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Perfusion computer tomography: imaging and clinical validation in acute ischaemic stroke

Andrew Bivard, Neil Spratt, Christopher Levi and Mark Parsons

Department of Neurology and Hunter Medical Research Institute, HMRI Clinical Research Centre, Level 3 John Hunter Hospital, New Lambton Heights, NSW 2310 Australia

Correspondence to: Mark Parsons, MD, FRACP,
Department of Neurology and Hunter Medical Research Institute,
HMRI Clinical Research Centre,
Level 3 John Hunter Hospital,
Lookout Road, New Lambton Heights,
NSW 2310, Australia
E-mail: mark.parsons@hnehealth.nsw.gov.au

Computed tomography perfusion imaging in acute stroke requires further validation. We aimed to establish the optimal computed tomography perfusion parameters defining the infarct core and critically hypoperfused tissue. Sub-6-h computed tomography perfusion and 24-h magnetic resonance imaging were analysed from 314 consecutive patients with ischaemic stroke. Diffusion-weighted imaging lesion volume at 24 h was used to define the extent of critically hypoperfused tissue (in patients without reperfusion between acute and 24-h time points), and infarct core (in patients with major reperfusion at 24 h). Pixel-based analysis of co-registered computed tomography perfusion and diffusion-weighted imaging was then used to define the optimum computed tomography perfusion thresholds for critically hypoperfused at-risk tissue and infarct core. These optimized acute computed tomography perfusion threshold-based lesion volumes were then compared with 24-h diffusion-weighted imaging infarct volume, as well as 24-h and 90-day clinical outcomes for validation. Relative delay time >2 s was the most accurate computed tomography perfusion threshold in predicting the extent of critically hypoperfused tissue with both receiver operating curve analysis (area under curve 0.86), and the volumetric validation (mean difference between computed tomography perfusion and 24-h diffusion-weighted imaging lesions = 2 cm^2, 95% confidence interval 0.5–3.2 cm^2). Cerebral blood flow $<40\%$ (of contralateral) within the relative delay time >2 s perfusion lesion was the most accurate computed tomography perfusion threshold at defining infarct core with both receiver operating characteristic analysis (area under curve = 0.85) and the volumetric validation. Using these thresholds, the extent of computed tomography perfusion mismatch tissue (the volume of 'at-risk' tissue between the critically hypoperfused and core thresholds) salvaged from infarction correlated with clinical improvement at 24 h ($R^2 = 0.59$, $P = 0.04$) and 90 days ($R^2 = 0.42$, $P = 0.02$). Patients with larger baseline computed tomography perfusion infarct core volume (>25 ml) also had poorer recovery at Day 90 ($P = 0.039$). Computed tomography perfusion can accurately identify critically hypoperfused tissue that progresses to infarction without early reperfusion, and the computed tomography perfusion cerebral blood flow infarct core closely predicts the final volume of infarcted tissue in patients who do reperfuse. The computed tomography perfusion infarct core and at-risk measures identified are also strong predictors of clinical outcome.

Keywords: perfusion CT; DWI; infarct core; penumbra; clinical outcome

Abbreviations: DWI = diffusion-weighted imaging; NIHSS = National Institutes of Health Stroke Scale

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Introduction

An individually tailored approach to the selection of acute patients with stroke for acute reperfusion therapies using tissue pathophysiology involves assessment of irreversibly injured tissue (infarct core) and the extent of salvageable brain (critically hypoperfused 'at-risk' tissue) (Barber *et al*., 1998; Davis *et al*., 2005; Nakashima and Minematsu, 2009). Perfusion CT is more widely available than MRI and has the potential to provide similar pathophysiological information to stroke MRI more rapidly (Parsons, 2008). There is still validation needed to determine the most appropriate perfusion thresholds for identification of critically hypoperfused at-risk tissue for both modalities. However, for perfusion CT there is the added complexity that thresholds to identify both infarct core and critically hypoperfused tissue accurately are required. We have shown recently that a relative cerebral blood flow threshold defined the infarct core accurately with perfusion CT (Bivard *et al*., 2010). When compared with other perfusion techniques such as PET (Shinohara *et al*., 2010) and single-photon emission CT (Sasaki *et al*., 2009), perfusion CT cerebral blood flow absolute values for infarct core are underestimated, but the relative values are very similar.

The specific aims of the current study were: (i) to identify the most accurate perfusion threshold for critically hypoperfused tissue; (ii) to assess whether the application of a more stringent perfusion threshold within the critically hypoperfused region would more accurately identify the infarct core; and (iii) to validate these perfusion CT infarct cores and critically hypoperfused lesion measures clinically by correlating them with clinical recovery and tissue outcome.

Patients and methods

Patients

We prospectively studied consecutive patients with hemispheric ischaemia presenting within 6 h of symptom onset. All patients underwent baseline multimodal CT examination and follow-up MRI at 24 h. A subset of these patients also had acute MRI within 60 min of perfusion CT. Clinical stroke severity using the National Institutes of Health Stroke Scale (NIHSS) was performed immediately prior to imaging, and level of disability at 3 months was measured with the modified Rankin scale. If eligible, patients were treated with intravenous thrombolysis according to standard guidelines. The study was approved by the institutional ethics committee and all patients gave informed consent.

