td>32.79 (40)</td>
</tr>
<tr>
<td>Partial recanalization (N), %</td>
<td>31.15 (38)</td>
</tr>
<tr>
<td>Complete recanalization (N), %</td>
<td>36.07 (44)</td>
</tr>
<tr>
<td>Thrombolytic treatment</td>
<td></td>
</tr>
<tr>
<td>Patients received thrombolysis (N), %</td>
<td>63.93 (78)</td>
</tr>
<tr>
<td>Time to thrombolysis (IQR), min</td>
<td>180 (78)</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institute of Health Stroke Scale score; mRS indicates modified Rankin Score; IQR indicates interquartile range.
Part1: optimal thresholds for measuring ischemic lesions on whole-brain CTP

We previously validated delay corrected DT>2s and CBF<40% as the most accurate thresholds to define penumbra and core on limited slice coverage CTP. [15], However, on whole-brain CTP, these thresholds substantially overestimated penumbra and infarct core (Table 3.2).

With delay time (Figure 3.3a), 3 seconds was the threshold resulting in the least volumetric difference of penumbra between CTP and DWI (the mean difference was 4.14 ml, p>0.05). With CBF (within a DT>3S setting, Figure 3.3b), the threshold of 30% measured the infarct core closest to DWI; the mean volumetric difference was -2.26 ml and -1.34 ml respectively to acute DWI and 24-hour DWI (p>0.05, Table 3.2). Noticeably, on measuring infarct core, CTP had better agreement with acute DWI than with 24-hour DWI (Supplemental Material, Figure 3S and Table 3S). Thus, acute DWI is used as the reference for infarct core in following pixel and coverage analysis.

Overall, DT>3s and CBF<30% showed excellent accuracy (>99 %) and precision (>95%) in identifying the volume of infarct core and penumbra, as well as good specificity (>91%) and good sensitivity (>78%) in predicting core and penumbra pixels (Table 3.3). In addition to CBF<30%, CBV<55% (within DT>3S) also showed excellent performance on measuring infarct core (Table 3.3).
Table 3.2 Volumetric difference of CTP and DWI on measuring ischemic lesions

<table>
<thead>
<tr>
<th>No recanalization group</th>
<th>CTP map</th>
<th>Threshold</th>
<th>Penumbra volume (ml)</th>
<th>Volumetric difference (CTP - 24h DWI, ml)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DT 2s</td>
<td></td>
<td>180.40 ± 99.54</td>
<td>40.82 ± 32.49</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>DT 3s</td>
<td></td>
<td>143.72 ± 89.99</td>
<td>4.14 ± 25.69</td>
<td>0.31</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complete recanalization group</th>
<th>CTP map</th>
<th>Threshold</th>
<th>Infarct core volume (ml)</th>
<th>Volumetric difference (CTP – 24h DWI, ml)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF 40%</td>
<td></td>
<td>39.41 ± 26.23</td>
<td>20.37 ± 15.13</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>CBF 30%</td>
<td></td>
<td>17.71 ± 15.61</td>
<td>-1.34 ± 7.57</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute DWI subgroup</th>
<th>CTP map</th>
<th>Threshold</th>
<th>Infarct core volume (ml)</th>
<th>Volumetric difference (CTP – acute DWI, ml)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF 40%</td>
<td></td>
<td>69.89 ± 73.89</td>
<td>21.72 ± 20.28</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>CBF 30%</td>
<td></td>
<td>45.91 ± 61.18</td>
<td>-2.26 ± 7.01</td>
<td>0.12</td>
<td></td>
</tr>
</tbody>
</table>

In no recanalization group, the lesion volume is 139.58 ± 88.96 ml on 24-hour DWI; in complete recanalization group, the lesion volume is 19.04 ± 17.27 ml on 24-hour DWI; in subgroup with acute DWI, the lesion volume is 48.16 ± 60.88 ml. Lesion volume is summarized by mean ± standard deviation. CTP maps are acquired from 320-detector scanner and post-processed by dSVD.
Figure 3.3 The volumetric difference between CTP and DWI varies across CTP threshold. For penumbra measurement, the threshold results in least difference between CTP and 24-hour DWI is 3 seconds on DT (A) and 6 seconds on Tmax (C). Within DT>3S, the threshold resulting in the least difference between CTP and acute DWI is CBF<30% (B); within Tmax<6s, the threshold is CBF<25% (D) resulting in the least difference on measuring infarct core.
Table 3.3 CTP measures whole-brain penumbra and infarct core with high accuracy and precision, reasonable sensitivity, and good specificity.

<table>
<thead>
<tr>
<th></th>
<th>CTP thresholds from dSVD post-processing</th>
<th>CTP thresholds from sSVD post-processing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Penumbra DT&gt;3s</td>
<td>Infarct core CBF&lt;30%</td>
</tr>
<tr>
<td></td>
<td>Infarct core CBV&lt;55%</td>
<td>Infarct core CBV&lt;55%</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td>99.90%</td>
<td>99.90%</td>
</tr>
<tr>
<td></td>
<td>99.80%</td>
<td>99.70%</td>
</tr>
<tr>
<td><strong>Precision</strong></td>
<td>95.90%</td>
<td>99.30%</td>
</tr>
<tr>
<td></td>
<td>97.80%</td>
<td>98.80%</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>78.59%</td>
<td>79.93%</td>
</tr>
<tr>
<td></td>
<td>81.91%</td>
<td>78.16%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>91.04%</td>
<td>91.24%</td>
</tr>
<tr>
<td></td>
<td>90.10%</td>
<td>90.90%</td>
</tr>
</tbody>
</table>

Performance of the penumbral threshold is derived from patients with 24-hour DWI (no recanalization group), and performance of the infarct-core threshold is derived from patients with acute DWI.

Although we previously showed a delay-corrected algorithm was more accurate in identifying infarct core and penumbra on limited slice CTP [16], in the exploratory analysis we were interested in assessing the performance of the SVD algorithm without delay correction on whole brain perfusion data. For maps generated from standard SVD, Tmax>6s and CBF<25% had minimal volumetric difference to DWI lesion (p>0.05, Figure 3.3c and 3.3d). Tmax>6s and CBF<25% had similar performance to the best thresholds with the delay correction algorithm (DT>3S and CBF<30%) in terms of measuring core and penumbra with
high accuracy (>99%), high precision (95%), good specificity (>90%), and good sensitivity (>78%, Table 3.3).

As much of the original CTP literature used MTT to define penumbra [20], we also explored the performance of MTT in measuring the penumbral lesion on whole brain CTP data. We found that MTT>145%, with or without delay correlation, did not perform as well as DT or Tmax in measuring penumbra low sensitivity <60% and low accuracy <80%). With the ‘best’ MTT>145% threshold, CTP was significantly different to the reference DWI lesion (volumetric difference = 68.99 ± 50.61 ml, p<0.05).

Part 2: Whole-brain versus limited-slice-coverage CTP for measuring ischemic lesions

For slice coverage comparisons, DT>3 s/CBF<30% were applied to define the penumbra/core on CTP. As shown in Figure 3.4, both penumbral and infarct-core volume had a normal distribution across the 32 axial slices. The fitted curve for penumbra and core were $Y = \exp(-0.025X^2 + 0.940X -6.433)$ and $Y = \exp(-0.027X^2 + 1.047X -8.569)$ separately. The two curve parameters had same mean location (around slice 19) and similar standard deviation of slice numbers (4.51 and 4.28 respectively). For penumbra measurement, 95% of values were located within the range of mean±2SD, which was slice 11-28 (90 mm coverage); for infarct core measurement, 95% of values located at the range of slice 11-27 (85 mm coverage). Thus, the ‘tolerance’ interval for penumbra and infarct core was 90 mm and 85 mm respectively.
Figure 3.4 The distribution of ischemic lesion across slices on 320-detector CTP. The distribution fits bell curve (Gaussian distribution). (A) For penumbra distribution, mean value locates at the slice level of 19.14 with standard deviation of 4.5 slices; therefore, 95% values locate at the range of slice 11 to slice 28 (mean±2SD), which equals to 90mm brain coverage. (B) For infarct core distribution, the curve has mean value of 19.14 and standard deviation of 4.28; similarly, 95% values locate at slice 11-27(mean±2SD), which equals to the brain coverage of 85mm. Notice: Penumbra is defined as DT>3s; Infarct core is defined as CBF<30%.
From the lesion distribution curve, we observed that fewer lesions were included as brain coverage decreased (Figure 3.4). The observation was further validated on measuring penumbra in the group of patients with no recanalization, and measuring infarct core in the group of patients with acute DWI. Results were summarized in Table 3.4 and Table 3.5. In predicting both true penumbra and infarct core, the 320-detector coverage had almost perfect accuracy (>99%) and excellent precision (>95%) as well as excellent specificity (>91%) and good sensitivity (>78%). By limiting the brain coverage to 100mm, CTP still had excellent performance with minimal difference to whole-brain coverage (P>0.05). However, by limiting the coverage to 80mm, CTP significantly underestimated the volume of infarct core (volumetric difference of CTP and DWI was -4.81 ± 8.67ml, p<0.05), and resulted in a drop of sensitivity (66.72%) on measuring the penumbra. Further limitation of CTP coverage to 40mm or 20mm resulted in substantial underestimation of both penumbra and infarct core (p<0.05), and dramatic drops in accuracy (<86%) and sensitivity(<49%).
Table 3.4 Lesion volume decreases with the decrease of axial coverage on CTP. The volume of penumbra and infarct core is measured respectively by DT>3s and by CBF<30% on CTP. The penumbra volume is 139.58 ± 88.96 ml with 24-hour DWI measurement in no recanalization group; infarct core is 48.16 ± 60.88 ml with acute DWI measurement.

<table>
<thead>
<tr>
<th>No recanalization group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP coverage</td>
</tr>
<tr>
<td>160mm</td>
</tr>
<tr>
<td>100mm</td>
</tr>
<tr>
<td>80mm</td>
</tr>
<tr>
<td>40mm</td>
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<tr>
<td>20mm</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute DWI subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP coverage</td>
</tr>
<tr>
<td>160mm</td>
</tr>
<tr>
<td>100mm</td>
</tr>
<tr>
<td>80mm</td>
</tr>
<tr>
<td>40mm</td>
</tr>
<tr>
<td>20mm</td>
</tr>
</tbody>
</table>

Lesion volume is summarized by mean ± standard deviation
Table 3.5 In predicting true penumbra and infarct core, performance of CTP decreases with the decrease of brain coverage. Penumbra is defined by DT>3s, and infarct core is defined by CBF<30%. Performance of the penumbral coverage is derived from patients with 24-hour DWI (no recanalization group), and performance of the infarct-core coverage is derived from patients with acute DWI.

<table>
<thead>
<tr>
<th>Penumbra coverage</th>
<th>Accuracy</th>
<th>Precision</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>160mm</td>
<td>99.90%</td>
<td>96.00%</td>
<td>78.59%</td>
<td>91.04%</td>
</tr>
<tr>
<td>100mm</td>
<td>99.90%</td>
<td>96.00%</td>
<td>74.85%</td>
<td>91.39%</td>
</tr>
<tr>
<td>80mm</td>
<td>99.80%</td>
<td>96.00%</td>
<td>66.72%**</td>
<td>91.91%</td>
</tr>
<tr>
<td>40mm</td>
<td>70.30%*</td>
<td>93.50%</td>
<td>39.77%**</td>
<td>94.89%</td>
</tr>
<tr>
<td>20mm</td>
<td>27.70%*</td>
<td>90.80%</td>
<td>20.57%**</td>
<td>97.42%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infarct core coverage</th>
<th>Accuracy</th>
<th>Precision</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>160mm</td>
<td>99.90%</td>
<td>99.10%</td>
<td>79.93%</td>
<td>91.24%</td>
</tr>
<tr>
<td>100mm</td>
<td>99.90%</td>
<td>99.20%</td>
<td>79.89%</td>
<td>91.31%</td>
</tr>
<tr>
<td>80mm</td>
<td>99.50%</td>
<td>99.10%</td>
<td>75.17%</td>
<td>92.02%</td>
</tr>
<tr>
<td>40mm</td>
<td>85.10%</td>
<td>97.60%</td>
<td>48.06%**</td>
<td>94.47%</td>
</tr>
<tr>
<td>20mm</td>
<td>51.00%*</td>
<td>95.40%</td>
<td>25.18%**</td>
<td>96.85%</td>
</tr>
</tbody>
</table>

*low accuracy<75%, **low sensitivity<75%
DISCUSSION

This is the first study to comprehensively assess the thresholds for infarct core and penumbra in hyperacute stroke using whole-brain CTP. Using several different methods, our results indicate that whole brain CTP can measure the ischemic core and penumbra not only accurately and precisely, but also sensitively and specifically. However, the good performance of CTP is dependent on two factors: 1) brain coverage over 90mm and 2) right threshold setting for penumbra and infarct core.

In CTP, dual-perfusion-threshold setting is a common approach to define penumbra and infarct core separately [7], with the upper threshold differentiating normal tissue from penumbra, and with the lower threshold differentiating penumbra from infarct core. However, the recognition for the optimal threshold setting varies across centres [18]. Various time-domain maps, MTT or Tmax or DT, have been reported suitable for setting the upper threshold [15, 20, 24, 25]. The lower threshold has been reported existing on either CBF [15, 26] or CBV [20, 27]. Our results suggest that this variation is, at least partially, due to these previous studies being carried out on CTP data that has limited brain coverage. By repeating these analyses on whole-brain CTP, we have eliminated one source of error. Our whole-brain CTP data confirms that both relative CBF and CBV can accurately define infarct core, and that Tmax and DT, but not MTT, are valid in defining penumbra.

Another source of variation of core and penumbra thresholds in the literature is the different perfusion post-processing algorithms [16]. Our finding—the similar performance between DT (generated from delay-corrected SVD) and Tmax (generated from standard SVD)—disagrees with a commonly accepted theory that delay correlation should lead to perfusion results closer to the true ischemic lesion [28-30]. Instead, we found that between perfusion maps with and without delay correction, the accuracy of detecting ischemic lesions was similar, but
the optimal threshold to achieve the high accuracy was different. With delay correction, a slightly higher threshold of CBF was required for infarct core, which could be explained that CBF threshold is relative to the value of normal tissue that is increased after delay correlation [17, 28, 31]. With delay correction, a lower threshold was required to accurately define penumbra on time-domain maps. Therefore, for standard SVD (sSVD), $T_{max} > 6s/CBF < 25\%$ is recommended for the dual threshold setting; for delay-corrected SVD (dSVD), $DT > 3s/CBF < 30\%$ is recommended.

