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The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke

Ferdinand Miteff,[1,2] Christopher R. Levi,[1,2] Grant A. Bateman,[1] Neil Spratt,[1,2] Patrick McElduff[2] and Mark W. Parsons[1,2]

1 Department of Neurology, John Hunter Hospital, Newcastle Region Mail Centre, New South Wales, Australia
2 Hunter Medical Research Institute, Faculty of Health, University of Newcastle, Australia

Correspondence to: Ferdinand Miteff,
Department of Neurology,
John Hunter Hospital,
Locked Bag 1,
Hunter Region Mail Centre,
NSW 2310,
Australia
E-mail: ferdi.miteff@hnehealth.nsw.gov.au

It is unknown whether collateral vessel status, as seen on computed tomography angiography, can predict the fate of penumbral tissue identified on perfusion computed tomography and thereby influence clinical outcome. We tested this hypothesis in consecutive patients who underwent perfusion computed tomography/computed tomography angiography within 6 h of anterior circulation stroke, who also had repeat perfusion/infarct volume imaging at 24 h, and modified Rankin Scale at 3 months. Collateral status was graded as good or reduced depending on the extent of contrast visualized distal to the occlusion on computed tomography angiography. 'Perfusion computed tomography mismatch' ratio was calculated from the ratio of the mean transit time lesion/cerebral blood volume lesion. Of 92 patients with proximal intracranial vessel occlusion, good collateral status (51/92) was significantly associated with reduced infarct expansion and more favourable functional outcomes (modified Rankin Scale 0–2). Significant univariate predictors of favourable outcome were good collateral status, major reperfusion at 24 h, presence of perfusion computed tomography mismatch (for a range of ratios: $\geqslant$1.2, $\geqslant$2, $\geqslant$3, $\geqslant$3.5) and baseline National Institutes of Health Stroke Scale score. Notably, none of the 37 patients with a perfusion computed tomography mismatch ratio $<$3.0 had a favourable outcome. In patients with perfusion computed tomography mismatch, significant independent predictors of favourable outcome were good collateral status, major reperfusion and baseline National Institutes of Health Stroke Scale score. There was also a strong interaction between major reperfusion and good collateral status in the regression models. In patients with proximal vessel occlusion, perfusion computed tomography mismatch is a prerequisite for a favourable clinical response, but good collateral status appears a critical determinant of ultimate outcome, particularly if major reperfusion occurs.

Keywords: leptomeningeal collateral vessel status; CT angiography; CT perfusion; acute ischaemic stroke; multimodal CT imaging

Abbreviations: CBV = cerebral blood volume; CTP = cerebral CT perfusion; DSA = digital subtraction angiography; MCA = middle cerebral artery; MRI = magnetic resonance imaging; MTT = mean transit time

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Introduction

Brain at risk of infarction following cerebral arterial occlusion may remain potentially salvageable even beyond the currently accepted therapeutic time-window for thrombolysis (Markus *et al*., 2004). The presence of such penumbral tissue can be demonstrated on cerebral CT perfusion scanning (CTP) by volumetric analysis of mismatch between contrast transit and cerebral blood volume (CBV) lesions (Wintermark *et al*., 2002; Parsons *et al*., 2007). The advantage of advanced CT imaging supports a developing argument for applying more sophisticated imaging assessment in patient selection for thrombolysis (Schaefer *et al*., 2008). Penumbral imaging techniques are, however, limited by offering only a snapshot assessment of brain tissue viability, providing relatively little insight into how much longer the tissue might survive, with or without subsequent reperfusion. An improved measure of penumbral 'life expectancy' could significantly increase the clinical utility of baseline perfusion imaging.

Leptomeningeal collateral circulation provides crucial nutritional support to the penumbra (Brozici *et al*., 2003). Despite variation in how leptomeningeal collateral status is graded on angiography, studies generally confirm the importance of adequate collaterals (Bozzao *et al*., 1989; Knauth *et al*., 1997; Roberts *et al*., 2002; Schramm *et al*., 2002; Kucinski *et al*., 2003; Kim *et al*., 2004; Christoforidis *et al*., 2005; Bang *et al*., 2008*b*; Rosenthal *et al*., 2008). In particular, the retrograde reconstitution of the middle cerebral artery (MCA) up to the distal end of its occlusion appears to be a valid digital subtraction angiography (DSA) measure for defining good collateral status, and predicting smaller subsequent infarction in proximal anterior circulation occlusion (Roberts *et al*., 2002; Christoforidis *et al*., 2005). However, DSA alone provides no clear information about the amount of hypoperfused tissue at risk, whereas CTA can be performed with concurrent CTP as part of a 'multimodal' penumbral assessment (Parsons, 2008). We had previously adapted this DSA collateral scale to CTA in a small pilot study with high inter-observer agreement (Miteff *et al*., 2008).