Imaging

Whole-brain non-contrast CT (NCCT) was followed by perfusion CT, comprising two 60-s series (16-slice Philips Mx8000 or 64-slice Philips Brilliance). CT perfusion imaging was performed with an intravenous bolus injection of contrast agent (40 ml of ultravist 370; Bayer HealthCare) injected at a rate of 6 ml/s, with 45 time points acquired each 1.33 s. Each perfusion series covered 24- to 40-mm sections acquired as four to eight adjacent 5- to 6-mm slices (depending on whether 16- or 64-slice CT). The first section was at the level of the basal ganglia/internal capsule, and the second was placed 6 mm towards the vertex to avoid overlap. CT angiography was performed after perfusion CT with acquisition from the aortic arch to the top of the lateral ventricles (Parsons *et al*., 2009).

MRI was performed on a 1.5T MRI (Siemens Avanto). The stroke MRI protocol included an axial isotropic diffusion-weighted imaging (DWI) echoplanar spin-echo sequence, time of flight magnetic resonance angiography and bolus-tracking perfusion weighted imaging (Parsons *et al*., 2009).

Image analysis

Perfusion CT maps were calculated by commercial software MIStar (Apollo Medical Imaging Technology) (Parsons *et al*., 2005, 2007). This required selection of a global arterial input function from a normal major artery (such as the anterior cerebral artery) and a venous outflow function from a large draining vein (such as the sagittal sinus). Deconvolution of the tissue enhancement curve and the arterial input function was performed using a model-free singular value decomposition with a delay and dispersion correction (Yang, 2005, 2010). This methodology produces delay time maps, rather than the more widely known Tmax map, as well as maps of cerebral blood flow, cerebral blood volume and mean transit time. For more technical details on the difference between delay time and Tmax, see Supplementary material. Areas of no blood flow, chronic infarction or CSF regions were masked from the perfusion maps: no blood flow pixels were removed by eliminating areas where cerebral blood flow = 0 and CSF/ventricle and skull pixels were removed using a Hounsfield unit threshold and geometric analysis.

Before perfusion post-processing, each perfusion CT slab (source image data) was individually co-registered to the corresponding acute and 24-h DWI ($b = 1000$ image) anatomical location. Images that failed to register in the first attempt using a rigid body 3D registration ($n = 42$) were subjected to a standardized sequence of alternate registration procedures, including manual initialization as well as scaling and shear transforms to correct for echoplanar imaging artefacts. Cases that failed these coregistration attempts were excluded ($n = 7$).

Acute and 24-h DWI lesions were delineated based on signal intensity and highlighted using an area of interest tool. Next, the areas of interest were transferred to the co-registered acute perfusion CT maps for statistical volume analysis. A range of relative and absolute thresholds were then investigated at constant increments as shown in Table 1. Both relative thresholds (as a percentage of perfusion parameters in contralateral hemisphere, excluding large vessels), and absolute thresholds were tested. For the delay time thresholds, absolute

Table 1 Range and increments used for receiver operating characteristics analysis to investigate perfusion CT thresholds to define critically hypoperfused tissue

Perfusion CT parameter	Range	Increments
Relative cerebral blood volume (%)	0–100	5
Absolute cerebral blood volume (ml/100g)	1–5	0.5
Relative cerebral blood flow (%)	0–100	5
Absolute cerebral blood flow (ml/100g/min)	1–20	1
Relative delay time (s)	1–10 + baseline	0.5
Absolute delay time (s)	0–10	0.5
Mean transit time (%)	100–500	25

measures of delay time were used, as well as a relative measure where absolute delay was added to the average delay time in normal tissue ('baseline delay'). Normal tissue baseline was defined as mean perfusion values from tissue in the unaffected hemisphere, with large vessel voxels being excluded from analysis. Thresholds tested also included those reported in previous studies as predictive of tissue fate (Murphy *et al*., 2006; Wintermark *et al*., 2002, 2008).

Patient grouping based upon reperfusion status

Patients were divided into three groups: major reperfusion (>80% at 24 h), no reperfusion (<20% reperfusion at 24 h) and partial reperfusion (between 20% and 80%) based on change between acute CT and 24-h magnetic resonance perfusion lesion volume (Miteff *et al.*, 2009; Parsons *et al.*, 2009). As per previous studies, the same perfusion map (mean transit time) was used for both acute perfusion CT and MRI, with the same threshold applied to define lesion volume (the most commonly used for CT perfusion lesion determination: mean transit time > 145% of normal tissue) (Wintermark *et al.*, 2006).

Although we have used acute perfusion CT-mean transit time and 24-h magnetic resonance-mean transit time previously to measure reperfusion, we performed an analysis in the sub-group of patients with acute MRI to assess further the validity of perfusion CT- versus magnetic resonance-mean transit time lesion comparisons. This involved a volumetric correlation between the acute perfusion CT-mean transit time lesion (>145% threshold) with the acute magnetic resonance-mean transit time lesion (>145% threshold).