There are some vocal critics toward the methods used to validate CTP measurement in stroke. Some of the more valid criticisms apply to our study: the use of 24-hour DWI could potentially bring bias to infarct core assessment. The use of 24-hour DWI as infarct core reference assumes that no infarct expansion happens between acute CTP and follow-up DWI. Therefore, only patients with complete recanalization, assessed at 24 hours, were used to define infarct core in this study. However, in reality, recanalization does not necessarily occur immediately and infarct core might expand before recanalization. In that case, 24-hour DWI might overestimate the size of acute infarct core. Realizing the limitation of this method, we introduced a second set of reference standard: acute DWI was used to strength the threshold definition for infarct core on CTP. Both reference standards (acute DWI and 24-hour DWI) resulted in none-significant volumetric difference with CTP infarct core defined by CBF<25-30%. However, we did find acute DWI, compared to 24-hour DWI, had higher agreement with CTP infarct core, lending some weight to the argument that 24-hour DWI is less ideal for defining infarct core. Nonetheless, the volumetric agreement between acute DWI and CTP infarct core was very high across a wide range of infarct volumes (from 0 to 241 mL), which against the criticisms that CTP is not valid to measure ischemic core.

Regarding brain coverage of CTP, we found that 90mm is the minimum requirement to identify the complete extension of penumbra and infarct core in axial direction in cases with
anterior circulation ischemia. According to this finding, current CT scanners can be divided into three groups. The first group, including the 320-detector scanner [32] and 128-detector spiral scanner [33], have coverage above 90mm. Their ability of measuring true ischemic lesions was validated in this study, thus, we recognize this type as whole-brain CTP and recommend it to be applied in clinical practice and in future trials. The second group includes the 256-detector scanner [34], which has coverage of close to 90mm. This coverage extent showed acceptable performance in measuring infarct core, but slightly compromised sensitivity in measuring penumbral lesion. The third group are the older multi-slice CT scanners with coverage well below 90mm. Previous studies [8, 34] found that ischemic lesions were detected incompletely or missed completely by CTP with coverage of 20-40mm. Even with two acquisitions, the 16 detector scanners do not provide adequate coverage. Some 64 detector scanners can cover 80 mm with two acquisitions, which, again is not optimal, but probably acceptable for clinical practice. However, it is important to note that these inferences are made from data is all simulated from our 320-detector CTP results. Currently, we are collecting data from multiple scanners in an international study to further assess the issues regarding thresholds and limited slice CTP coverage. It is also noted that our findings regarding optimal thresholds and required brain coverage are limited to patients with anterior circulation occlusion.

In conclusion, whole-brain CTP can accurately measure both ischemic penumbra and core. It outperforms limited-coverage CTP in this manner. These are important messages for use of CTP in clinical practice.
Figure 3S CTP has better agreement with acute DWI than with 24-hour DWI on measuring infarct core volume. (A) In the group of patients with both CTP and DWI performed acutely (N=25), the two imaging modalities has the concordance correlation coefficient of 0.99 [95% confidence interval, 0.98 to 0.99] on measuring infarct core. (B) In the group of patients with acute CTP and 24-hour DWI data and with complete recanalization at 24 hours (N=45), between the two imaging modalities, concordance correlation coefficient is 0.89 with 95% confidence interval of 0.83 to 0.95. Infarct core is defined by CBF<30% (within DT>3s) on CTP.
Table 3S the subgroup of patients with acute CTP and acute DWI data. Infarct volume on CTP is measured by CBF<30% within DT<3s.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Infarct volume on acute CTP (ml)</th>
<th>Infarct volume on acute DWI (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38.67</td>
<td>43.04</td>
</tr>
<tr>
<td>2</td>
<td>7.48</td>
<td>9.48</td>
</tr>
<tr>
<td>3</td>
<td>1.16</td>
<td>6.37</td>
</tr>
<tr>
<td>4</td>
<td>8.66</td>
<td>9.49</td>
</tr>
<tr>
<td>5</td>
<td>8.66</td>
<td>10.07</td>
</tr>
<tr>
<td>6</td>
<td>104.19</td>
<td>111.60</td>
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<td>7</td>
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<td>8</td>
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<td>31.56</td>
<td>18.41</td>
</tr>
<tr>
<td>10</td>
<td>0.00</td>
<td>0.77</td>
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<td>11</td>
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</tr>
<tr>
<td>12</td>
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<td>25</td>
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REFERENCE


CHAPTER 4:

VALIDATION WHOLE-BRAIN CTP MEASUREMENT FOR REPERFUSION

Introduction: This chapter tests the hypothesis that reperfusion of the ischemic lesion on whole-brain CTP predicts good clinical outcome of ischemic stroke patients. From Chapter 3, Tmax at threshold of 6 seconds has been identified to be the optimal threshold for measuring the extent of ischemic region. In this chapter, reperfusion of the ischemic region defined by Tmax>6s is further tested in terms of its sensitivity and specificity in predicting clinical outcome.

Results of this chapter have been submitted to the journal Stroke. Lin L, Bivard A, Levi CR, Parsons MW. Reperfusion of Tmax predicts good clinical outcome of stroke (STROKE/2015/009565).
PUBLICATION 2: REPERFUSION OF TMAX PREDICTS GOOD CLINICAL OUTCOME OF STROKE

ABSTRACT

Background: Approach for reperfusion quantification varies across studies. In this study, using computed tomography perfusion (CTP) data with whole-brain coverage, we aimed to derive the reperfusion measurement best predicting clinical outcome. Materials and Methods: Two centres, equipped with 320-detector and 256-detector CT scanner respectively, recruited 172 patients in this study. All patients were scanned by multi-model CT within 6 hours of stroke onset and repeated at 24 hours. Reperfusion index was defined by the percentage of the ischemic region resolved from acute CTP to 24-hour CTP. Recanalization was graded by Thrombolysis in Myocardial Infarction (TIMI) scoring system. Logistic regression and receiver operator characteristic (ROC) were performed to assess the sensitivity and specificity of reperfusion and recanalization in predicting good clinical outcome. Good clinical outcome referred to was defined as modified Rankin Score of 0-2 at 90 days. Results: Only with Tmax>6s measurement did reperfusion index result in higher sensitivity and specificity than recanalization in predicting good clinical outcome (ROC area was 0.88 and 0.75 respectively, P<0.01). Reperfusion index defined by Tmax>2s or by MTT>145% had no significant difference to recanalization in predicting clinical outcome (P=0.55 and 0.70 respectively). Patients with successful reperfusion (>61.48%) in Tmax>6s region, compared to patients with no successful reperfusion (≤61.48%), had the odds of having good clinical outcome increase by almost 28 times (odds ratio=27.9 [10.1, 77.1], P<0.01). Conclusion: Reperfusion of the ischemic region defined by Tmax>6s is optimally to predict clinical outcome of ischemic stroke.
INTRODUCTION

Reperfusion refers to the restoration of blood flow to ischemic cerebral tissue. Normal brain function requires constant blood perfusion to capillaries, supplying oxygen and other essential nutrition [1]. During ischemic stroke, the perfusion is blocked by an occlusion in upstream cerebral artery, resulting in ischemic region with low blood flow [2]. If the ischemic region regains blood flow, either from the recanalization of upstream occluded artery or from collateral flow [3, 4], reperfusion occurs and the ischemic area can be salvaged from infarction.

Reperfusion of the ischemic region and recanalization of occluded artery have been reported predicting good outcome of stroke in separate studies [5, 6]. Recent studies start to focus on the comparison of recanalization and reperfusion and conclude that reperfusion is superior to recanalization in predicting tissue outcome and clinical outcome of ischemic stroke [7-9]. However, before applying the conclusion in clinical setting, two issues of previous reperfusion studies need to be addressed. The first issue is the variation of reperfusion measurement. Across research groups, different perfusion parameters have been used to quantify reperfusion, varying from Tmax>2s [8, 10, 11], Tmax>6s [7, 12, 13], to MTT>145% [9, 14, 15]. From our past study, the accuracy of defining ischemic region varies with different perfusion parameter [16, 17]. Thus, it is reasonable to assume the reperfusion calculation would vary across perfusion measurement, which might effects the sensitivity and specificity of reperfusion in predicting outcome of stroke. The other issue is the inaccuracy of reperfusion calculation by limited-coverage computed tomography perfusion (CTP). Previous reperfusion studies were carried out on CTP with limited brain coverage (16- or 64-slice scanner), which provides incomplete cerebral perfusion information in axial direction [18, 19]. Thus, the assessment of reperfusion from acute to follow-up CTP might be underestimated.
In the present study, CTP with whole-brain coverage was used to ensure the accuracy of reperfusion measurement. With the whole brain data, we compared different reperfusion measurements and aimed to derive the optimal one with highest sensitivity and specificity in predicting clinical outcome.

**METHODS**

**Patient**

Stroke patients were recruited in two centres, John hunter hospital (Newcastle, Australia) and Huashan Hospital (Shanghai, China). All patients were scanned by multi-model computed tomography (CT) within 6 hours of stroke onset and repeated by multi-model CT at 24-48 hour. Patients eligible for thrombolysis were treated according to standard institutional guidelines. Patients with a basilar occlusion or haemorrhage on follow-up imaging were excluded from this study. We also excluded patients with severe motion artefact and truncated AIF curve on CTP. The study was approved by the ethical committee of both hospitals.

**CT acquisition**

In John Hunter Hospital, multi-modal CT images were acquired on 320-detector Toshiba scanner (Toshiba Aquilion ONE; Toshiba, Tokyo, Japan). The standard multi-modal CT protocol included non-contrast CT (NCCT), CT angiography (CTA), and CT perfusion (CTP). The intracranial CTA and CTP were acquired simultaneously. Imagine acquisition commenced seven seconds after non-ionic iodinated contrast injection into an antecubital vein (40 ml, 6ml/s; Bayer HealthCare, Berlin, Germany) and lasted for 65 seconds with 19 time frames acquired. The whole acquisition process was divided into three phases: phase one, 1 frame was generated (80kV, 310mA) as baseline; phase two, 13 frames were generated at
rate of one frame per second (80kV, 150/300mA); phase three, 5 frames were generated at rate of one frame per five seconds (80kV, 150mA). Spatially, one gantry rotation resulted in 320 slices with the thickness of 0.5mm, which covered 160mm on axial direction. FOV was 220×220mm, and Matrix was 512×512.

In Hua Shan Hospital, multi-modal CT images were acquired on 256-detector scanner (Philips iCT-256; Philips, German). NCCT was acquired first, followed by CTP with Intracranial CTA being reconstructed from the CTP raw data. CTP data were acquired by “shuttle mode” with 4 seconds interval between shuttles. The acquisition lasted for 60 seconds, resulted in 13 time frames (80kV, 375 mA). Spatially, 125mm was covered on axial direction, by 25 slices with 5mm thickness. FOV was 220×220mm, and Matrix was 512×512. Comparison of the CTP acquisition between the two hospitals was summarized in Table 4.1.

**CTP post-processing**

After acquisition, CTP data was processed by commercial software MIStar (Apollo Medical Imaging Technology, Melbourne, Victoria, Australia). The software allows selection of various algorithms to generate perfusion maps, among which, singular value decomposition (SVD) is the common approach [16, 17]. Our study selected two types of SVD, standard SVD (sSVD) and delay-corrected SVD (dSVD). sSVD generated four perfusion maps as cerebral blood flow (CBF), cerebral blood volume (CBV), mean time transport (MTT), and time to peak of the residual function (Tmax); dSVD generated delay-corrected CBF (dCBF), delay-corrected CBV (dCBV), delay-corrected MTT (dMTT), and delay-corrected Tmax (DT).

**CTP analysis**

*Measuring Perfusion of the None-ischemic hemisphere*
From literatures [7, 9], reperfusion has been measured by the perfusion change between acute CTP and 24-hour CTP. However, not all perfusion change is caused by the reperfusion of blood flow from acute CTP and 24-hour CTP. It could also be caused by the systematic bias of perfusion measurement between the two CTP modalities. If the systematic bias was significant, it would lower the accuracy of reperfusion measurement. This has been ignored by previous studies. In this study, the first step of imaging analysis was to test the existence of such bias on non-ischemic hemisphere.

CTP data was segmented to ischemic and none-ischemic hemisphere on MIStar software. For each patient, two regions of interest (ROI) were drawn on CTP: ROI1 covered the none-ischemic hemisphere of acute CTP and ROI2 covered the none-ischemic hemisphere of 24-hour CTP. Absolute CBF (dCBF), CBV (dCBV), MTT (dMTT), and Tmax (DT) were calculated for ROI1 and ROI2 separately. Then, difference of ROI1 and ROI2 was assessed on measuring perfusion value of the same parameter. Perfusion parameter with significant difference was considered unsuitable for reperfusion quantification in following analysis.

**Quantifying Reperfusion of the ischemic Hemisphere**

Reperfusion measured the reduction of ischemic lesion from acute to 24-hour CTP scans, which was quantified by an index in the following equation:

$$\text{Reperfusion index} = \frac{(\text{Ischemic region}_{\text{acute CTP}}) - (\text{Ischmeic region}_{24h\ CTP})}{(\text{Ischemic region}_{\text{acute CTP}})} \times 100$$

On CTP, Ischemic region had one of the following changes as deceased CBF (dCBF), decreased CBV (dCBV), prolonged MTT (dMTT), and prolonged Tmax (DT). Setting threshold to the perfusion maps quantified ischemic region (Figure 4.1). In this study, a wide range of maps and thresholds were covered to assess the variation of reperfusion index across perfusion measurements (Figure 4.1). Threshold range for CBF (dCBF) and CBV (dCBV)
was 0-100% with 5% increments; for MTT (dMTT), it was 100-200% with 5% increment; for Tmax (DT), the range was 0-10 seconds with 0.5 seconds increment. This assessment included previously reported measurements of reperfusion index such as Tmax>2s [10, 11], Tmax>6s [12, 13], and MTT>145% [14, 15]. Although reperfusion has mainly been quantified by the time-domain perfusion parameters, CBF<50% and CBV<80% were also used in a recent reperfusion study [7].

Figure 4.1 Threshold setting on perfusion maps. Each threshold corresponds to one ischemic region on acute CTP and to one reperfusion index from acute CTP to 24-hour CTP. Perfusion maps are generated by standard SVD.
Recanalization classification

Recanalization status was graded on 24-hour CTA by evaluating the restoration of the previously occluded vessel with Thrombolysis in Myocardial Infarction (TIMI) scoring system. A TIMI score of 0 was considered as no recanalization, score of 1-2 was considered as partial recanalization, and score of 3 was complete recanalization. Patients with TIMI score of 3 were also considered having successful recanalization. The recanalization classification was performed by M.P. who was blinded to the reperfusion assessment (performed by L.L.). No inter-observer agreement was performed for the recanalization analysis.