There are no prior studies investigating whether collateral status on CT angiography provides additive predictive utility for tissue fate over that of CTP. We hypothesized that CT angiography collateral status would independently influence the probability of penumbra progressing to infarction, and thus, ultimately influence clinical outcome.

Methods

Consecutive acute ischaemic stroke patients presenting to our institution within 6 h of stroke symptom onset and being evaluated for stroke thrombolysis eligibility were prospectively entered into our acute stroke imaging and clinical outcome database between July 2006 and June 2008. This study was approved by our institutional Ethics Committee and individual patient consent was obtained. All patients underwent non-contrast CT (NCCT)/CTP/CTA at baseline and follow-up (24 h) magnetic resonance imaging (MRI), unless there were contraindications to MRI, in which case repeat NCCT/CTP/CTA was performed. National Institutes of Health Stroke Scale (NIHSS) was performed immediately before acute CT, at 24 h imaging, and the modified Rankin Scale (mRS) was performed at Day 90.

Imaging

CT scans were obtained with a multi-detector scanner (16-slice Philips Mx8000; Philips, Cleveland, OH, USA). Whole-brain NCCT was performed: 120 kV, 170 mA, 2 s scan time, contiguous 6 mm axial slices.

This was followed by CTP, comprising two 40-s series. Each series consisted of one image per slice per second, commencing 5 s after intravenous administration of 40 ml non-ionic iodinated contrast at a rate of 5 ml/s via a power injector. Acquisition parameters were 80 kVp and 120 mA. Each perfusion series covered a 24 mm axial section acquired either as two adjacent 12 mm slices or four adjacent 6 mm slices. The first section was at the level of the basal ganglia/internal capsule, and the second was placed directly above, toward the vertex. Thus, the two CTP series allow assessment of two adjacent 24 mm cerebral sections (viewed as either four contiguous 12 mm or eight contiguous 6 mm slices).

CTA was performed after CTP, using the following parameters: 120 kV, 125 mA, slice thickness 1.5 mm, pitch 1.5:1, helical scanning mode and intravenous administration of 70 ml non-ionic contrast at 4 ml/s. Bolus-tracking software was used to acquire images at peak contrast arrival. Data acquisition was from base of skull to the top of lateral ventricles.

Follow-up imaging used a 1.5T MRI (Siemens Vision; Siemens, South Iselin, NJ, USA), unless there was a contraindication, in which case NCCT/CTP/CTA were repeated using the above protocol. In brief, the stroke MRI protocol included an axial spin-echo T_2-weighted series, an axial isotropic diffusion-weighted echo planar spin-echo sequence, time of flight MR angiography, and perfusion-weighted imaging with an axial T_2*-weighted echo planar sequence (Parsons *et al*., 2002).

Imaging analysis

All CTA images were de-identified and reviewed digitally at a workstation (Philips MxView). Maximum intensity projection (MIP) reconstructions of baseline CTA in three planes (axial, coronal, sagittal) were independently assessed by two experienced observers: one stroke neurologist and one stroke fellow, blinded to patient clinical information, perfusion scans and other imaging. The proportion of agreement between observers was calculated.

CTA assessments

Patients were initially identified if complete occlusion on CTA was present. Complete occlusion within either the M1 segment of the MCA or terminal internal carotid artery was defined as a segment of one of these vessels with no visible contrast, isolating the distal MCA from the circle of Willis. In these patients with complete occlusion, contrast within the distal MCA (beyond the occlusion) was presumed secondary to retrograde filling via leptomeningeal collaterals. Collateral status was simply divided into 'good' or 'reduced' based on degree of reconstitution of the MCA up to the distal end of its occlusion on CTA (Fig. 1):

(i) CTA in patients with good collateral status showed the entire MCA distal to the occluded segment reconstituting with contrast. CTA maximum image projection reconstructions clearly demonstrated the MCA branches, with abrupt termination of