There is little data on what the ideal 'no reperfusion' cut-point at 24 h is; thus we chose <20% to be consistent with the major reperfusion cut-point. The partial reperfusion group was excluded from further analyses with 24-h DWI because of uncertainty about the potential for infarct growth between the acute and 24-h time points. Again, to assess further the validity of these reperfusion categories in the patients with acute MRI, we compared growth of the DWI lesion (acute to 24 h) in the three reperfusion categories (major, partial and none). The hypothesis was that major reperfusion should lead to minimal infarct growth, no reperfusion would be associated with significant infarct growth and there would be a broad range of infarct growth (i.e. minimal to large) in the partial reperfusion group.

Analyses

Defining critically hypoperfused tissue in patients with no reperfusion using 24-hour DWI

The 24-h DWI lesions in the no reperfusion group were used as the reference to define the critically hypoperfused tissue perfusion CT threshold using receiver operating characteristic analysis.

Defining the infarct core within critically hypoperfused tissue in patients with major reperfusion using 24-hour and acute DWI

Once the most accurate perfusion CT critically hypoperfused at-risk threshold for the perfusion lesion had been identified from the non-reperfused group, two analyses were performed to derive infarct core thresholds. First, the 24-h DWI lesion was used as the reference in patients with major reperfusion to define the perfusion CT infarct core perfusion threshold using receiver operating characteristics analysis. Secondly, in the sub-group of patients who had concurrent acute MRI, the acute DWI lesion was used as the reference to define the perfusion CT infarct core threshold using receiver operating characteristics analysis.

For these analyses we hypothesized that the infarct core thresholds would be more accurate when restricted within predefined critically hypoperfused lesion thresholds. This was tested using the most accurate critically hypoperfused thresholds from the three best performing perfusion maps from the patients with no reperfusion using 24-h DWI analysis.

Statistical analysis

Receiver operating characteristic curve analysis was used to test the predictive performance of perfusion CT in relation to the DWI infarct core. The DWI image was considered to be the 'true' lesion and the pixels where the DWI lesion and perfusion CT lesion overlapped were considered to be 'true positive'. DWI pixels not within the perfusion CT lesion were considered to be 'true negative'. Pixels within the perfusion CT lesion but not within the DWI lesion were assigned as 'false positive', and pixels within the DWI lesion but not within the perfusion CT lesion were assigned as 'false negative'. Specificity [true negative/(true negative + false positive)] and sensitivity [true positive/(true positive + false negative)] were calculated for each perfusion map. Results presented are area under curve [and 95% confidence intervals (CIs)] for the whole receiver operating characteristics curve for a specific perfusion map. Specificity, sensitivity, positive predictive value and negative predictive value were calculated for each threshold increment (e.g. cerebral blood flow or mean transit time).

In order to provide balance in the number of pixels being measured and prevent a large true negative value from overwhelming the ratio to false positives in the calculation of specificity, only hemispheric (ischaemic side) brain pixels were analysed rather than whole brain. Without this correction the false negative values would have a much greater influence upon the area under curve than the false positives, producing results that could substantially overestimate the true lesion volume.

Volumetric validation

To validate internally the receiver operating characteristics results, a lesion volume analysis was also undertaken to determine the closeness of fit between the perfusion CT threshold-derived infarct core and 24-h DWI lesion volumes in the major reperfusion group; and perfusion CT threshold-derived critically hypoperfused lesion volumes versus 24-h DWI lesion volumes in the no reperfusion group. For each patient, lesion volumes were calculated from the relevant perfusion CT threshold and plotted against the corresponding 24-h DWI lesion volume.

Clinical validation

Finally, there were statistical analyses performed to test the clinical validity of the core and critically hypoperfused at-risk thresholds. The perfusion lesion defined by the 'best' perfusion CT threshold for critically hypoperfused tissue was correlated with both acute and 24-h NIHSS. Infarct core volumes determined from the most accurate perfusion CT core threshold were correlated with change in acute 24-h NIHSS, and Day 90 modified Rankin scale, as recent studies have suggested baseline infarct core volume is an important predictor of ultimate clinical outcome. Additionally, patients were dichotomized on the basis of acute infarct core volume to determine whether a larger perfusion CT defined infarct core (>25 ml) was predictive of poor clinical outcome, as has recently been found for acute DWI-defined infarct core (Parsons, 2010). Early and late clinical recovery was also correlated with the volume of perfusion CT 'mismatch' tissue

(defined as tissue between the critically hypoperfused and core thresholds) salvaged from infarction in all patients.

Results

During the study period (2005–10), 314 patients with ischaemic stroke underwent perfusion CT within 6 h of symptom onset and a 24-h diffusion and perfusion MRI. The median age was 70 years (range 23–89 years), median acute NIHSS was 13 (range 5–24) and median time from symptom onset to end of perfusion CT was 162 min (interquartile range 185–240 min). One hundred and forty-four patients had no reperfusion, 106 had major reperfusion and 64 patients had partial reperfusion. Intravenous thrombolysis was administered to 61 patients with no reperfusion (39%), 82 patients with major reperfusion (77%) and 35 with partial reperfusion (55%). In the 67 patients with additional acute MRI, the median time to start of acute magnetic resonance scan was 240 min from stroke onset (interquartile range 210–270 min). The median time between the end of CT scanning and the start of MRI scanning was 19 min (interquartile range 15–40 min).