Clinical outcome

Modified Rankin Score (mRS) on 90 days was the primary clinical outcome, according to which, patients were divided into two types: those with good clinical outcome (mRS≤2), and those with poor clinical outcome (mRS>2).

Statistical analysis

Patient characteristics were summarized by median and IQR; the differences between patient populations in the Chinese and Australian sites were assessed by Wilcoxon test. Perfusion values in the ROI of none-ischemic hemisphere were summarized by mean and standard deviation (SD); the differences of acute CTP and 24h CTP perfusion values were assessed by paired t-test.

Logistic regression was performed to assess the significance of reperfusion index or recanalization in predicting good clinical outcome. For recanalization variable, a simple logistic regression was performed. For reperfusion index, two types of logistic regression were performed: 1) the simple logistic regression measured the predictive power of individual
reperfusion index corresponding to one perfusion threshold; 2) The longitudinal logistic regression with threshold level set as longitudinal unit, measured the mean predictive power of reperfusion index on each perfusion map. Each perfusion map consisted of 20 threshold levels that fulfilled the requirements of longitudinal data structure (Figure 4.1).

Receiver Operator Characteristic (ROC) was performed after logistic regression, measuring the sensitivity and specificity of reperfusion index or recanalization in predicting clinical outcome. Then ROC comparison was performed to compare the area under ROC curve of reperfusion index and recanalization. ROC comparison was also carried out among various reperfusion index measurements to derive the optimal one with the largest area under ROC curve. After ROC analysis, the cut-off point for successful reperfusion was derived on with highest Yuden Index. All the analysis was done on STATA 13.0, with confidence interval (CI) set at 95%, and significant level set at 0.05.

RESULTS

Patients

Between June 2011 and April 2014, 75 patients were recruited at the John Hunter Hospital, with 15 being excluded (3 due to motion artefact of CTP images, 3 due to truncation of AIF curve, 4 due to the lack of ischemic lesion on acute CTP, 3 due to the ischemic lesion existing on cerebellum or brain stem, 2 patient due to haemorrhagic transformation on 24-hour NCCT). In Huashan Hospital, 97 patients were recruited, of which 41 were excluded from the analysis (5 due to motion artefact on CTP images, 3 due to truncation of AIF curve, 29 due to the lack of ischemic lesion on acute CTP, 3 due to the existence of ischemic lesion on cerebellum or brain stem, 1 due to haemorrhagic transformation on 24-hour NCCT). Overall 116 patients were eligible for study analysis. The characteristic of the patients was shown in
Table 4.1. Between the two sites, significant difference exists on age (P<0.01), baseline NIHSS (P=0.04), and time from stroke onset to acute CTP (p<0.01).

<table>
<thead>
<tr>
<th>Table 4.1 Patient characteristics and image features of the two sites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Patients characteristic</strong></td>
</tr>
<tr>
<td>Age (Median ± IQR, year)</td>
</tr>
<tr>
<td>Baseline NIHSS (Median ± IQR)</td>
</tr>
<tr>
<td>24-hour NIHSS (Median ± IQR)</td>
</tr>
<tr>
<td>90-day mRS (Median ± IQR)</td>
</tr>
<tr>
<td>Good clinical outcome (mRS≤2, %)</td>
</tr>
<tr>
<td>Acute ischemic lesion (Median ± IQR, ml)</td>
</tr>
<tr>
<td>Acute infarct core (Median ± IQR, ml)</td>
</tr>
<tr>
<td>Final Infarct volume (Median ± IQR, ml)</td>
</tr>
<tr>
<td>Thrombolytic rate (%)</td>
</tr>
<tr>
<td>Time from stroke onset to thrombolysis (Median ± IQR, hours)</td>
</tr>
<tr>
<td>Time from stroke onset to acute CTP (Median ± IQR, hours)</td>
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<tr>
<td>Time from acute CTP to follow-up CTP (Median ± IQR, hours)</td>
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<table>
<thead>
<tr>
<th><strong>B. CTP features</strong></th>
<th><strong>JHH site</strong></th>
<th><strong>Huashan site</strong></th>
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</thead>
<tbody>
<tr>
<td>Scanner type</td>
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<td>256-detector</td>
</tr>
<tr>
<td>Scanning mode</td>
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<td>Shuttle</td>
</tr>
<tr>
<td>Axial coverage (mm)</td>
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<td>125</td>
</tr>
<tr>
<td>Acquisition time (seconds)</td>
<td>67</td>
<td>57</td>
</tr>
<tr>
<td>Post-processing software</td>
<td>MIStar</td>
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</tr>
<tr>
<td>Processing algorithm</td>
<td>sSVD/dSVD</td>
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</tr>
<tr>
<td>AIF selection</td>
<td>ACA</td>
<td>ACA</td>
</tr>
</tbody>
</table>

NIHSS indicates The National Institutes of Health Stroke Scale; mRS indicates modified Rankin Scale; acute ischemic lesion is defined by $T_{max}>6S$ and acute infarct core is defined by $CBF<25\%$ within $T_{max}>6S$ region; final infarct volume is the lesion on 24-hour NCCT.
Cerebral perfusion on acute CTP and 24-hour CTP

Between acute CTP and 24-hour CTP, no significant difference was found in the perfusion values of the non-ischemic hemisphere when using the same post-processing algorithm (Table 4.2). Comparing acute CTP and 24-hour generated from sSVD, P value was 0.86 for CBF, 0.66 for CBV, 0.42 for MTT, and 0.54 for Tmax. Comparing acute CTP and 24-hour generated from dSVD, P value was 0.80 for dCBF, 0.61 for dCBV, 0.42 for dMTT, and 0.44 for DT.

Table 4.2 Cerebral perfusion values of the none-ischemic hemisphere

<table>
<thead>
<tr>
<th></th>
<th>Perfusion maps from sSVD</th>
<th>Perfusion maps from dSVD</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Acute CTP</td>
<td>24h CTP</td>
</tr>
<tr>
<td></td>
<td>(Mean ±SD)</td>
<td>(Mean ±SD)</td>
</tr>
<tr>
<td>CBF (ml/100g/min)</td>
<td>29.63 ± 6.34</td>
<td>29.52 ± 6.88</td>
</tr>
<tr>
<td>CBV (ml/100g)</td>
<td>2.70 ± 0.40</td>
<td>2.72 ± 0.48</td>
</tr>
<tr>
<td>MTT (second)</td>
<td>5.47 ± 0.60</td>
<td>5.52 ± 0.63</td>
</tr>
<tr>
<td>Tmax (second)</td>
<td>0.45 ± 0.39</td>
<td>0.47 ± 0.30</td>
</tr>
<tr>
<td>dCBF (ml/100g/min)</td>
<td>30.08 ± 6.61</td>
<td>29.92 ± 6.81</td>
</tr>
<tr>
<td>dCBV (ml/100g)</td>
<td>2.71 ± 0.41</td>
<td>2.73 ± 0.48</td>
</tr>
<tr>
<td>dMTT (second)</td>
<td>5.37 ± 0.66</td>
<td>5.42 ± 0.66</td>
</tr>
<tr>
<td>DT(second)</td>
<td>0.28 ± 0.16</td>
<td>0.30 ± 0.17</td>
</tr>
</tbody>
</table>

For both acute CTP and 24h CTP, perfusion values are generated from standard SVD.
Part one: reperfusion index on maps post-processed by sSVD

Variation of reperfusion measurements among perfusion maps

In predicting good clinical outcome, the significance of reperfusion index differed among perfusion maps. For reperfusion index defined by Tmax, MTT, and CBF thresholds, a higher value indicated increased odds of having good clinical outcome (lower confidence interval of odds ratio>1, P<0.05). However a reperfusion index defined by CBV did not predict good patient outcome (OR=1.00 [0.99, 11], P=0.18).

Reperfusion indexes of Tmax, MTT, and CBF were further compared in terms of the sensitivity and specificity at predicting good clinical outcome (Figure 4.2). Reperfusion of Tmax ischemic regions predicted good clinical outcome with largest ROC area (mean ROC=0.80, 95% CI [0.79, 0.82]), followed by MTT (mean ROC=0.75, 95% CI [0.73, 0.77] and CBF (mean ROC=0.64, 95% CI [0.62, 0.66]. Therefore, to predict outcome of ischemic stroke patients, reperfusion of the ischemic regions on Tmax was superior to that on other perfusion maps (P<0.01 for ROC comparison).

Variation of reperfusion index across perfusion thresholds

Within Tmax map, different threshold setting resulted in different ischemic region (Figure 1). Reperfusion of the different ischemic region varied at predicting good clinical outcome (ROC area of reperfusion index varied from 0.67 [0.57, 0.77] to 0.88 [0.81, 0.94], P<0.01 for ROC comparison). Threshold setting of 2 seconds and 6 seconds, both of which have been used to quantify reperfusion in previous study, was then compared (Figure 4.3). Reperfusion of the ischemic region of Tmax>6s, compared to reperfusion of ischemic region of Tmax>2s, had
significantly higher sensitivity and specificity in predicating good clinical outcome (ROC area was 0.88 [0.81, 0.94] and 0.71 [0.62, 0.81] respectively, P<0.01 for ROC comparison).

Figure 4.2 Variation of reperfusion index among perfusion maps. Mean ROC area of each map is derived by averaging the roc curve of 20 threshold regions of the map. Comparing the

Figure 4.2 Variation of reperfusion index among perfusion maps. Mean ROC area of each map is derived by averaging the roc curve of 20 threshold regions of the map. Comparing the
four perfusion maps, Tmax has the largest area under ROC curve in predicting good clinical outcome. Perfusion maps are generated by standard SVD.

Superiority of reperfusion to recanalization in predicting clinical outcome

Among previous published reperfusion measurement, only with a threshold of Tmax>6s did the reperfusion index result in higher sensitivity and specificity than recanalization in predicting good clinical outcome (Figure 4.3). The ROC area of reperfusion was significantly higher than that of recanalization (ROC area was 0.88 [0.81, 0.94] and 0.75 [0.66, 0.83] respectively, P<0.01 for ROC comaprison). Rerfusion index defined by Tmax>2s and MTT>145%, on the other hand, had no significant difference to recanalization in predicting clinical outcome (P>0.05 for ROC comaprison, Figure 4.3). A reperfusion index defined by CBV<80% or CBF<50%, was worse than recanalization in predicting clinical outcome with significantly lower ROC area (the ROC area of CBV<85% and CBF<40% was 0.65 [0.55, 0.75] and 0.46 [0.35, 0.57] respectively).

For reperfusion index measured by the Tmax>6s region, the optimal index that resulted in the highest Youden Index was 61.48% (Youden Index=66.83%). Successful reperfusion of the Tmax>6s region (>61.48%) had the sensitivity of 88.57% and specificity of 78.26% in predicting good clinical outcome. In comparison, successful recanalization (TIMI=3) had much lower sensitivity (70%) in predicting good clinical outcome for the same group of patients. Of the 70 patients with good clinical outcome in this study, 62 had successful reperfusion, whereas only 49 have successful recanalization (Figure 4.4). Patients with successful reperfusion (>61.48%), comparing to those with unsuccessful reperfusion (≤61.48%), had almost 28 times higher chance of having a good clinical outcome (odds ratio=27.9 [10.1, 77.1], P<0.01). Patients with successful recanalization, comparing to those
with no successful recanalization, only increased the odds of having good clinical outcome by around 6 times (OR=6.61 [2.87, 15.21], P<0.01).

Figure 4.3 Ischemic region of Tmax>6s has the best performance in predicting good clinical outcome. Reperfusion index measured by Tmax>6s, compared to Tmax>2s and MTT>145%, has the largest area under ROC curve in predicting good clinical outcome (90-day mRS<2). Only with Tmax>6s measurement, reperfusion index results in larger ROC area than recanalization. The ROC curve of reperfusion index defined by MTT>145% or Tmax>2s is similar to that of recanalization. Perfusion maps are generated from standard SVD.
Figure 4.4 A stroke case showing reperfusion is better than recanalization in predicting clinical outcome. Female, 31, admitted to John Hunter Hospital with baseline NIHSS 10. Acute brain scanning shows occlusion of middle cerebral artery (MCA, green arrow) on CTA and corresponding ischemic region on CTP (region defined by $T_{\text{max}}>6s$, generated from standard SVD). 24-hour scanning shows the persistence of occlusion on MCA (blue arrow), but the reduction of ischemic region on CTP. The patient has no occlusion recanalization but achieves 81.05% reperfusion. The good reperfusion explains the lack of infarct expansion from acute DWI to 24-hour DWI. It also explains her clinical improvement at 24 hours (NIHSS=4) and good clinical outcome at 90 days (mRS=1).
Comparison of reperfusion index between the two sites

Above analysis was performed using data from the two hospitals. For each site, reperfusion of Tmax>6s region predicted good clinical outcome significantly (p<0.01). The reperfusion index of Tmax>6s resulted in similar area under ROC curve for the two sites (AUC=0.89 [0.81, 0.98] and 0.87 [0.76, 0.98] respectively), each of which was significantly larger than the ROC curve of the recanalization at predicting good clinical outcome (P=0.04 and 0.02 for each site).

Part two: Comparison of the reperfusion index from SSVD and that from dSVD

For Tmax generated from dSVD (DT), a threshold setting of 3 seconds measured the reperfusion index that predicted good clinical outcome with the highest ROC curve (ROC area=0.87 [0.80, 0.94], P<0.01). Reperfusion index of the DT>3s region (dSVD), compared to reperfusion index of the Tmax>6s region (sSVD), had almost the same ROC curve in predicting good clinical outcome (P=0.88 for ROC comparison, Figure 4.5). Moreover, DT>3s and Tmax>6s region had similar cut-off point for optimal reperfusion index (64.1% vs. 61.48%). Successful reperfusion of the DT>3s region (over 61.48%) had 84.29% sensitivity and 73.91% specific in predicting good clinical outcome.
Figure 4.5 ROC Comparison of the reperfusion index generated from DT>3s and Tmax>6s. Reperfusion index defined by DT>3s (from dSVD) and by Tmax>6s (from sSVD) has similar ROC curve in predicting good clinical outcome (mRS≤2 at 90 days).
DISCUSSION

Finding of this study challenges the statement that reperfusion is better than recanalization in predicting good clinical outcome of ischemic stroke. The statement is only true under the condition that reperfusion index is defined by the change of ischemic region of Tmax>6s (or DT>3s).