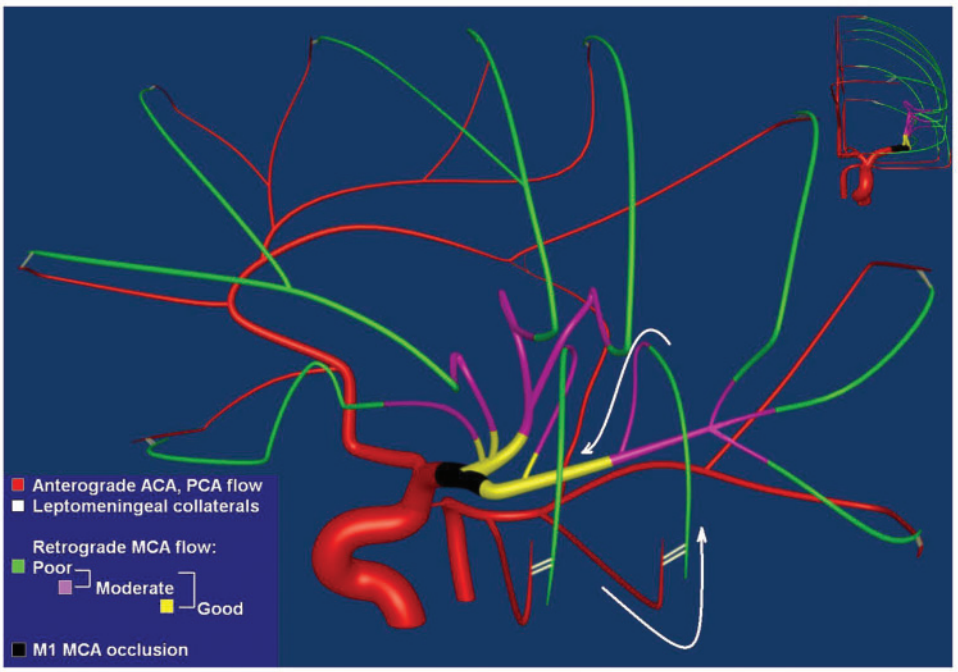

Figure 1 Schematic representation of the left cerebral hemisphere arteries, with proximal MCA occlusion (indicated in black) and variable grades of retrograde distal MCA blood flow (arrows) via the leptomeningeal collaterals (white). This includes 'poor' retrograde flow in superficial vessels only (through the green vessel segments), 'moderate' flow into the Sylvian fissure (through the green and purple segments) or 'good' flow up to the occlusion (through the green, purple and yellow segments).

the reconstituted vessels at the distal end of the occlusion within the M1 or proximal M2 segments (Fig. 2A).

(ii) In patients with reduced collateral status, the distal MCA reconstituted only partially. Although the primary aim of this study was to compare 'good' versus 'reduced' collateral status on CTA, we further subdivided the 'reduced' collaterals group based upon the following. If some of the MCA branches reconstituted within the Sylvian fissure this was designated 'moderate' collateral status (Fig. 2B), and if only the distal superficial MCA branches reconstituted this was designated 'poor' collateral status (Fig. 2C).

We also used dynamic CTP source image assessment as a 'quality control' to ensure that contrast visualized beyond an apparent complete occlusion on CTA was truly due to retrograde flow. Thus, dynamic CTP source images were reviewed to confirm that distal MCA branches filled with contrast prior to the proximal M2 divisions (Supplementary Fig. 1). If this could not be confirmed, these patients were excluded from further analysis. For this assessment, the CTP source images were reformatted into MIP images using commercial software (MIStar, Apollo Medical Imaging, Melbourne, Australia). This generated a dynamic arterial map allowing comparison of initial contrast arrival in different vessel segments (Supplementary Fig. 1).

Independent observer CTA assessments were then compared and regraded by consensus where independent grading differed. Follow-up MRA and CTA were also reviewed and graded as normal, partial occlusion or complete occlusion.

Assessment of baseline and follow-up perfusion lesions, and follow-up infarct volume

De-identified CTP and perfusion MR data were analysed with MIStar software using an identical deconvolution algorithm to generate both

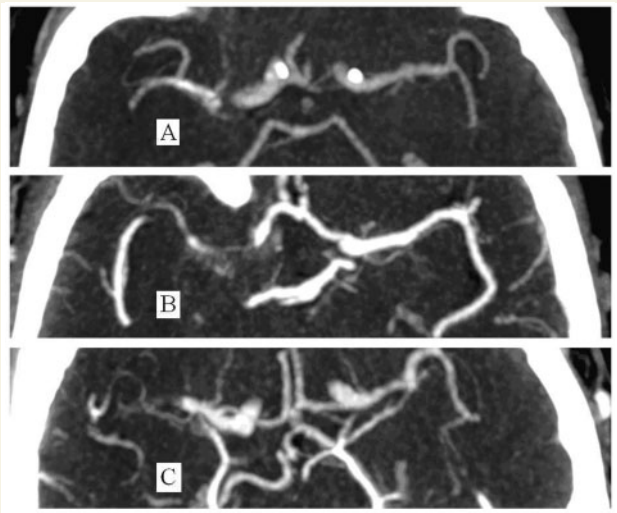

Figure 2 CT angiograms showing axial views of three right MCA occlusions with (**A**) good, (**B**) moderate and (**C**) poor reconstitution of the distal MCA.