Validation of the reperfusion measures and classification system

In the 67 patients with acute perfusion CT and perfusion MRI (Supplementary Fig. 1), the perfusion CT- and magnetic resonance-mean transit time >145% lesion volumes were highly correlated ($R^2 = 0.81$, $P = 0.01$). Also confirming the effectiveness of major reperfusion at preventing infarct growth, there was a no significant difference between the acute and 24-h DWI in patients with major reperfusion (mean lesion growth 1.5 cm^3, 95% CI −0.3 to 2.2 cm^3, $P = 0.24$). Furthermore, none of these patients showed significant lesion reduction between the acute and 24-h DWI time points. In contrast, there was a significant increase in lesion size in the no reperfusion group (mean lesion growth 12cm^3, $P = 0.01$), also the partial reperfusion group (mean lesion growth 8 cm^3, $P = 0.005$). Infarct growth in the no reperfusion group was significantly greater than in the major reperfusion group ($P = 0.035$), but the partial reperfusion group had a wide range of infarct growth, overlapping with the other two groups (Supplementary Fig. 2).

Defining critically hypoperfused tissue in patients with no reperfusion

Of the 144 patients without significant (<20%) reperfusion, 124 were suitable for analysis, seven patients were excluded due to inadequate co-registration from very large shear coefficients, nine had inadequate-quality perfusion CT maps (three due to slow arrival of contrast and four due to severe patient movement) and four had basilar artery occlusion.

The most accurate map using receiver operating characteristics analysis to predict subsequent infarction in this group was relative delay time (area under curve = 0.86, 95% CI 0.84–0.88). The 'best' relative Delay time threshold was > 2 s (specificity 0.89, 95% CI 0.86–0.92; sensitivity 0.85, 95% CI 0.81–0.90). The absolute delay time map was also very accurate at predicting infarction at 24 h (area under curve = 0.85, 95% CI 0.83–0.87). The most accurate absolute delay time threshold was > 2 s (specificity 0.86, 95% CI 0.80–0.89; sensitivity 0.85, 95% CI 0.79–0.89). These two relative and absolute delay time thresholds were also the most closely correlated with the 24-h DWI lesion in the volumetric analysis (Fig. 1). The relative delay time >2 s threshold overestimated the DWI infarct by a small amount, mean 2 cm^2 (95% CI 0.5–3.2 cm^2), while the absolute delay time >2 s threshold was slightly less accurate, overestimating infarction by a mean of 3 cm^2 (95% CI 1.7–4.6 cm^2).

Of note, the relative delay time >3 s threshold was also very accurate in predicting 24-h infarction (specificity 0.93, sensitivity 0.72). However, as the relative delay time >3 s threshold was more specific but less sensitive than relative delay time >2 s (Table 2), it tended to underestimate the subsequent infarct (mean difference −3.2 cm^3; 95% CI −5.1 to 0.3 cm^2).

Defining the infarct core within critically hypoperfused tissue in patients with major reperfusion using 24-hour DWI

Of the 106 patients studied with major reperfusion, 89 were suitable for analysis, with 17 patients being excluded; nine due to very large sheer coefficient leading to poor co-registration, three due to basilar occlusion and five due to poor-quality perfusion CT maps (two due to mistimed injection of contrast and three due to patient movement).

From the data of patients with no reperfusion (Table 3), the three most accurate perfusion maps and their respective best thresholds to define critically hypoperfused tissue were relative delay time (>2 s), absolute delay time (>2 s) and mean transit time (>140%). Relative cerebral blood flow was the most accurate perfusion CT map to define the infarct core within all three critically hypoperfused tissue thresholds (Table 3), with relative cerebral blood flow <40% being the best performing threshold on each occasion (Table 4). Using relative cerebral blood flow, infarct core was defined most accurately within the critically hypoperfused tissue threshold relative delay time >2 s (area under curve = 0.86, 95% CI 0.83–0.89; relative cerebral blood flow <40%, specificity 0.78, specificity 0.93). Relative cerebral blood flow also defined the infarct core very accurately within absolute delay time >2 s tissue (area under curve = 0.85, 95% CI 0.8–0.87; relative cerebral blood flow <40% specificity 0.92, specificity 0. 71). Relative cerebral blood flow defined infarct core less accurately within critically hypoperfused tissue defined by the mean transit time >140% threshold, (area under curve = 0.8, 95% CI 0.76–0.83; relative cerebral blood flow <40%, specificity 0.86, specificity 0.63). The relative cerebral blood flow <40% infarct core threshold (within relative delay time >2 s critically hypoperfused tissue) was also the most closely correlated with the 24-h DWI lesion in the volumetric analysis (Fig. 1 and Table 4). Volumes obtained from this threshold overestimated the DWI lesion by a small amount, mean 3.6 cm^3 (95% CI = −0.7 to 5.4 cm^3), with few outliers (Fig. 1).