Three different approaches have been used to define reperfusion in previous stroke trials: reperfusion of the Tmax>2s region has been used in EPITHET [10] and DEFFUSE [11], reperfusion of the Tmax>6s region has been used in DEFFUSE-2 [13] and EXTEND [12], and reperfusion of the MTT>145% region has been used in DIAS [14] and TASTE [15]. Of the three approaches, our finding supports the use Tmax>6s region for future stroke trials, since its reperfusion has the highest sensitivity and specificity in predicting good clinical outcome. The superior performance of Tmax>6s over Tmax>2s could be explained by previous findings that threshold setting of 6 seconds on Tmax delineated the ischemic region accurately [20-23], whereas 2 second of Tmax overestimated the ischemic region by including partial benign oligemia [20]. Benign oligemia is the region where brain tissues experience mild hypoperfusion but the hypoperfusion tissues do not contribute to clinical symptoms [24]. Therefore, reperfusion of this region does not improve clinical outcome, which explains the lower sensitivity of reperfusion index defined by Tmax>2s in predicting good clinical outcome. Similarly, MTT with the threshold of 145% has been found in our previous study (Chapter 3) overestimating the ischemic region. Reperfusion of the MTT>145% region, therefore, includes tissues with benign oligemia. This explains its less ideal performance in predicting good clinical outcome.

This study also finds poor performance of the reperfusion index when the ischemic region is defined by CBF or CBV threshold. 1) The poor performance of CBF can be explained by the
partial volume effect (PVE). In this study, AIF was derived from anterior cerebral artery which is a relative small artery. AIF measurement from the small artery would be underestimated because of PVE [25], which would then affect the CBF calculation [26]. More critically, since the PVE changes from one patient to another, it could increase the inter-subject variance in CBF measurement. The inter-subject variance indicates that the CBF threshold might be accurate in delineating ischemic region in one patient but not so in another. Therefore, reperfusion the ischemic region defined by any CBF threshold has low sensitivity and specificity in predicting good clinical outcome. 2) The PVE also effects the calculation of CBV. However, the main factor that contributes to the poor performance of CBV is that the CBV value can be increased, normal, or decreased in cerebral ischemic tissues [27], which make it very difficult to differentiate the ischemic region to none-ischemic region by individual CBV threshold. This is why reperfusion of the CBV region has no predictive power for good clinical outcome in this study.

Delay effect on the measurement of reperfusion index has also been assessed in present study. Delay effect refers to the delay time between the contrast bolus arriving at the feeding artery and arriving at the brain, which has been reported to overestimate Tmax value [28]. In our previous study (Chapter 3), delay correction has been proved to change the optimal threshold for ischemic region. Threshold of 3 seconds on delay-corrected Tmax (DT) has been reported to be as accurate as 6 seconds on standardized Tmax in delineating ischemic region. Present study agrees with the finding by showing that reperfusion of the DT>3s region has the same the sensitivity and specificity to reperfusion of the Tmax>6s region in predicting good clinical outcome.

The advantage of present study is using whole-brain CTP to calculate reperfusion index. In previous studies [7-9], reperfusion was assessed with limited-slice CTP that covers 20-40mm on the axial plain. The limited coverage may lead to biased calculation of the reperfusion
index: as the brain coverage reduces, the full extent of the ischemic lesion is incompletely detected or even missed. Subsequently, reperfusion of the ischemic region would be overestimated if the ischemic lesion was incompletely detected on acute CTP but underestimated if the ischemic lesion was incompletely detected on 24-hour CTP. According to our previous finding (Chapter 3), brain coverage over 90mm is the minimal requirement to detect the whole extent of ischemic region. In this study, the two sites both use scanners that fulfil the coverage requirement, one has brain coverage of 160mm and the other one has the coverage of 125mm. Therefore, the measurement error due to limitation of brain coverage has been avoided in this study. Moreover, according to the previous finding (Chapter 3), the difference in delineating ischemic region is non-significant among CTP scanners that are over 90mm coverage. It explains why the two scanners in this study, 125mm coverage and 160mm coverage respectively, have no difference in measuring reperfusion index of the ischemic region.

Main limitation of this study is that it was carried out on a highly selected group of patients by excluding posterior circulation occlusion. Thus, optimal reperfusion index derived from this study cannot be applied to stroke patients with posterior circulation occlusion. Moreover, the thrombolytic rate is very high in this study since patients with thrombolysis were more likely to undergo perfusion imaging at 24 hours. Thus, patients in this study do not represent the whole stroke population; they are more representative for patients eligible for thrombolytic treatment.

In summary, this is not the first study comparing reperfusion and recanalization after ischemic stroke. However, our finding highlights the importance of selecting the right perfusion map and threshold to define reperfusion. Only with the ischemic region defined by Tmax>6s (or DT>3s), does reperfusion of the ischemic region outperform recanalization of the occluded artery in predicting good clinical outcome. The superior performance of
reperfusion can explained that the Tmax>6s (or DT>3s) region can still be resolved in the absence of recanalization. Reperfusion measures the restoration of blood flow to the ischemic region that comes from two sources: recanalization of the occluded artery and collateral flow. In patient with no recanalization, good clinical outcome may still be achieved from the restoration of blood flow from collaterals. The contribution of collateral flow needs further study.

**REFERENCE**


CHAPTER 5:

COMPARISON OF CTP AND MRP MEASUREMENTS IN ACUTE ISCHEMIC STROKE

Introduction: This chapter tests the hypothesis that whole-brain CTP is as good as MRP in quantifying the ischemic region and providing treatment guidance. From Chapter 3 and Chapter 4, Tmax>6s has been identified as optimal in defining extent of the ischemic region and in quantifying reperfusion index. This chapter assesses the agreement between CTP and MRP in identifying ischemic region defined by Tmax>6s. Reperfusion of the ischemic region defined by Tmax>6s across the two perfusion modalities is also assessed.

PUBLICATION 3: COMPARISON OF CT AND MR PERFUSION MEASUREMENTS IN ACUTE ISCHEMIC STROKE: A BACK-TO-BACK QUANTITATIVE ANALYSIS

ABSTRACT

Background and Purpose: MR perfusion (MRP), and CT perfusion (CTP), are being increasingly applied in acute stroke trials and clinical practice, yet the comparability of their perfusion values is not well validated. The aim of this study was to validate the comparability of CTP and MRP measures. Methods: A three step approach was used. Step 1 was a derivation step where we analyzed 45 acute ischemic stroke patients who had both CTP and MRP performed within two hours of each other and within nine hours of stroke onset. In this step, we derived the optimal perfusion map with the least difference between MRP and CTP. In step 2, the optimal map was validated on whole-brain perfusion data of 15 patients. Step 3 was to apply the optimal perfusion map to define cross-modality reperfusion from acute CTP to 24-hour MRP in 45 patients, and, in turn, to assess how accurately this predicted 3-month clinical outcome. Results: Among eight different perfusion maps included in this study, Tmax was the only one with a non-significant difference between CTP and MRP in delineating perfusion defects. This was validated on whole-brain perfusion data showing high concordance of Tmax between the two modalities (Lin’s concordance correlation coefficient > 0.91); the best concordance was at 6 seconds. At Tmax>6s threshold, MRP and CTP reached substantial agreement in mismatch classification (Kappa>0.61). Cross-modality reperfusion calculated by Tmax>6s strongly predicted good functional outcome at 3 months (AUC=0.979, P<0.05). Conclusion: MRP and CTP can be used interchangeably if one uses Tmax measurement.
INTRODUCTION

Magnetic resonance perfusion (MRP) imaging has been used in several past and current clinical trials [1, 2]. The role of MRP is to triage patients for reperfusion treatment by quantifying acute ischemic lesion and classifying mismatch pattern. More recently, computed tomography perfusion (CTP) has been applied in a similar manner [3, 4]. In the interest of timely recruitment, a number of studies now include both MRP and CTP in their protocols [5, 6]. However, in terms of triaging patients, it is unclear whether the use of same criterion is appropriate across the two imaging modalities.

In clinical practice, MRP and CTP are also being increasingly used not only to triage patients but also to assess the success of reperfusion treatment [7]. In many centers, stroke patients often receive CTP acutely, since it is more rapidly accessible; then after treatment, MRI (including MRP) might be the preferred option to avoid additional radiation and to provide maximum pathophysiologic information. In this situation, success of reperfusion therapy is assessed by comparing perfusion change across the two modalities. Assessment of cross-modality reperfusion seems a common-sense approach for clinicians, but its accuracy has not been studied.

In summary, to properly combine the use of MRP and CTP in the above roles, the two imaging modalities are assumed to be interchangeable. The comparability of MRP and CTP has been shown in our previous study [8], but it was restricted to one single perfusion threshold and limited brain coverage data. In current study, we are going to compare the two modalities across a broad range of thresholds and on whole-brain data. Ultimately, we aim to validate that MRP and CTP measurement have strong enough agreement to be used
interchangeably in triaging patient for acute reperfusion therapy and in assessing subsequent reperfusion.

METHODS

Study design:

The study comprised three steps. Step 1 was a derivation step, where a wide range of perfusion parameters and thresholds were analyzed to identify the perfusion measure with the least volumetric difference between CTP and MRP. Step 2 and Step 3 were validation steps on whole-brain data. Step 2 was to test the agreement of acute CTP and acute MRP in detecting mismatch pattern to select patients for treatment. Step 3 was to test the accuracy of reperfusion from acute CTP to 24-hour MRP to predict clinical outcome.

Patients

We retrospectively analyzed the patient database of John Hunter Hospital from 2005 to 2013, and selected patients multi-modal CT (NCCT+CTA+CTP) done within 9 hour of stroke onset. All patients had an acute neurological deficit consistent with ischaemic stroke on middle cerebral artery (MCA), and received intravenous t-PA if they were clinically eligible (otherwise they received standard care). Then, the selected patients were divided into three groups corresponding to each step analysis. For the agreement analysis (Step 1 and Step 2), patients were selected with both CT and MR (DWI+MRP+MRA) performed within 9 hours of stroke onset and within 2 hours of each other; then, the group of patients with 16-slice CTP were assigned to Step 1 analysis and the group of patients with 320-slice CTP were assigned to Step 2 analysis. In both groups, patients with evidence of any recanalization between acute CTA and acute MRA were excluded. For the reperfusion analysis (Step 3), patients with MR
scanned 24-48 hours after CT were selected. The data collection and analysis were approved by the institutional ethics committee.

**CTP acquisition**

For patients admitted before 2010, CTP images were acquired on 16-slice Philips scanner (Philips Mx8000; Philips, Cleveland, OH, USA). The image scanning commenced 4 seconds after intravenous injection (40 ml, injected at 5ml/s) of non-ionic iodinated contrast (Ultravist 370; Bayer HealthCare, Berlin, Germany). It lasted for 60 seconds, with acquisition of one image per second per slice. The acquisition parameters were 90 kV, 170 mA, Field of View (FOV) 210×210mm, and Matrix 512×512. The 60-second series had brain coverage of 24mm, which consisted two adjacent 12mm axial slices.

For patients admitted from 2010 to 2013, CTP images were derived from 320-slice Toshiba scanner (Toshiba Aquilion ONE; Toshiba, Tokyo, Japan). The scanner had an axial coverage of 160mm, generating 320 slices with the thickness of 0.5mm by one gantry rotation. Image scanning started 7 seconds after intravenous injection (40 ml, injected at 6ml/s) of non-ionic iodinated contrast (Ultravist 370; Bayer HealthCare, Berlin, Germany). It lasted for 60 seconds, acquiring 19 images per slice. The whole acquisition process was divided into three phases: phase one, 1 image was generated (80kV, 310mA) as a mask for all subsequent volumes; phase two, 13 images were generated at rate of one image per second (80kV, 150/300mA); phase three, 5 images were generated at rate of one image per five seconds (80kV, 150mA). For all three phases, FOV was 220×220mm, and Matrix was 512×512.

**MRP acquisition**

MRP was performed on a 1.5-Tesla scanner (Siemens Avanto, Erlangen, Germany). It was using dynamic susceptibility contrast technique and gradient-echo echo-planar imaging
technique (GE-EPI). Following a bolus of gadolinium contrast (Magnevist; Bayer HealthCare, Berlin, Germany) into the antecubital vein (0.2mmol/kg, injected at speed of 5ml/s), perfusion image was obtained with acquisition parameters as follows: TR 1400 msec, TE 30 msec, Flip 90, FOV 230×230mm, and Matrix 128×128. The scanning lasted for 60 seconds, resulting in 40 images per slice. A total 19 slices were obtained with the thickness of 5mm, and with a slice gap of 1.5mm.

**Perfusion image post-processing**

CTP and MRP data were processed by the same commercial software MIStar (Apollo Medical Imaging Technology, Melbourne, VIC., Australia) [9, 10]. Details of MIStar can be found in the following links [http://www.apollomit.com/](http://www.apollomit.com/). In summary, the software runs on all sorts of consoles from different manufacturers, and provides a broad choice of processing algorithm. In this study, two algorithms were selected. Those were standard singular value decomposition (sSVD) and delay-corrected singular value decomposition (dSVD) [11, 12]. From sSVD, we generated four perfusion maps: cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak of the residual function (Tmax). From dSVD, we generate delayed corrected CBF, delay-corrected CBV, delay-corrected MTT, and delay-corrected Tmax (also known as delay time, DT). For Simplify following analysis, maps from dSVD were marked as BF1, CBV1, MTT1, and DT; maps from sSVD were labeled as CBF2, CBV2, MTT2, and Tmax (Fig.S1).

To improve the comparability of the two modalities, same post-processing protocol was used for MRP and CTP. To be more specific: (1) the same deconvolution model was set to generate perfusion maps; (2) the same artery (anterior cerebral artery) was selected as the arterial input function (AIF); and (3) the same approaches were applied to remove noise from perfusion maps. Regarding noise removal, following two approaches were applied; firstly, the
software automatically detected voxels without clear contrast peak and these voxels were allocated with zero perfusion value of CBF/CBV and maximum perfusion value of MTT/Tmax/DT; secondly, the Gaussian smoothing was applied manually (sigma=0.5, kernel size =3×3) to all maps.

**Imaging and statistical analysis**

*Step 1: Comparison of MRP and CTP on two perfusion-measurement levels*

By setting perfusion thresholds, regions with hypoperfusion were delineated on acute CTP and concurrent MRP separately. Hypoperfusion refers to the ischemic area with lower CBF/CBV, and prolonged MTT/DT/Tmax. To include most of the definitions for ischemia, a wide range of thresholds were covered in this study (Figure 5.1). For CBF1, CBF2, CBV1, and CBV2, the threshold ranged from 95% to 5%, with 5% decrements; for MTT1 and MTT2, the threshold range was from 105% to 195%, with 5% increment; for DT and Tmax, it was from 0.5 seconds to 9.5 seconds with increment of 0.5 seconds. Above threshold level was defined relative to the mean tissue perfusion value of the unaffected hemisphere.