CTP and MR perfusion maps, including mean transit time (MTT) and CBV (Parsons *et al*., 2005, 2007). A MTT delay of >145% compared with the contra-lateral hemisphere was used to calculate automated CTP MTT lesion volumes (Wintermark *et al*., 2006). Within the CTP MTT lesion, baseline infarct core volume was determined from CBV maps using an automated threshold of <2.0 ml/100 g (Wintermark *et al*., 2006). Thus, penumbral volume was automatically determined from the difference between the baseline CTP MTT lesion and CBV

lesions, and the 'CTP mismatch' ratio was calculated from MTT lesion volume/CBV lesion volume (using the above thresholds for MTT and CBV lesion volumes). The same software was used to measure follow-up infarct volume on 24 h imaging using automated signal intensity thresholds for MR-DWI, or Hounsfield unit thresholds for CT (Parsons *et al*., 2007). The follow-up infarct maps were co-registered with baseline CTP maps to obtain volumes from the same spatial position and axis orientation. To determine reperfusion, the same automated threshold (MTT delay of >145% compared with contra-lateral hemisphere) was used to calculate 24 h MR (or CTP)-MTT lesion volumes. The MR–MTT maps were co-registered with baseline CTP so that MR–MTT volumes were only obtained from the same spatial position and axis orientation as the CTP–MTT maps. All lesion volumes were obtained from the average of measurements taken on separate occasions by a stroke neurologist and stroke fellow. Reperfusion was defined as 'major' in patients with >80% reduction in baseline-24 h MTT lesion volume and/or complete vessel re-canalization (Parsons *et al*., 2005, 2007).

Statistical analysis

Statistical analysis was performed using STATA (Version 10, 2001; College Station, TX, USA).

The principal analysis was the use of logistic regression to determine the independent predictors of a favourable outcome (mRS 0–2). The predictors of interest were age, baseline NIHSS, the extent of CTP 'mismatch' (assessing a range of mismatch ratios: $\geqslant$1.2, $\geqslant$2, $\geqslant$3 and $\geqslant$3.5), administration of thrombolysis, good collateral status and major reperfusion. Each of these predictors was examined in a simple logistic regression model, and a selection of those with $P<0.10$ were included in two subsequent multiple logistic regression models. These models differed in terms of the particular predictors included. Combined predictors were also considered for addition in the multiple regression models to test for statistically significant interaction between these predictor variables. Due to the high level of correlation and interaction between the predictor variables, we developed a 'decision tree' to illustrate the interactions between independent variables in the multiple regression model.

Good and reduced collateral groups were compared in terms of baseline NIHSS, baseline infarct core and mismatch volumes, baseline 24 h infarct expansion, presence of a favourable outcome (mRS of 0–2) and stroke onset to CT imaging time. The same analyses were repeated for the good versus moderate, and moderate versus poor collateral status sub-groups. The comparison between collateral groups and the presence of a favourable outcome was done using a Fisher's exact test and the comparisons between collateral groups and continuous outcomes were done using a Wilcoxon rank sum test for two groups and Kruskall Wallis test for three groups.

Finally, inter-observer variability for assessment of collateral status (good, reduced, moderate and poor) between the two observers was tested using kappa statistics.

Results

Among 162 consecutive acute ischaemic stroke patients assessed for thrombolysis eligibility within 6 h of symptom onset, 92 patients (60 of whom received intravenous thrombolysis) were included in this study. The remainder were excluded due to having no visible occlusion ($n=19$), occlusion(s) originating beyond the M1 MCA ($n=18$), incomplete vessel occlusion ($n=4$), posterior circulation occlusion ($n=9$) and poor quality or no baseline CTA or CTP ($n=15$). There were also five patients with apparent complete occlusion on CTA excluded due to our inability to confirm retrograde filling of the MCA distal to the clot location on review of dynamic CTP source images, in view of the CTP volume not containing the vessel occlusion. There were 39 men and 53 woman with a median age of 74 years (inter-quartile range, IQR 64–81) and a median acute NIHSS of 17 (IQR 12–20).