Defining the infarct core within critically hypoperfused tissue in patients with acute DWI

Sixty-seven patients comprised the analysis with acute DWI, 24 of who received thrombolysis. Of these 67 patients, 23 had major

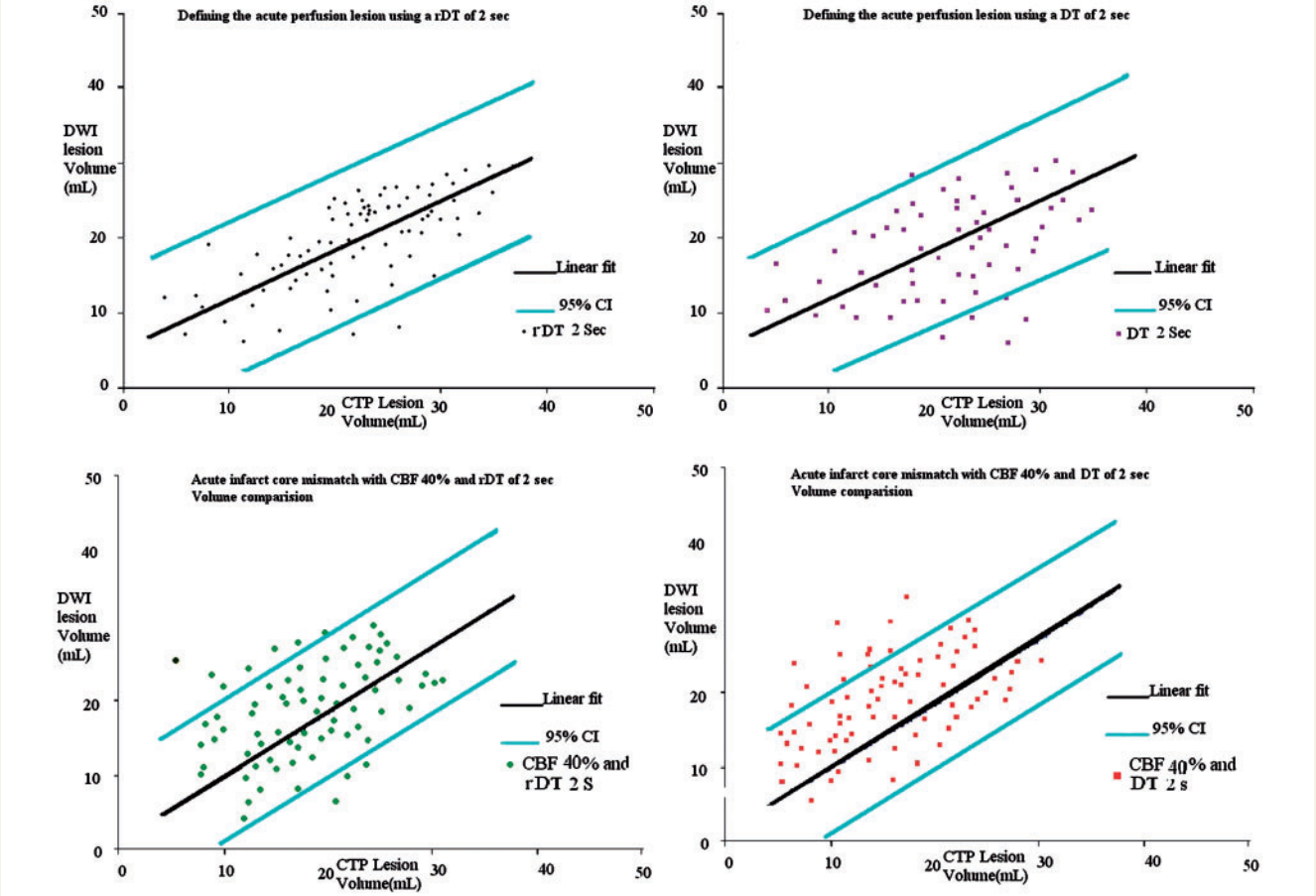

Figure 1 Four graphs plotting the volumes derived from the two most accurate acute perfusion CT (CTP) thresholds for critically hypoperfused tissue (*top*) and the infarct core (*bottom*) against the volume of the 24-h DWI. Note that for both the perfusion lesion and infarct core threshold correlations with 24-h DWI, relative delay time (rDT) performs slightly better than absolute delay time with less outliers outside the 95% CI lines (light blue lines). CBF = cerebral blood flow.

Table 2 Relative delay time thresholds: accuracy at defining critically hypoperfused tissue in the receiver operating characteristics analysis and in lesion volume correlation with 24-h DWI

Relative delay time threshold (s)	Specificity	Sensitivity	PPV	NPV	Perfusion CT-DWI volume mean difference (95% CI) (cm^2)
>1	0.57	0.94	0.63	0.92	3.1 (0.1 to 5.3)
>2	0.91	0.85	0.79	0.88	2.1 (−0.5 to 3.2)
>3	0.93	0.72	0.85	0.82	−3.2 (−5.1 to −0.3)
>4	0.94	0.59	0.88	0.77	−4.7 (−1.2 to −6.1)
>5	0.96	0.51	0.91	0.74	−5.38 (−2.1 to −8.7

These analyses were performed in patients with no reperfusion.
NPV = negative predictive value; PPV = positive predictive value.

reperfusion at 24 h, of which 17 received intravenous thrombolysis.