Then, difference of the two imaging modalities (MRP-CTP) was calculated in terms of hypoperfusion volume measured by the same threshold setting. To accurately compare the result of the two imaging modalities, MRP was co-registered to CTP with a 3D orientation to adjust for anatomic variation between the two modalities. One slice (12mm in depth, at the level with the biggest perfusion defect) of each imaging modality was chosen to calculate the difference.

For statistical analysis, a multi-level random effect model was used. In the model, the volumetric difference was treated as dependent variable; perfusion map was set as level-one
random effect, and threshold as level-two random effect. The model was estimated by maximum-likelihood estimation.

**Figure 5.1. Data structure of perfusion modality.** Each imaging modality is post-processed by two mathematical models, delayed SVD (dSVD) and standard SVD (sSVD), resulting in 8 perfusion maps. For each map, 19 thresholds are set to derive corresponding perfusion defect regions. Comparison of MRP and CTP is based on perfusion region of the same threshold of the same map.

**Step 2: Inter-modality agreement**

In this step, agreement of MRP and CTP was validated on whole-brain data. The cross-modality agreement included two aspects: (i) measuring the acute ischemic lesion; and (ii) selecting patients with mismatch pattern. To calculate ischemic lesion volume, the perfusion measure with the least cross-modality difference (from Step 1) was applied. To classify mismatch pattern, two criteria were used in the study. The first was the EXTEND trial criteria[6]: mismatch ratio>1.2, mismatch volume >10ml, and infarct core <70ml; the second was the DEFUSE 2 trial criteria[13]: mismatch ratio>1.8, mismatch volume>15ml, infarct core<70ml, Tmax 10s<100ml. Mismatch ratio=ischemic lesion volume/infarct core volume;
mismatch volume = ischemic lesion volume - infarct core volume; infarct core was defined by CBF <30% of the contralateral hemisphere on CTP[14], and by the DWI lesion on MRI[15]; CBF<30% was proved to correspond well to DWI on measuring infarct core[14]. Patients who met the criteria were marked as mismatch pattern (+).

Statistically, agreement of MRP and CTP was quantified by Lin’s concordance correlation coefficient (CCC) on measuring acute ischemic lesion. In terms of selecting patient with mismatch pattern, the agreement was quantified by Kappa coefficient.

Step 3: Cross-modality reperfusion index

Reperfusion was assessed by the change of perfusion status from acute CTP to 24-hour MRP. To quantify the cross-modality reperfusion, a reperfusion index was introduced:

\[
\text{Reperfusion index} = \frac{(\text{Hypoperfusion region}_{\text{acute CTP}}) - (\text{hypoperfusion region}_{\text{24h MRP}})}{(\text{Hypoperfusion region}_{\text{acute CTP}})} \times 100
\]

The hypoperfusion region was defined by the perfusion threshold with minimal difference between CTP and MRP (from Step 1 analysis).

The cross-modality reperfusion index was then used as the independent variable into logistic regression to predict good clinical outcome at 90 days (modified Rankin Score, mRS 0-2). Afterwards, receiver operating characteristic (ROC) analysis was performed to examine how well cross-modality reperfusion predicted clinical outcome. All Statistical analyses were done on STATA 11.0, and a significance level of 0.05 was set.

RESULTS

Patients

For Step 1, 57 patients were eligible. However, 7 cases were excluded due to the motion artifact of perfusion images, and 5 cases were excluded due to vessel recanalization between
CTP and MRP. For Step 2, 22 patients were included, of which 7 patients were excluded later for the above reasons. For Step 3, 47 patients were eligible, but 2 were excluded because of substantial motion artefact of perfusion images.

In summary, image data of 45 patients were used in Step 1, 15 patients were used in Step 2, and 45 cases were used in Step 3. Demographics of patients were shown in Table 5.1.

Table 5.1 Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>Patients in Step1 analysis</th>
<th>Patients in Step2 analysis</th>
<th>Patients in Step3 analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median</strong></td>
<td><strong>IQR</strong></td>
<td><strong>Median</strong></td>
<td><strong>IQR</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>75</td>
<td>18</td>
<td>70</td>
</tr>
<tr>
<td><strong>Baseline NIHSS</strong></td>
<td>17</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td><strong>Time to CTP (hour)</strong></td>
<td>3.13</td>
<td>0.4</td>
<td>3.33</td>
</tr>
<tr>
<td><strong>Time to MRP (hour)</strong></td>
<td>3.67</td>
<td>0.77</td>
<td>4.33</td>
</tr>
<tr>
<td><strong>CTP to MRP (hour)</strong></td>
<td>0.5</td>
<td>0.17</td>
<td>1.23</td>
</tr>
</tbody>
</table>

Step 1: Deriving the map with the least difference between CTP and MRP

For each imaging modality, 6840 perfusion regions were derived. Results of the random-effect model showed that variance between perfusion maps was large (mean difference of MRP and CTP=1.11ml, standard deviation among perfusion maps=3.84 ml with 95% CI [2.34 – 6.28]), however, within each parameter, the variance between thresholds was quite small (standard deviation among thresholds=0.24 ml, with 95% CI [0.26 - 1.07]). Thus, the relationship of CTP and MRP varied significantly among perfusion parameters, but was quite consistent among thresholds within each parameter.

We then further assessed the exact difference between CTP and MRP for each respective perfusion map (Table 5.2). For CBF and CBV, MRP volume was significantly smaller than
the respective CTP volume (P<0.01); for MTT and DT, MRP volume was significantly
greater than its CTP comparator (P<0.01). The only perfusion map with no significant volume
difference between the two modalities was Tmax (P=0.1333). Tmax was therefore identified
as the perfusion parameter to take forward to the next two steps.

Table 5.2 Difference of hypoperfusion regions between MRP and CTP on each map

<table>
<thead>
<tr>
<th>Perfusion maps</th>
<th>MRP-CTP difference (ml)</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF1</td>
<td>-2.22</td>
<td>-2.82</td>
<td>-1.66</td>
</tr>
<tr>
<td>CBF2</td>
<td>-2.30</td>
<td>-3.05</td>
<td>-1.60</td>
</tr>
<tr>
<td>CBV1</td>
<td>-2.17</td>
<td>-2.81</td>
<td>-1.46</td>
</tr>
<tr>
<td>CBV2</td>
<td>-2.11</td>
<td>-2.51</td>
<td>-1.70</td>
</tr>
<tr>
<td>MTT1</td>
<td>7.80</td>
<td>7.03</td>
<td>8.65</td>
</tr>
<tr>
<td>MTT2</td>
<td>6.41</td>
<td>5.60</td>
<td>7.27</td>
</tr>
<tr>
<td>DT</td>
<td>2.81</td>
<td>2.33</td>
<td>3.28</td>
</tr>
<tr>
<td>Tmax</td>
<td>0.67</td>
<td>-0.20</td>
<td>1.54</td>
</tr>
</tbody>
</table>

*Difference of MRP and CTP is non-significant on Tmax map

Step 2: Inter-modality agreement of measuring ischemic lesion with Tmax

From Tmax, three definitions were chosen to define the ischemic lesion: Tmax>2 seconds,
Tmax>4 seconds, and Tmax>6 seconds [16-18]. For each threshold, whole-brain lesion
volume was extremely close between MRP and CTP (Figure 5.2, Figure 5.3, and Table 5.3).
The definition with best cross-modality concordance was Tmax>6 seconds, with CCC of 0.93
(P<0.01). Setting the threshold of Tmax>6s, CTP resulted in a mean acute perfusion lesion
volume 102.61±78.3 ml, and MRP had 102.91±75.81 ml (P>0.05).

Tmax>6s was then used as the definition for the extent of the ischemic lesion for both
imaging modalities to classify mismatch patterns. In selection of patients with mismatch
patterns, CTP and MRP reached substantial agreement (Kappa>0.61) [19]. With the EXTEND criteria, 3 of 15 patients differed in classification across modality (Kappa=0.613, P<0.01), and with DEFUSE there were 2 of 15 misclassified (Kappa=0.746, p<0.01). More details could be found in Table 5.4.

Table 5.3 Agreement of MRP and CTP on measuring whole-brain lesion with Tmax

<table>
<thead>
<tr>
<th>Tmax</th>
<th>MRP volume (ml)</th>
<th>CTP volume (ml)</th>
<th>Concordance correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Estimation</td>
</tr>
<tr>
<td>Tmax&gt;2s</td>
<td>175.58 ± 112</td>
<td>171.09 ± 108.61</td>
<td>0.89</td>
</tr>
<tr>
<td>Tmax&gt; 4s</td>
<td>136.69 ± 95.29</td>
<td>131.91 ± 92.37</td>
<td>0.91</td>
</tr>
<tr>
<td>Tmax &gt;6s</td>
<td>102.91 ± 75.81</td>
<td>102.61 ± 78.3</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Table 5.4 Patient classification by mismatch pattern

EXTEND criteria

<table>
<thead>
<tr>
<th>MR classification</th>
<th>Mismatch pattern (-)</th>
<th>Mismatch pattern (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mismatch pattern (-)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Mismatch pattern (+)</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

DEFFUSE-2 criteria

<table>
<thead>
<tr>
<th>MR classification</th>
<th>Mismatch pattern (-)</th>
<th>Mismatch pattern (+)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1</td>
</tr>
<tr>
<td>Mismatch pattern (+)</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>
Figure 5.2 Concordance of the acute ischemic lesion between MRP and CTP. (A) Distribution of whole-brain lesion volume measured by Tmax>2s, >4s, and >6s separately; (B) Concordance of MRP and CTP with Tmax>2s measurement (CCC=0.89, slope of reduced major axis=0.97); (C) Concordance of MRP and CTP with Tmax>4s measurement (CCC=0.91, slope of reduced major axis=0.97); (D) Concordance of MRP and CTP with Tmax>6s measurement (CCC=0.93, slope of reduced major axis=1.03). For all measurements, lesion distribution is quite similar between MRP and CTP, and slope of reduced major axis is very close to 1 (line of perfect concordance).
Figure 5.3 A case with good agreement of acute ischemic lesion between MRP and CTP. 85-year old, male, presented with left MCA syndrome (NIHSS=11). CTP and MRP were performed successively, 190 minutes and 231 minutes after stroke onset. With Tmax>2s setting, CTP and MRP detect the ischemic lesion volume of 187.41ml and 179.86 ml separately; with Tmax>4s setting, the volume are 130.51 ml and 134.66 ml separately; with Tmax>6s setting, the volume are 92.45 ml and 100.37 ml separately.
Step 3: Cross-modality reperfusion index with Tmax measurement

To calculate reperfusion index, Tmax>6s was applied to delineate the perfusion lesion on acute CTP and 24-hour MRP. Increasing cross-modality reperfusion was associated with improving clinical outcome (Figure 5.4a, and Table 5.5). With each 1% increase in reperfusion, the odds of good clinical outcome (mRS 0-2) increased by 1.1 (95%CI [1.04-1.16], P<0.05). More importantly, ROC results (Figure 5.4b) suggested that the prediction of good clinical outcome by reperfusion was highly sensitive and specific with an area under the curve (AUC) value of 0.98 (95% CI [0.95-1]). The cross-modality reperfusion index>77% predicted a good clinical outcome with 94.12% sensitivity and 93.33% specificity.

Table 5.5 Cross-modality reperfusion and clinical outcome

<table>
<thead>
<tr>
<th>Modified Rankin Score (mRS)</th>
<th>Patient number (N)</th>
<th>Reperfusion index (Median ±IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11</td>
<td>100% ± 9.82%</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>100% ± 1.89%</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>95.27% ± 26.9%</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>71.29% ± 41.23%</td>
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<tr>
<td>4</td>
<td>4</td>
<td>28.58% ± 20.75%</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>26.86% ± 11.45%</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>0% ± 7.36%</td>
</tr>
</tbody>
</table>
Figure 5.4 Cross-modality reperfusion and clinical outcome. Reperfusion index is calculated by the change of Tmax abnormality from acute CTP to follow-up MRP. In the scatter plot of modified Rankin Score (mRS) and the reperfusion index (A), we observe a trend that mRS decreases steadily as reperfusion increases from 0 to 100%. Difference of the reperfusion index is significant between bad clinical outcome (mRS 3-6) and good clinical outcome (mRS 0-2). For Receiver operator characteristic (ROC) curve of the reperfusion index in prediction good clinical outcome (B), area under curve is high (AUC= 0.9790), which is very close to perfect prediction (AUC=1). The cut-off point of reperfusion index with best prediction is 77%, which has the value of 0.9412 for sensitivity and 0.0667 for 1-specificity.
DISCUSSION

Overall, the difference in acute perfusion lesions across MRP and CTP modality was not dramatic. However, we did observe some variance across perfusion maps. Among the eight different perfusion maps assessed in this study, Tmax was clearly the best performer with minimal difference between MRP and CTP.

The finding adds evidence to current data (Chapter 3 & 4) that Tmax has superior performance to other perfusion maps in stroke. Previous MRP studies [16, 17] showed that Tmax 4-6s was the most accurate measurement for ischemic lesion. The MRP-Tmax definition was validated later by showing high correlation to the ischemic reference on PET image (measured by CBF <20 mL/100 g/min; noticeably, CBF was calculated differently in PET and MRP) [20]. Current study found that Tmax 4-6s measurement had good agreement between MRP and CTP (CCC>0.91) and was superior to other perfusion maps and thresholds. This finding allows more confidence in generalizing the ischemic definition from MRP to CTP, which is one step forward to standardize perfusion lesion assessment.

This has major significance for the application of perfusion imaging in current and future acute stroke trials, particularly in multi-center trials where both modalities are used for patient triaging [5, 6]. It improves patient recruitment, but may cause inconsistency of patient selection across the two modalities. The inconsistency might have contributed to the negative results of the of DIAS-2 trial [5]. In this study, we have shown that there is a strong agreement (CCC>0.61) between MRP and CTP in patients selecting based on mismatch pattern, provided our validated ischemic lesion are used. These are max>6s/CBF<30% for penumbra/core mismatch on CTP, and Tmax>6s/DWI lesion for the mismatch on MRP. This will maximize the likelihood that the same treatment decision is made by MRP and by CTP.
For the first time, this study validates the cross-modality assessment of reperfusion.