The area under curve results and lesion volume analysis yielded virtually identical results in patients with major reperfusion where the infarct core was defined by 24-h DWI. Relative cerebral blood flow within relative delay time >2 s critically hypoperfused tissue again had the highest area under curve (area under curve = 0.86, 95% CI 0.81–0.88), with relative cerebral blood flow <40% being the best performing threshold in the receiver operating characteristics and volumetric analyses.

Clinical validation of perfusion CT thresholds

The acute NIHSS score was highly correlated with the volume of the total acute relative delay time >2 s lesion ($R^2 = 0.71$, $P = 0.01$). The volume of perfusion CT 'mismatch' tissue (i.e. tissue critically hypoperfused, with relative delay time >2 s, but above the infarct core threshold of relative cerebral blood flow <40%) salvaged from infarction at 24 h was highly correlated with acute to 24-h NIHSS improvement ($R^2 = 0.59$, $P = 0.04$), as well as with 90-day modified Rankin scale ($R^2 = 0.42$, $P = 0.02$). Patients with a larger baseline (>25 ml) infarct core (tissue relative delay time > 2 s and with relative cerebral blood flow <40%),

Table 3 Accuracy of thresholds to define the acute perfusion lesion

Best threshold per map	Area under curve	95% CI	PPV	Sensitivity	Specificity	R^2
Relative delay time >2 s	0.86	0.89–0.81	0.8	0.82	0.9	0.81*
Cerebral blood flow <50%	0.72	0.74–0.71	0.66	0.7	0.74	0.71
Cerebral blood volume <55%	0.63	0.65–0.61	0.6	0.76	0.51	0.53
Mean transit time >140%	0.78	0.79–0.77	0.74	0.77	0.79	0.62
Absolute delay time >2 s	0.83	0.87–0.79	0.79	0.82	0.83	0.8*
Cerebral blood flow <10 ml/100g/min	0.74	0.76–0.73	0.5	0.67	0.83	0.61
Cerebral blood volume <2 ml/100g	0.63	0.6–0.66	0.69	0.82	0.44	0.6
Mean transit time >8 s	0.71	0.74–0.68	0.64	0.63	0.76	0.68

This is the characterization of the perfusion lesion showing the most accurate thresholds for each perfusion map tested in the study. The area under curve and 95% CI refer to the perfusion map and the positive predictive value, sensitivity and specificity refer to the best threshold for that particular map. R^2 and *P*-value relate to the perfusion CT threshold-generated lesion volume correlation with 24-h DWI (in patients with no reperfusion).
*$P < 0.05$ for the regression equation.
PPV = positive predictive value.

Table 4 Infarct core threshold results

Perfusion lesion threshold	Infarct core threshold	Area under curve	95% CI	Sensitivity	Specificity	PPV	R^2
Relative delay time >2 s	Cerebral blood flow <40%	0.86	0.92–0.82	0.93	0.78	0.77	0.79*
	Cerebral blood flow <50%	0.86	0.92–0.82	0.96	0.62	0.73	0.62
Mean transit time >140%	Cerebral blood flow <40%	0.8	0.83–0.76	0.86	0.63	0.65	0.66
	Cerebral blood flow <4 ml/100g/min	0.8	0.83–0.76	0.84	0.55	0.56	0.68
Absolute delay time >2 s	Cerebral blood flow <40%	0.86	0.89–0.84	0.92	0.71	0.72	0.76*
	Cerebral blood volume <90%	0.8	0.84–0.76	0.92	0.71	0.65	0.71

This is the characterization of the infarct core within the perfusion lesion showing the most accurate thresholds for every measure tested across three perfusion lesion measures. The area under curve and 95% CI refers to the perfusion map and the positive predictive value (PPV), sensitivity and specificity refer to the best threshold for that particular map. R^2 and *P*-value relate to the perfusion CT threshold-generated lesion volume correlation with 24-h DWI (in patients with major reperfusion).
*$P < 0.05$ for the regression equation.

appeared to have less early clinical improvement (median acute to 24-h NIHSS change = 4, IQR −1 to 6) compared with those with a smaller baseline infarct core (median acute to 24-h NIHSS change = 8, interquartile range 5–11). This difference was not statistically significant ($P = 0.27$). However, patients with a large baseline perfusion CT-defined infarct core (>25 ml) clearly had poorer 3-month outcome than those with a small baseline infarct core (median modified Rankin scale = 5 versus 2, respectively, $P = 0.039$).

Discussion

This study has shown that acute perfusion CT can accurately identify the acute infarct core and critically hypoperfused tissue. Additionally, the volume of baseline perfusion CT infarct core and the amount of perfusion CT mismatch tissue subsequently salvaged from infarction had a major influence on early and late clinical outcome. Although there are also important implications in terms of perfusion post-processing methods, our study primarily has major clinical implications, demonstrating that perfusion CT can accurately measure irreversible and reversibly ischaemic tissue. As perfusion CT is widely available, the stage is set to finally have a truly generalizable tissue-based acute stroke imaging technique.

This study provides strong evidence for the clinical validity of perfusion CT in acute ischaemic stroke. The acute perfusion CT critically hypoperfused lesion volume was closely correlated with the baseline clinical deficit (NIHSS), indicating significant functional impairment of this tissue, consistent with many other studies using different perfusion modalities (Parsons *et al*., 2005; Takasawa, 2008). The similarly strong relationship of clinical recovery with perfusion CT mismatch tissue salvaged from infarction by reperfusion emphasizes the potential clinical importance of using this information to predict outcome (particularly with thrombolysis). Conversely, the high rate of progression of perfusion CT mismatch tissue to infarction in patients without reperfusion, and the strong association with poor clinical outcome in this group, is also extremely valuable clinical information. Another novel finding of this study is the crucial influence of the volume of the baseline perfusion CT infarct core upon clinical outcome, paralleling recent data from studies using DWI measures of acute infarct core (Furlan *et al*., 1996; Singer *et al*., 2008; Campbell *et al*., 2010, 2011; Christensen *et al*., 2009).

Although the clinical impact of our results is very important, the current study also describes a number of advances in perfusion CT post-processing methodology to define infarct core and critically hypoperfused tissue. Perfusion CT accurately defined hypoperfused 'at-risk' tissue by closely predicting subsequent infarction in patients who did not reperfuse using a single perfusion

threshold (relative delay time >2 s). Additionally, use of a relative cerebral blood flow threshold within critically hypoperfused tissue (elative cerebral blood flow <40% of normal and within tissue with relative delay time >2 s) accurately defined the acute infarct core (Fig. 2). Notably, this is the first perfusion CT study to demonstrate that a physiological delay time threshold provides an accurate definition of tissue at risk. This is in keeping with the perfusion magnetic resonance field where a similar measure to delay time, Tmax is the most commonly used perfusion definition of critically hypoperfused tissue (Shih *et al*., 2003; Olivot *et al*., 2009*a*, *b*; Asdaghi *et al*., 2011). Currently, the most widely used CT perfusion measure to identify critically hypoperfused tissue is mean transit time (Wintermark *et al*., 2008). Mean transit time maps were also reasonably accurate in our study, but did not perform as well as the delay time perfusion maps (Table 4 and Fig. 1).

While our perfusion CT study is the first to parallel the magnetic resonance literature in finding that delay time is more accurate than mean transit time, it is important to understand that although delay time and Tmax are related, they are not exactly the same measure (see Supplementary material). Notably, previous magnetic resonance perfusion studies have identified critically hypoperfused tissue thresholds of Tmax between 5 and 6 s, whereas we have shown that delay time between 2 and 3 s is more accurate when identifying critically hypoperfused tissue. Delay time is derived from a vascular transport model correcting for both arterial delay and dispersion effects. Thus, delay time is expected to reflect more precisely the physiological process of contrast transit than Tmax, and possibly more accurately identify critically hypoperfused tissue. Because of these corrections for arterial delay and dispersion, our physiologically modelled delay time threshold is expected to be less than the Tmax threshold for infarction. Whether delay time is more accurate at identifying critically hypoperfused tissue than Tmax warrants further study.

Some previous perfusion CT studies have also found that cerebral blood volume, or combined cerebral blood flow and cerebral blood volume, thresholds can predict the infarct core (Bandera *et al*., 2006; Wintermark *et al*., 2006). The current study also showed that relative cerebral blood volume maps were reasonably accurate in area under curve analysis at defining the infarct core (Fig. 2). However, the most accurate relative cerebral blood volume threshold (<90% of normal tissue) is too high to be clinically useful. Such a high relative cerebral blood volume threshold in infarct core most likely relates to the fact that the infarct core threshold was calculated within critically hypoperfused tissue. This suggests that virtually the entire infarct core has (at least) a small reduction in cerebral blood volume, in combination with significant delay (e.g. >2 s). As such, tissue with relative cerebral blood volume <90% and delay time >2 s was highly sensitive for detecting infarct core. However, we found that tissue with relative cerebral blood flow <40% and delay time >2 s was as sensitive but a more specific marker of infarct core (Table 2).

Despite the large data set, some limitations should be acknowledged. These relate particularly to the reperfusion definitions.