Reperfusion is a potent predictor of early recovery and later clinical outcomes after stroke [21-23] and also a powerful biologic marker of acute treatment efficacy [2, 4, 6]. Our previous study (Chapter 4) suggests that reperfusion is a stronger predictor of patient outcome than recanalization. Past validation of reperfusion has been limited to the use of single imaging modality. That is, it was calculated either by acute CTP minus follow-up CTP, or by acute MRP minus follow-up MRP. It omits one common clinical scenario where reperfusion success is examined after acute reperfusion therapy (particularly IV tPA), using pre-treatment CTP and post-treatment MRP to minimize radiation dose. Our study confirms the accuracy of such cross-modality reperfusion. We found that cross-modality reperfusion, with Tmax>6s measurement, had extremely high sensitivity and specificity in predicting good 3-month outcome. This agrees with a recent CTP only study [23] that Tmax measurement of reperfusion, compared to other perfusion measurements, best predicted clinical outcome after stroke. We have now generalized this finding to cross-modality reperfusion assessment.

In summary, MRP and CTP are interchangeable on Tmax measurement. We use the term “interchangeable” when MRP and CTP reached a reasonable degree of agreement (CCC>0.9 or Kappa>0.61). This does not mean that they are in perfect concordance, since their technical differences are unavoidable [24]. The interchangeability of Tmax measurement on MRP and CTP is contingent upon the following two conditions being met. Firstly, the same software should be used to process MRP and CTP. However, it may not necessary need to be the software used in this study (MIStar). An in-house software also resulted in a good cross-modality agreement on Tmax>6s in one previous study [8]. Secondly, either with MIStar or other software, standard SVD should be selected as the post-processing algorithm. Although delay-corrected SVD, in comparison to standard SVD, has been reported to generate
perfusion value more accurately [25, 26], the delay correction brings variation in measuring ischemic lesions between MRP and CTP in this study. This could be explained by how delay correction works differently in MRP and in CTP. Delay correction adjusts the difference in tracer arrival time between arterial input function and the brain tissue on a pixel-by-pixel basis and it is affected by the signal-to-noise ratio of each pixel [27]. According to previous studies [28], the signal-to-noise ratio is much lower in CTP than that in MRP, as MRP uses the susceptibility effect to detect the passage of gadolinium through brain in much larger measurable signals. Therefore, the difference in signal-to-noise ratio between MRP and CTP may lead to variation in the time-shifting process by delay correction. The noise-induced variation explains less ideal agreement on delay-corrected Tmax (DT), as compared to the good agreement on Tmax measurement between MRP and CTP.

This is not the first study comparing MRP and concurrent CTP. However, previous studies were quite limited with only one-threshold comparison [29, 30], and on very limited slice coverage [8, 31-35]. Comparatively, this study has two major advantages. Firstly, in the derivation step, we systematically compared the two imaging modalities with multi-level perfusion information, including 19 threshold levels and 8 parameter levels. Secondly, we further validated our findings in a new dataset, using whole brain perfusion information of both CTP and MRP. This is the first time such comparison has been done on a whole-brain spatial level.

There are limitations in this study. Firstly, MRP and CTP are assumed to be concurrent, but there was a short interval time between the two. Changes might have happened between modalities. We excluded patients with any recanalization, but we might have included with partial reperfusion or infarct growth. These changes would underestimate the agreement between MRP and CTP. Secondly, we were limited by relatively small patient numbers with whole brain data as the technology is relatively new. The small sample size in step 2 may, of
course, have limited our ability to find better agreement between the modalities. Thirdly, stroke patients had exclusively hemispheric ischemia with relatively large lesion volumes. Further study is needed in a broad range of stroke patients.

CONCLUSION

This study provides evidence for researchers and clinicians that MRP and CTP can be used interchangeably if one uses Tmax measurement. It also adds considerably to the evidence that CTP, with whole-brain-coverage, is comparable to MRI in acute stroke imaging.
REFERENCE


CHAPTER 6:

CLINICAL APPLICATION OF WHOLE-BRAIN CTP: A CASE

BY CASE REVIEW

Introduction: This chapter applies the finding of previous chapters in different clinical settings using individual ischemic stroke case for illustration. Analyses in above three chapters have been limited to patients with anterior circulation stroke. Cases excluded from the analysis, such as posterior circulation stroke are presented here.

ABSTRACT

CT perfusion (CTP) has been applied increasingly in research of ischemic stroke. However, in clinical practice, it is still a relatively new technology. For neurologists and radiologists, the challenge is to interpret CTP results properly in the context of the clinical presentation. In this article, we will illustrate common CTP patterns in acute ischemic stroke using a case-based approach. The aim is to get clinicians more familiar with the information provided by CTP with a view towards inspiring them to incorporate CTP in their routine imaging workup of acute stroke patients.
INTRODUCTION

Cerebral perfusion refers to the capillary or tissue level of blood flow. Under physical condition, the human brain has a high demand for energy to maintain its function. Accounting for only 2% of whole body weight, the brain consumes about 20% of the total oxygen supply at rest [1]. To match this high metabolic rate, a large proportion of cardiac output perfuse into the brain.

The cerebral perfusion is detectable by modern imaging technology with various hemodynamic parameters [2]. These parameters include cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), time to peak (TTP). CBV is defined as the total volume of flowing blood in a given volume of the brain; CBF is defined as the volume of blood passing through the given volume of brain per unit time; MTT represent the average time for blood transiting through the given brain region; TTP is an index of time between the beginning of blood perfusion and maximum enhancement in the given region. Depending on mathematical model, Tmax (time to the peak of the residual function) or DT (delay time to the peak of the residual function) can be generated instead of TTP.

Deconvolution is a commonly applied post-processing mathematical process whereby the brain tissue contrast concentration-time curves from each pixel are ‘scaled’ to the tissue concentration-time curve from a feeding artery (arterial input function). This gives each pixel a residual function tissue concentration-time curve that is used to measure parameters such as CBF, Tmax and DT.

In ischemic stroke, reduction of perfusion occurs, typically in an affected vascular territory (focal cerebral hypoperfusion). Regions with hypoperfusion are shown at least one of the following changes: decreased CBF, decreased CBV, prolonged MTT, and prolonged measures of contrast transit such as TTP, Tmax or DT. Since these parametric changes are
detectable minutes after stroke onset, they are of great use for early diagnosis of ischemic stroke. More importantly, perfusion parameters can be used to differentiate ischemic penumbra from infarct core. Penumbra refers to area with hypoperfusion severe enough to cause neuronal dysfunction (and clinical symptoms), but still salvageable if blood supply is restored promptly. Salvage of penumbra, which is the target of thrombolytic/reperfusion treatment, correlates with better clinical outcome. Infarct core, on the other hand, is tissue that is severely hypoperfused and already irreversibly injured. With perfusion maps, penumbra can be estimated by delayed MTT/TTP/Tmax/DT [3, 4], while infarct core can be delineated as insufficient CBV/CBF [3]. In previous study (Chapter 3), we have validated the threshold setting of Tmax>6s/CBF<25% or DT>3/CBF<30% differentiates penumbra and core accurately on whole-brain CTP. 

Currently, there are two perfusion approaches with good application in acute stroke, Magnetic Resonance (MR) perfusion and Computed Tomography (CT) perfusion. According to the finding from Chapter 5, CT perfusion (CTP) is as good as MR perfusion (MRP) in delineating ischemic lesions. From practical point, CTP has the advantage of rapidity and wide accessibility in emergency room [5]. Thus, it is promising to apply CTP as a routine examination for acute stroke patients. For neurologists, the challenge would be to interpret CTP results properly. To help them achieve this goal, in this article, we will illustrate CTP patterns of stroke with a case by case approach.

**IMAGING PROTOCOL**

For the cases shown in this paper, we used following protocols to generate perfusion maps. Firstly, CTP was performed on 320-slice scanner (Toshiba Aquilion ONE). Typically, 19 time points were obtained commencing 4 seconds after non-ionic iodinated contrast injection
into an antecubital vein (50 ml, 5ml/s; Bayer HealthCare). With each time point acquisition, a total of 320 slices were obtained with the thickness of 0.5mm, which covers the whole brain (160 mm). The acquisition parameters were 80 kVp and 100 mA. This acquisition also allows the generation of intracranial CT angiography (CTA) along with perfusion maps, while whole brain non-contrast CT (NCCT) was acquired before CTP. After acquisition, CTP data was processed by commercial software Mistar (Apollo Medical Imaging Technology) with delay-corrected singular value decomposition (dSVD) algorithm. From the post-processing, four perfusion maps were generated: CBV, CBF, MTT, and DT. Then, DT>3s and CBF<30% were set manually on to generate penumbra/core map on Mistar software.

CLASSICAL CTP PATTERNS OF STROKE

Ischemic stroke is most commonly from an occlusion of the middle cerebral artery (MCA). In those with a proximal (M1 or M2) segment occlusion, there are two classical types of perfusion pattern

Favorable pattern

The favorable pattern refers to a ‘small core and big penumbra’ on CTP, shown in Case 1 and Case 2 (Figure 6.1 and Figure 6.2). Case 1 is a 63-year-old female, admitted to hospital with sleep-onset stroke. Her neurologic deficit was severe, with NIH stroke scale (NIHSS) of 20. No abnormality was observed on NCCT (suggesting stroke likely occurred not long before awakening). CTA showed occlusion of the proximal M2 segment of left MCA, with corresponding hypoperfusion on CTP maps (Figure 6.1). Visual assessment of CTP showed a small region with decreased CBF and CBV, but a much bigger area with prolonged DT and MTT. Quantitative calculation of CTP maps showed only a few regions of infarct core (i.e.
with severely reduced CBF below the threshold), surrounded by large regions of penumbra (i.e. with prolonged DT above the threshold). Although onset time was unclear, thrombolytic treatment (t-PA) was given to this patient based on the favourable tissue imaging pattern. A dramatic clinical recovery was observed as NIHSS dropped to 2 at 24 hours, with complete reperfusion and recanalization of the MCA observed. Follow-up MR diffusion-weighted image (DWI) showed only a small infarct, consistent with the baseline CTP core prediction (Figure 6.2). This indicates that penumbra was successfully salvaged from progression to infarction through successful thrombolysis. However, such success is not always achieved, as seen in Case2. Case 2 is a 78-year-old female, imaged two hours after stroke onset, with a distal M1 occlusion, and an NIHSS of 17. CTP showed a similar pattern to case 1 (big penumbra and small infarct core, Figure 6.2). Thrombolysis with IV t-PA was also given but no reperfusion occurred and follow-up DWI showed that virtually all the penumbra progressed to infarction (Figure 6.2). There was no clinical recovery.

These two cases illustrate following two points: 1) For patients with a favourable pattern on acute CTP, they have the potential of benefiting from thrombolytic treatment. 2) However, whether the treatment leads to a good outcome depends on whether reperfusion is achieved in a timely fashion. Successful early reperfusion leads to salvage of the penumbra, a small final infarct and good clinical recovery; lack of reperfusion leads to a much bigger final infarct (recruiting initial penumbral area), and lack of clinical recovery. Notably, a small core/large penumbra pattern on CTP may be seen <3 hours after stroke, but can commonly be observed in patients outside the current 3 or 4.5 hour time window of thrombolytic therapy. Although unproven, this suggests that some patients may still respond to acute reperfusion therapy outside the standard time window.
Figure 6.1 Baseline brain images of Case 1. Acute CTA shows occlusion of the proximal M2 segment of left middle cerebral artery (blue arrow), which results in lesions on CTP maps as prolonged MTT and DT, and decreased CBF and CBV in the left MCA territory. By setting thresholds to DT and CBF, acute CTP differentiates penumbra (green) from infarct core (red). This patient has a small infarct core with relatively big penumbra.
Figure 6.2 The tissue outcome of Case 1 and Case 2. Both cases have a ‘favourable penumbral pattern on acute CTP, and both received thrombolytic treatment. In Case 1, follow-up DWI (24 hours) shows small lesions that correspond to pre-treatment infarct core map, with complete salvage of penumbra. In Case 2, there is a large infarct at 24 hours representing the progression of pre-treatment penumbral tissue to infarction. Note that both cases had normal baseline NCCT with no early ischemic changes.
Unfavorable pattern

An unfavorable pattern is one with a ‘big infarct core and small penumbra’. Such a pattern was observed in Case 3 (Figure 6.3). Case 3 is a 54-year-old male, imaged with multimodal CT 4 hours after stroke onset. There was only minor, subtle change seen on NCCT (Figure 6.3b). However, acute CTP showed severe hypoperfusion, with the region of prolonged DT matching the region of severely reduced CBF. Therefore, the infarct core affected virtually all of the M2 MCA territory, with very small amount of salvageable tissue (Figure 6.3a).

Although thrombolytic treatment was given to this patient and recanalization was achieved (Figure 6.3d and 6.3e), no clinical improvement was observed (NIHSS maintained at 18 from acute to 24 hours). Thus, recanalization failed to lead to improved outcome in this case and could be considered futile reperfusion.

Lessons learned from this case are as follows: 1) For patients with unfavorable CTP pattern, their room for clinical improvement is limited. 2) Treatment would be futile (and perhaps harmful, with increased risk of haemorrhage), even if reperfusion is achieved. Notably, this pattern can be seen early after stroke onset (within 4.5 hours). This is one of the major reasons that patients do not always benefit from thrombolysis within the standard window time.
Figure 6.3 Brain image of Case 3. Acute CTP (A) reveals a big infarct core (red) with limited penumbra (green), while no obvious abnormality is shown in acute NCCT(B). Acute CTA (D, blow arrow) shows the existence of occlusion on M2 segment of MCA. Thrombolytic treatment was given to this patient. Follow-up MRA (E, blow arrow) confirms the recanalization of the occlusion. Follow-up DWI (C) shows a big infarct consistent with the pre-treatment CTP core map.
In summary, the two major perfusion patterns (favorable versus unfavorable) have completely different response to treatment. This challenges current treatment guidelines for acute stroke patients. Currently, onset time is the major selection criterion for intravenous thrombolysis [6]. One problem is that we treat patients in the current window often without knowing whether they have a ‘favourable’ (small core/large penumbra) or ‘unfavourable’ (large core/small penumbra) pattern. Thus, we have no way of predicting response in an individual patient. We rely on the principal that treating as many people as fast as possible will benefit at least some of them. Unfortunately, even treating patients within 90 minutes still means only 1 in 3 benefits. The other problem with the current time-based approach is that we exclude patients with a ‘favourable’ pattern if they have onset time >4.5 hours or they have an unclear onset time. Studies have validated that the existence and duration of penumbra differs from patient to patient, varying from 3 hours to 48 hours after stroke onset [7]. Take Case1 for example, ordinarily, this patient would receive no thrombolysis based upon conventional selection. However, based on the CTP finding of a favourable CTP pattern, t-PA was given to this patient resulting in an almost complete clinical recovery. Therefore, perfusion pattern is promising to replace time window to select stroke patients for thrombolytic treatment. The next step is to generate level 1 evidence for such a treatment selection approach.