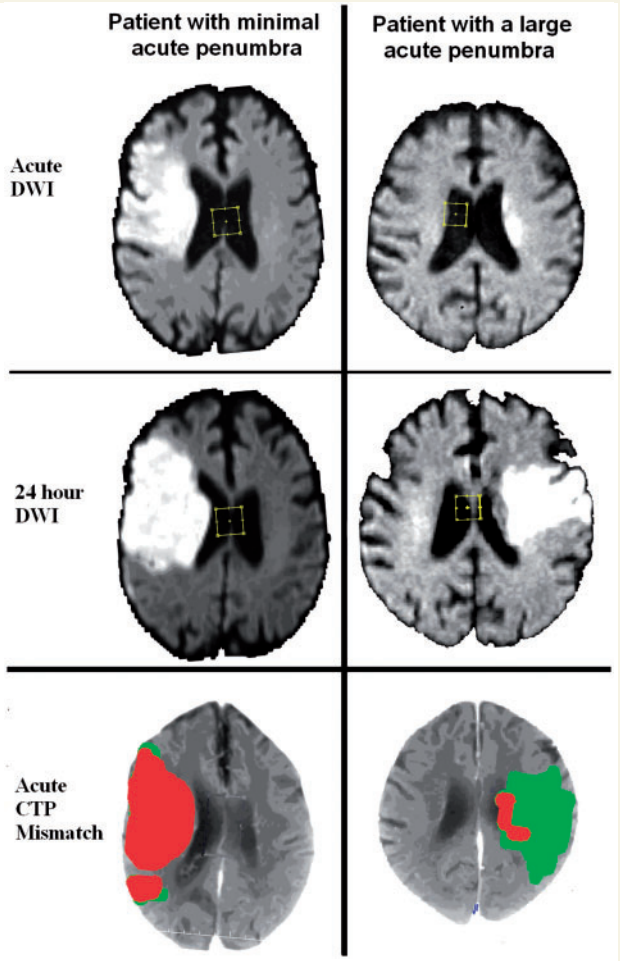

Figure 2 Two patients (*left* and *right* columns) in whom there was no reperfusion at 24 h. The acute and 24-h DWI were 're-sliced' after co-registration, with the bottom images showing the respective perfusion CT core/penumbra map overlaid on the perfusion CT (CTP) source image from the same slice location as the DWI. Note the green and red masks reflect acute perfusion CT penumbra and core maps, respectively. Note these maps are 'smoothed' and generated by cluster analysis to remove isolated 'noisy' artefactual pixels typically observed on perfusion CT maps. The examples show that it is possible to accurately predict the acute infarct core and the critically hypoperfused at-risk tissue using acute perfusion CT. Note in both patients the perfusion CT infarct core is very similar to the acute DWI lesion, while the 24-h DWI closely matches the full extent of acute perfusion CT perfusion lesion (green + red) in these two patients with no reperfusion. These two patients were both imaged within 4.5 h of symptom onset. The baseline perfusion CT data strongly suggest that the patient *left* would not benefit from reperfusion treatment (having a large infarct core at baseline—in red), while the second patient (*right*) would be highly likely to benefit should treatment result in early reperfusion as the at-risk (green) tissue has a very high probability of being salvaged. The perfusion CT core and critically hypoperfused at-risk tissue maps were generated using the 'best' thresholds of relative delay time of 2 s for critically hypoperfused tissue and relative cerebral blood flow <40% for the infarct core.

We decided to aim for as 'pure' reperfusion and no reperfusion groups as possible to define the most accurate acute perfusion thresholds for infarct core and critically hypoperfused tissue. The cut-points (>80 and <20%) we chose were based on our previous work (Mitef *et al*., 2008). We also made the assumption that patients with partial reperfusion (between 20% and 80%) would have a broader range of infarct growth, and thereby not allow derivation of an accurate perfusion threshold for critically hypoperfused tissue. Reassuringly, our reperfusion definitions seem valid, based on the data from the patients with acute and 24-h DWI. There was no significant infarct growth in the major reperfusion group, those in the no reperfusion group had extensive infarct growth and those with partial reperfusion did have a broad range of infarct growth (Supplementary Fig. 2). Notably, we also found the different reperfusion sub-groups had a gradient in clinical outcomes as well as for infarct growth, further indicating the validity of the reperfusion classification. Our reperfusion definition could also be criticized as it compared acute perfusion CT with 24-h magnetic resonance perfusion lesion volume. In fact, we have demonstrated that using the same threshold to define lesion volume (mean transit time >145%), acute CT-mean transit time and acute magnetic resonance-mean transit time lesions were extremely closely correlated. Others have suggested performing follow-up perfusion CT to measure reperfusion, but we now consider that it is very difficult to ethically justify exposing the patients to a doubling of radiation dose when we have an alternative technique (MRI) that can measure reperfusion accurately and, at the same time point, can also determine infarct volume more precisely than CT (Wintermark *et al*., 2008).

While we believe that our results have widespread applicability in terms of the potential for perfusion CT to accurately predict tissue and clinical outcome, we must emphasize that the specific thresholds used in our study only apply to the particular software used. It is widely recognized that the absolute values of perfusion maps derived from the same data can be dependent on the post-processing algorithms and corrections implemented by different software (Kudo *et al*., 2010). The novel post-processing methodology used in the current study has produced accurate (and clinically valid) measures of perfusion CT infarct core and penumbra. However, alternative post-processing algorithms may be equally valid, and our study provides a template for how CT perfusion post-processing methods can be validated for use in the future.

In conclusion, perfusion CT provides rapid and accurate information on stroke tissue pathophysiology. This information has been shown to be critical for prediction of tissue and clinical outcomes. Given the major influence of subsequent reperfusion (or lack thereof) on the baseline perfusion CT measures of core and penumbra, our results have extremely important implications in the use of perfusion CT to select patients for acute reperfusion therapies.

Supplementary material

Supplementary material is available at *Brain* online

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