**INTERMEDIATE CTP PATTERN**

To design trials to produce level 1 evidence for core/penumbra selection for acute reperfusion therapies, one grey area cannot be avoided. That is the existence of what we call the ‘intermediate pattern’ of CTP in acute stroke. This refers to patients with a ‘moderate-sized core and moderate-sized penumbra’. A typical example can be seen in Case 4 (Figure 6.4),
who had a similar size of infarct core and penumbra. For such patients, we do not really have much data on the extent of the benefit from reperfusion treatment. They are generally less likely to have an excellent clinical outcome (e.g. Rankin Score 0-1), but it is possible we may ‘shift’ them from a Rankin Score 5 or 4 to a 3 for example. Overall, this is a difficult area, for both clinical trials and clinical practice, but also a very important area requiring further studies. In particular, cut-off points should be defined to differentiate ‘small’ penumbra (minimal benefit from reperfusion) from ‘moderate’ penumbra (likely to have some benefit from reperfusion). At the moment, we do not deny such patients thrombolysis if they fulfill the standard treatment criteria.

Figure 6.4 Acute CTP images of Case 4. It shows a region in right MCA territory with reduced CBV and CBF, and a larger region with prolonged MTT and DT. Penumbra and core volume is similar in this case, with 32ml and 30ml separately.
OTHER CTP PATTERNS

Besides the classical stroke patterns, in acute clinical practice, sometimes we see other patterns on CTP. These less common CTP stroke patterns relate to lesion size, topography, or timing of CTP.

**Malignant CTP pattern**

Malignant stroke refers to an extensive severely ischemic lesion in the anterior circulation, and is associated with poor outcome. This phenomenon was first observed on NCCT with hypodensity greater than 1/3 of the MCA territory, known as “one-third rule”[8]. Later, the malignant infarction was defined as DWI lesion>145ml [9]. Then, from advanced MR technology, the concept of malignant mismatch profile was formally raised [10]. This was where, despite the existence of significant penumbra, there was a large DWI (>100ml) and/or a large perfusion lesion (>100ml) with severe delay in contrast transit (>8seconds). Recently, the same group found that there appeared no benefit of reperfusion with DWI lesions above 80ml, or if the tissue with severe delay was > 85ml [11]. Perfusion areas with severe delay relate to very poor collateral supply, and are likely to infarct even with reperfusion. Thus, patients with a malignant profile have poor outcome regardless of treatment; moreover, reperfusion of such lesions may even be associated with worse outcome (due to hemorrhage).

So far, information about ‘malignant patterns’ mostly comes from MR research. There is no clear definition of the malignant profile of CTP, although one study [12] suggested that a large core (>53ml) was associated with a higher risk of ICH. Nonetheless, given the good data for strong correlation between CTP infarct core and DWI (Chapter 3), and the similarity of parameter measures on CT an MR perfusion maps (Chapter 5), similar criteria could be adapted from MR to CTP to predict poor treatment response. A malignant pattern of CTP is shown in Case 5 (Figure 6.5a).
Case 5 is 58-year-old male, imaged at one hour after stroke onset. NIHSS examination result a score of 17. CTA showed an occlusion of MCA-M1 (Figure 6.5b), and CTP maps revealed a perfusion lesion of the whole MCA territory (Figure 6.5a). Whole-brain volume of infarct core was 116 ml, although he still had considerable penumbral tissue (110 ml). t-PA was given to the patient as he was very early within the time window, and recanalization was achieved (Figure 6.5c). However, no clinical improvement was observed. His NIHSS score was 19 at 24 hour. Moreover, after treatment, follow-up NCCT showed a hemorrhagic transformation (Figure 6.5d). He had a modified Rankin score of 5 at three months and required institutional care.
Figure 6.5 Brain Images of Case 5. (A) Acute CTA shows on the whole right MCA territory with decreased CBV and CBF, and prolonged MTT and DT. By adding up whole brain lesion volumes, core (red area) results a volume of 116ml, and penumbra (green area) has a volume of 110 ml. (B) acute CTA reveals occlusion of the M1 segment of right MCA (blue arrow). (C) Follow-up CTA reveals the recanalization of right MCA. (D) Follow-up NCCT shows a big infarct (consistent with baseline core maps), with midline shift to the left. Inside of the lesion, there is hemorrhagic transformation (white arrow).
**Lacunar stroke**

Lacunar stroke, caused by occlusion of small penetrating artery, contributes to 15% of all ischemic strokes [13]. Typically, lacunar lesion is smaller than 1.8 ml or 15mm in diameter [14]. Thus, for imaging to detect lacunar infarction, high spatial resolution is required. Diffusion MR (DWI) meets the requirement, detecting acute lacunar stroke with high sensitivity and specificity, both over 90% [15]. Perfusion MR, on the other hand, does not perform so well [16]. Neither does perfusion CT. Low sensitivity for detection lacunar lesion has been observed in CTP images with limited slice coverage [17]. There are two explanations for this. Firstly, limited slice CTP (16-64 slices) only covers 40-80 mm of brain, so lesions may be outside the slice coverage. Additionally, the CTP data is acquired with slice thickness of 5-10 mm, thus the lacunar lesion may be missed due to partial volume effect, mixing of affected tissue pixels with adjacent normal pixels.

With newer technology, such as 320-slice CTP, sensitivity of detecting lacunar lesion is increased. 320-slice CTP has whole brain coverage and thin-slice (0.5-1 mm) acquisition, reducing partial volume effect [18, 19]. Thus, we often can see altered perfusion in the periventricular white matter. However, the specificity of detecting acute lacunar ischemic is still lower than DWI. It is difficult to distinguish a true acute perfusion lesion from ‘noise’, because thin-slice acquisition causes low signal to noise ratio. This is particularly an issue with lacunar infarction located in white matter, since white matter is more prone to noise due to lower flow rates and hence less signal to noise. Distinguishing between noise and true lesion appears especially a problem with CBV, CBF and MTT maps, whereas in our experience, the DT maps perform better (Figure 6.6). However, DWI is clearly superior to CTP in diagnosing lacunar stroke (Figure 6.6).
Nevertheless, CTP may be useful to predict progression of lacunar stroke. Neurological deterioration happens in a proportion of patients with lacunar infarction (e.g. capsular warning syndrome). Such group of patients has been reported to have lower CBF value and higher MTT value inside the lesion [20]. With further validation, severity of hypoperfusion may potentially divide lacunar stroke into two types: those at risk of progression and those with stable disease. In our experience, Delay Time may be the most useful map to identify and predict progression of lacunar stroke.

Figure 6.6 Acute DWI (A) and CTP (B) of Case 6. DWI, performed after CTP, reveals a lacunar infarct on right thalamus (yellow circle). In that area, MTT and DT are prolonged. However, outside the yellow circle, there are small areas with prolonged MTT and DT too. These are noise, but are less on the DT map. On CBF and CBV maps, it is not possible to distinguish low signal in normal white matter from the lacunar perfusion lesion.
Posterior circulation stroke

Posterior circulation stroke is often difficult to diagnose clinically [21], since patients often present with non-specific symptoms, such as dizziness, nausea, and vomiting. Traditionally, CTP was thought to play no useful role in diagnosis of posterior circulation stroke, because of limited brain coverage. However, this thinking is outdated with the availability of whole-brain-coverage ‘mega-slice’ CT scanners such as the Toshiba 320-slice CT scanner [18, 19]. Although this has only been addressed in case reports so far [22, 23], based on our experience, we can not only identify patients with posterior circulation ischemia but also we may be able to identify the presence of a favorable penumbral pattern. However, the criteria for a favorable penumbral pattern may be different both in terms of volume of core and penumbra and the perfusion thresholds used to derive them. The following case is an example.

Case 7, an 87-year-old male, imaged two hours after sudden onset of dizziness. Physical examination showed disordered coordination. He was then scanned by multi-model CT, including NCCT, CTA and CTP. Occlusion was observed on right superior cerebellar artery (SCA, Figure 6.7), but no obvious lesion was shown on NCCT at this early stage (Figure 6.7). 320-slice CTP revealed the prolonged DT in the right SCA territory, and quantitative calculation suggested most of this tissue was still penumbral (Figure 6.7). This patient received IV t-PA treatment, with complete recovery within 24 hours and recanalization of the SCA on MRA with only a small DWI lesion (Figure 6.7).
Figure 6.7 Cerebellum Images of Case 7. Acute CTA shows, compared to normal left side, right superior cerebellar artery (SCA) is absent. No obvious change is observed on acute NCCT. CTP reveals hypoperfused lesion on SCA territory with the existence of penumbra (green area). After treatment, DWI shows stroke lesion (high signal) corresponding to infarct core of CTP (red area) with at least some of the penumbra saved.
Reperfusion prior to CTP

Most published CTP studies are about the hyperacute/acute phase of stroke. Less attention has focused upon the performance of stroke CTP after thrombolysis. At our center, we often perform CTP at 24 hours after thrombolysis. In many of these cases, we have observed a “false normal” phenomenon. That is, due to successful reperfusion, hemodynamic parameters of infarct area on CTP return to normal level or even higher level (hyperperfusion).

A typical example is seen in Case 8, a 79-year-old male with sudden onset of left MCA symptoms. On admission, acute CTP was performed and showed a lesion with prolonged DT and reduced CBF on MCA territory (Figure 6.8a). Thrombolytic treatment was given to the patient, and recanalization was achieved. Follow-up image, 24-hour DWI and NCCT, showed the remained infarct lesion (Fig 6.8c and Figure 6.8d). However, no lesion was observed on 24-hour CTP (Figure 6.8b). The lesion area of DWI had normal DT and CBF parameters. The underlying mechanism is that blood flow of infarct area returns to normal level. The restoration might be from reperfusion with recanalization of occluded artery, from revascularization with development of collateral flow or, or from blood brain barrier injury. It is non-nutritional though, since cerebral tissue has already infarcted.

Notably, we have observed this phenomenon is not limited to post-thrombolysis CTP and may be observed more acutely. For example it can occur in acute stroke patients with spontaneous reperfusion before (or during) CTP scanning. In that case, one cannot make an accurate measure of infarct core with CTP, as CTP (opposed to DWI) relies on the presence of hypoperfusion to measure core. Unfortunately, this phenomenon is not well appreciated by many stroke clinicians or radiologists, and may lead to false negative diagnosis of ischemic lesion on CTP. A typical example is Case 9.
Case 9 is a 34-year-old male, who was admitted to hospital within 3 hour of stroke onset, and scanned by multi-model CT immediately. His NIHSS was 8 at admission but dropped to 1 immediately after scanning. Thus, we suspected that spontaneous reperfusion happened before or during CT scanning. No perfusion lesion was detected on the acute CTP parametric maps (Figure 6.9a), but the CTP source image (CTPSI) did show hypodensity in the right lentiform (Figure 6.9b) despite no obvious hypodensity on NCCT. We have noticed that the CTPSI is more sensitive at detecting early hypodensity than NCCT [24]. Follow-up DWI confirmed the existence of the lesion (Figure 6.9c).

To avoid misinterpretation of CTP results, in clinical practice, the ‘reperfusion pattern’ should be recognized. If CTP is performed acutely and there is already established hypodensity on CTPSI +/- NCCT, the absence of a perfusion abnormality on CTP indicating reperfusion has occurred. Such patients should not, in our opinion, be given thrombolytic treatment.
Figure 6.8 Cerebral Images of Case 8. (A) Acute CTP shows decreased CBF and DT on left MCA territory due to occlusion of M2 segment (blue arrow). (B) 24-hour CTP shows CBF and DT returns to normal level due to recanalization of occluded artery. (C, D) 24-hour NCCT and 24-hour DWI confirm that cerebral tissues are infarcted in reperfused area (red circle).

Figure 6.9 Cerebral images of Case 9. (A) Acute DT map shows no specific perfusion lesion. (B) Acute CTP source image shows hypodensity in the right lentiform (blue arrow). (C) Follow-up DWI confirms the existence of ischemic lesion in the posterior right lentiform nucleus.
CONCLUSION

Perfusion pattern varies among stroke subtypes. For stroke from MCA occlusion, which is the most common type, acute CTP has a high sensitivity and specificity of detecting the lesion. Moreover, it provides information of core and penumbra which may be used to guide thrombolytic treatment in the future [25]. Regarding other stroke subtypes, such as lacunar stroke, posterior circulation stroke, and in the setting of ‘reperfusion in progression’, the exact role of CTP has not been validated yet. More research should be encouraged on these topics. Clinically, from our experience, to manage such patients, it is important to combine CTP with the clinical picture as well the NCCT and CTA data.
REFERENCE


CHAPTER 7:

DISCUSSION
7.1 Overview

The translation of perfusion imaging research into clinical application in stroke management has focused on two key aspects: selecting patients for thrombolytic treatment acutely and assessing the success of such therapy post-treatment [1-3]. However, the application of CTP in clinic has been limited on its brain coverage that can lead to underestimation of the ischemic lesion volume [4]. Thanks to the development of imaging technology, this issue has recently been tackled by mega-detector scanners, especially by 320-detector CTP [5, 6]. It extends the axial scanning range to 160mm, which covers the whole brain. Prior to the completion of the studies presented in this thesis, the 320-detector CTP had undergone limited studies in acute stroke. In 2012, John Hunter Hospital installed 320-detector CT and has collected a substantial body of whole-brain perfusion data from stroke patients since scanner installation. With this dataset, we are able to validate the usage and examine the advantage of 320-detector CTP in acute ischemic stroke (Figure 7.1). This thesis has provided evidence that

- 320-detector CTP delineates penumbra and infarct core with high accuracy and precision, as well as good sensitivity and specificity (Chapter 3);
- 320-detector CTP has higher accuracy than limited-coverage CTP in measuring penumbra and infarct core (Chapter 3);
- Reperfusion, measured by 320-detector CTP, predicts good clinical outcome with high sensitivity and high specificity (Chapter 4).
- Penumbra measurement and reperfusion measurement with 320-detector CTP and MRP are interchangeable (Chapter 5).

However, above findings are dependent on the selection of appropriate post-processing algorithm and threshold setting for CTP maps (Figure 7.1):
• For maps post-processed by standard SVD, Tmax with a threshold set at 6 seconds is recommended to delineate ischemic region and to quantify reperfusion of the ischemic region; within the ischemic region, CBF threshold of 25% or CBV threshold of 55% is recommended to differentiate penumbra from infarct core (Chapter 3, Chapter 4).

• For maps post-processed by delay-corrected SVD, DT>3s is recommended to delineate ischemic region and to quantify reperfusion of the ischemic region; within DT>3s region, CBF<30% or CBV<55% is recommended to differentiate penumbra from infarct core (Chapter 3, Chapter 4).

• To combine the usage of CTP and MRP in detecting ischemic lesion size or in quantifying reperfusion, Tmax rather than DT is recommended from our findings (Chapter 5).

Importantly, the recommendation only applies to ischemic stroke patients with an anterior circulation lesion, whose perfusion pattern is shown in Chapter 6. For cases with other stroke types, their perfusion patterns are also discussed in Chapter 6 to guide future, raising possibilities for future research directions.
7.2 Main findings: update current knowledge on perfusion parameter Tmax

7.2.1 Current knowledge of Tmax

Tmax is a time domain parameter. It measures the time to maximum enhancement of the tissue residue function generated from deconvolution method. Physically, Tmax value depends on tracer delay and deconvolution algorithms [7, 8]. Pathologically, the value of Tmax is prolonged in the area with ischemic stroke [9]. In the stroke field, current knowledge of Tmax mainly comes from studies using the MR perfusion modality [10-13]. Not much work has been done on CT perfusion modality. Our study helps fill this gap and made following findings.
7.2.2 Tmax is better than MTT in defining ischemic region and quantifying reperfusion of the region

MTT>145% was reported optimal to delineate ischemic region from the previous work done by Wintermark et al [14] [15]. Their early study showed that MTT>145%, compared to other perfusion maps and thresholds, had the highest ROC area (sensitivity + specificity) in predicting the tissue at risk of infarction on DWI in case of persistent arterial occlusion[14]. A subsequent study found that MTT>145% resulted in high agreement between CTP and MRP in measuring the acute ischemic volume and in guiding clinical decision making [15]. According to their recent study, reperfusion of the region defined by MTT>145% accurately predicted final infarct core volume [16]. Notably, these findings were based on perfusion data with limited brain coverage (64-detector CTP). Beyond tissue covered by such a CTP scan, information is missed in terms of the existence of ischemic lesion and the occurrence of reperfusion. Thus, the accuracy of the MTT>145% measurement is questionable on whole-brain CTP.

The studies described in this thesis confirm that the Wintermark’s threshold is not ideal when similar imaging analysis is carried out on whole-brain CTP (standard SVD algorithm). This study found that MTT>145% overestimated the ischemic lesion size. The region delineated by MTT>145% was significantly bigger than ischemic area on DWI or on MRP. Compared to MTT>145%, Tmax>6s is more suitable to define ischemic lesion on whole-brain CTP. With Tmax>6s setting, CTP delineated ischemic region with high accuracy and precision. Reperfusion of the region defined by Tmax>6s predicted good clinical outcome with high sensitivity and specificity. Therefore, to apply whole-brain CTP in future stroke trials or clinical practice, Tmax rather than MTT is recommended.
7.2.3 Tmax enables the interchangeable usage of MRP and CTP

Tmax has long been used to define ischemic lesion in MR perfusion imaging. Our finding generalizes the usage of Tmax from MRP to CTP. In earlier trials, including DEFFUSE [17] and EPITHET [18], 2 seconds was set as the threshold on Tmax maps to delineate ischemic region. However, later studies proved that a Tmax greater than 6 seconds was a better threshold. One study [10] found that Tmax>6s, compared to Tmax>2s, estimated the region at risk to infarction more accurately; salvage of the Tmax>6s region outperformed that of Tmax>2s region in predicting good clinical outcome. Another study [11] compared MRP to positron emission tomography (PET), finding that a Tmax threshold of 5.5 seconds on MRP results in strongest correlation to the previously validated probabilistic penumbra on PET. These findings validate the usage of Tmax>6s in MR. Now, Tmax>6s is the automatic setting to generate MRP ischemic lesion in imaging software [19] and in stroke trials [20, 21]. On the other hand, the usage of Tmax has not previously been well studied on CTP. Our finding fills in the blank and proves that a threshold setting of Tmax>6s is as effective in CTP as it is in MRP for ischemic region delineation.

This finding supports the interchangeable use of CTP and MRP in stroke research and eventually in stroke clinical practice. Since the two imaging modalities each has their own advantages for acute stroke management, CTP is preferred in some clinical centres while others feel more comfortable using MRP [22]. Naturally, the combined usage of CTP and MRP occurs in trials involving multiple centres, such as DIAS-2[23]. However, this approach creates difficulties when pooling the data from CTP and MRP together for further analysis. The difference between CTP and MRP in perfusion measurement was considered as one source of variation leading to the negative finding of the DIAS-2 study. Our studies found that the difference of CTP and MRP does exist on measuring ischemic lesion, but it is parameter-dependent. On Tmax map, the lesion difference was smallest (non-significance)
between the two imaging modalities; defining the ischemic region using a threshold of Tmax>6s actually resulted in high agreement between CTP and MRP in selecting patients for thrombolysis. Thus, Tmax measurement is recommended to combine the use of CTP and MRP in ischemic stroke. Our conclusion is in agreement with a recent study by Campbell et al [24].

7.2.4 Tmax (sSVD) and DT (dSVD) have similar performance in ischemic stroke

Tmax has been reported to be susceptible to the contrast delay, and various algorithms have been developed to correct the delay effect [7, 8]. With delay correction, according to previous reports, value of time-domain parameter decreased and was supposedly more accurate [8, 25]. When applying the delay correction in stroke measurement, two hypotheses were put forward [26]: 1) threshold level to delineate ischemic lesion would decrease on perfusion maps with delay correction; 2) accuracy of lesion detection would be improved for perfusion map with delay correction. Surprisingly, our findings only support the first hypothesis not the second one. After delay correction, the optimal threshold for penumbra was 3 seconds on delay-corrected Tmax (also known as delay time, DT), while it was 6 seconds on standard Tmax. However, DT>3s did not show any advantage over Tmax>6s in the ischemic stroke application: DT>3s and Tmax>6s resulted in similar accuracy in delineating penumbra and similar sensitivity in predicting clinical outcome. Campbell et al [27] reported that the accuracy of detecting infarct core was not improved by excluding delay effect on MRP (although the exclusion of the delay factor was done with a different approach in their study. They also suggested that a different perfusion threshold should be set on map generated from different algorithms. Combining our study and Campbell’s study, we suggest that delay correction is optional in processing ischemic stroke data.
7.3 Clinical application of the findings

Intravenous thrombolysis by tissue plasminogen activator is the only FDA approved therapy for acute ischemic stroke [28]. However, not all patients are eligible for the treatment. Traditionally, emergency doctors or neurologists would make the treatment decision to a stroke patient if the patient presented with the absence of haemorrhage sign on NCCT and more importantly within the time window (3 hours and more recently 4.5 hours of stroke onset) [29-31]. However, this time-based criterion presents two issues. Firstly, there is a high probability that the selected patient will not benefit from the treatment. From pathophysiological perspective, any benefit from the thrombolytic treatment relies on the existence of salvageable tissue (penumbra), which cannot be detected by NCCT [32, 33]. The second issue of current criterion is that a big proportion of patients who would benefit from the treatment are excluded due to the delayed arrival time (beyond current time window).

From the post-hoc analysis of DEFFUSE and EPITHEPT trial [34], thrombolysis was found to be beneficial up to 6 hours post-onset in patients with penumbra. A recent study [35] showed the salvage of penumbra by thrombolysis was even evident up to 48 hours post stroke onset and the success of penumbra salvage resulted in favourable clinical outcome.

The two issues can be solved by the application of perfusion imaging in acute stroke. Perfusion imaging, either CTP or MRP, provides penumbra information that could help doctors to make better treatment decision for individual stroke patients [2, 36]. The role of perfusion imaging in acute stroke management has recently been acknowledged in the American Heart Association/American Stroke Association Stroke Council recommendations [28], stating that CTP and MRP imaging are recommended in acute stroke management work-up as long as they do not delay the initiation of treatment. In the future, as suggested by several reviews [37-39], penumbra imaging might replace the time window to guidance the
thrombolytic treatment decision. This will be especially useful for patients with unknown onset of stroke (e.g. those who experience a stroke while they are asleep).

To promote the clinical application of CTP, following concerns need to be addressed.

- **Concern 1:** Is CTP accurate in measuring ischemic lesion? The concern comes from findings of the following studies: Huisa et al [40] found that CTP had low sensitivity (40%) of detecting ischemic lesion in comparison to follow-up DWI lesion; González et al [41] showed that CTP had low precision (wide scatter in individual value) of detecting infarct core in comparison to acute DWI lesion. Reviewing these studies, their negative findings are most likely due to the selection of inappropriate perfusion threshold and the employed of limited brain coverage CTP. In the study of Huisa, ischemic lesion was defined on the MTT map and on 64-detector scanner CTP (40mm coverage), both of which compromise the sensitivity of lesion detection. By using a CT scanner with whole brain coverage and using Tmax measurement, as in this thesis, the sensitivity of lesion detection can be significantly increased (>90%) on CTP. In the study of González, infarct core was defined by CBF<15%, which underestimates the lesion size. By setting the threshold to 30%, as in this thesis, high precision (>90%) of infarct core detection is achievable. In summary, concerns regarding the accuracy of CTP measurement are addressed by choosing the right perfusion parameter and threshold as well as using the whole-brain CTP.

- **Concern 2:** Is CTP measurement reliable? This concern comes from the systematic review of perfusion studies, finding results of CTP from one clinical centre cannot be adapted to another [42, 43]. This concern was taken into consideration when designing studies in this thesis. Findings of this thesis confirm the existence of variation on ischemic lesion measurement across centres if their CTP scanners vary from limited-brain coverage to whole-brain coverage. However, according to our
finding, for centres equipped with CTP scanners that covers whole brain (100mm and above), same CTP threshold can be adapted from one centre to another to delineate ischemic region or to quantify reperfusion of the ischemic region. Therefore, whole-brain CTP (≥100mm) is recommended to be used in clinical centres to ensure the consistent performance of CTP in ischemic stroke.

- Concern 3: Is CTP as good as MRP in the application of ischemic stroke? MR perfusion modality has been well validated for ischemic measurement and well applied in stroke trials [19, 44, 45]. Therefore, it could be argued that there is no need to develop the CT perfusion modality. We disagree with this view, since CTP has the advantage of rapid imaging acquisition and easy access in the clinical setting [3]. Moreover, CTP can be performed in patients with pacemakers, metallic shunts, stents etc. A CT scan can be performed without any kind of safety screening, while the safety screening for an MRI scan can take several hours if the patient is unable to answer questions and is not accompanied by someone who is familiar with the finer details of their medical history. Therefore, from the practical point, it is necessary to develop CTP. In our study, we prove that CTP is as good as MRP in measuring penumbra and in selecting patients for treatment. However, this is not to suggest that CTP should replace MRP entirely. Rather, CTP should be used during the acute phase of stroke, when rapidity of imaging is extremely important, or in patients who are unsuitable for MRI because of metallic implants. MRP could be used for follow-up imaging which is often conducted 24 hours after the patient presents to the hospital. This provides ample time for effective safety screening before the patient undergoes an MRI scan, while allowing efficient and rapid treatment during the acute phase of the stroke management, and still minimises the exposure of the patient to ionising radiation.
7.4 Where to now?

There are a number of questions that have not been answered in this collection study.

- Firstly, how to classify mismatch pattern on CTP? It is relatively easy for a clinician to predict the clinical outcome of patients with big penumbra/small infarct core (favourable outcome) or patients with small penumbra/big infarct (unfavourable outcome). However, the prediction of outcome is difficult in the group of patients with similarly sized penumbra and infarct core, whose response to thrombolytic treatment depends on the ratio of penumbra to infarct core. Two ratios, >1.2 and >1.8 respectively, have been used in stroke trials to classify MRP-DWI mismatch pattern [20, 21]. These two ratios have been adapted to classify CTP mismatch pattern in this study. However, these two ratios are part of a likely continuum of potential benefit from reperfusion and further study is required to identify the spectrum of ratios where favourable outcome can occur along with the extent and probability of that outcome.

- Secondly, how to apply CTP in posterior circulation stroke? The findings of this study come from and apply to patients with anterior circulation stroke. Patients with posterior circulation stroke have been excluded due to the heterogeneity of blood supply, the uncertainty about threshold for ischemic penumbra, and the challenge with spatial resolution of perfusion imaging in the posterior fossa. To date, perfusion imaging research on posterior circulation stroke has been limited to case reports, showing that 320-detector CTP enables ischemic lesion detection in cerebellum or brain stem with the extended brain coverage [46, 47]. The detection of ischaemic lesion in the posterior fossa was also observed in our clinical centre. In the future, after recruiting more cases, a study will be performed to validate the advantage of 320-detector CTP on posterior circulation stroke and to derive penumbral threshold on posterior circulation stroke.
Thirdly, how to use the angiographic reconstruction from CTP? One advantage of the 320-detector CTP that has not been explored in this thesis is the dynamic CTA reconstructed from the perfusion acquisition. In other words, one bolus of contrast enables the generation of dynamic CTA and CTP simultaneously. Now that the endovascular therapy is rapidly becoming the mainstay for large vessel occlusion of ischemic stroke, non-invasive imaging of the carotid vessels prior to intervention becomes important for interventionist to plan the procedure. The dynamic CTA, reconstructed from 320-detector CTP, has the brain coverage of 160mm that can provide occlusion information of the intra-cranial section of the carotid artery. However, its coverage may not wide enough to include occlusions located at the cervical part of the carotid artery. Therefore, an acquisition of cervical CTA (with a second bolus of contrast) is necessary following the acquisition of CTP. Regarding the advantage and limitation of dynamic CTA in the application of endovascular treatment, further study is required.
7.5 Reference


APPENDICES

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**Abbreviations**

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<tr>
<th>Abbreviation</th>
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<tr>
<td>AIF</td>
<td>Arterial input function</td>
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<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
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<tr>
<td>CBV</td>
<td>Cerebral blood volume</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>CTA</td>
<td>Computed tomography angiography</td>
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<td>CTP</td>
<td>Computed tomography perfusion</td>
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<tr>
<td>dSVD</td>
<td>delay-corrected Single Value Deconvolution</td>
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<td>DT</td>
<td>Delay time</td>
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<td>DWI</td>
<td>Diffusion weighted imaging</td>
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<td>Magnetic resonance angiography</td>
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<td>MRP</td>
<td>Magnetic resonance perfusion</td>
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<td>MTT</td>
<td>Mean transit time</td>
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<td>None contrast computed tomography</td>
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<td>Positron emission tomography</td>
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<td>Standard Single Value Deconvolution</td>
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<td>SVD</td>
<td>Single Value Deconvolution</td>
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<td>Tmax</td>
<td>Time to peak of the residual function</td>
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