Logistic regression analysis

Predictors of a favourable functional outcome in the simple logistic regression models were baseline stroke severity, good collateral status, major reperfusion and the presence of CTP mismatch at all ratios tested (for example, the odds of a favourable outcome were 50.8 for a mismatch ratio $\geqslant$3.5 versus <3.5) (Table 1). Notably, mismatch cut-points up to $\geqslant$3.0 predicted a poor outcome perfectly (e.g. no patient with a mismatch ratio <3.0 had a favourable outcome). Thus, when fitting significant predictors of a favourable outcome into the multiple regression models, the mismatch ratio variable was automatically dropped from the regression model (because it predicted 'failure', or a poor outcome, perfectly). Therefore, we tested the other significant

Table 1 Odds ratios (95% confidence intervals) for the prediction of good functional outcome (mRS 0–2)

Variable	Percent with mRS 0–2 (%)	Odds ratio (95% confidence interval)	*P*-value
Major reperfusion			
No ($n=54$)	13.0	1.00	<0.001
Yes ($n=38$)	52.6	7.46 (2.97–20.64)	
Good collaterals			
No ($n=41$)	7.3	1.00	<0.001
Yes ($n=51$)	47.1	11.26 (3.08–41.22)	
Age		0.98 (0.95–1.01)	0.227
Acute NIHSS		0.54 (0.41–0.70)	<0.001
Time to CT		0.88 (0.56–1.38)	0.584
Mismatch ratio ($\geqslant$1.2)			
No ($n=3$)	0	–[a]	
Yes ($n=89$)	30.3		
Mismatch ratio ($\geqslant$2.0)			
No ($n=28$)	0	–[a]	
Yes ($n=64$)	42.2		
Mismatch ratio ($\geqslant$3.0)			
No ($n=37$)	0	–[a]	
Yes ($n=55$)	49.1		
Mismatch ratio ($\geqslant$3.5)			
No ($n=44$)	2.3	1.00	<0.001
Yes ($n=48$)	54.2	50.8 (6.46–399.6)	
tPA			
No ($n=32$)	18.8	1.00	0.108
Yes ($n=60$)	35.0	2.33 (0.83–6.56)	

a Mismatch ratio below the cut-point predicts poor outcome perfectly, therefore odds ratio of good outcome for mismatch above cut-point is undefined due to no good outcomes in the reference category.

Table 2 Odds ratios and 95% confidence intervals for prediction of good functional outcome (mRS 0–2) in multiple regression analyses involving variables with a $P<0.10$ in the simple logistic regression analyses—separately for sub-groups of various mismatch cut-points

	Mismatch ratio cut-points (number above the cut-point)			
	⩾1.2 (*n* = 89)	⩾2.0 (*n* = 64)	⩾3.0 (*n* = 55)	⩾3.5 (*n* = 48)
Model 1				
Acute NIHSS	0.55 (0.42–0.72)	0.59 (0.45–0.77)	0.63 (0.47–0.83)	0.66 (0.50–0.87)
Good collaterals	9.74 (2.02–46.9)	7.54 (1.45–39.2)	5.92 (1.13–30.8)	5.02 (0.93–27.3)
Model 2				
Acute NIHSS	0.46 (0.30–0.69)	0.43 (0.26–0.78)	0.48 (0.24–0.91)	0.51 (0.27–0.97)
Good collaterals	39.0 (3.28–464)	81.5 (2.99–2218)	–[a]	–[a]
Major reperfusion[b]	25.1 (3.03–208)	70.9 (3.71–1353)	–[a]	–[a]
–[c]				

a Odds ratios approached infinity due to the interaction effect between good collaterals and major reperfusion.
b The models differ by inclusion of major reperfusion in model 2.
c An interaction term combining good collaterals with major reperfusion was not added because the interaction predicts outcome perfectly.

predictors of favourable outcome in multiple regression models only in the patients above the various mismatch cut-points (Table 2). The interaction between major reperfusion and collateral status had a significant impact on the multiple regression models. Baseline NIHSS and good collateral status were independent predictors of favourable outcome included in the multiple regression model 1 (Table 2). When major reperfusion was added to the regression, model 2, there were substantial increases in the odds of favourable outcome for both the presence of good collaterals and major reperfusion, when compared with their respective simple odds ratios (Tables 1 and 2). This strong interaction between major reperfusion and good collateral status was present above all mismatch ratio cut-points (Table 2). Addition of the interaction term combining good collaterals with major perfusion was considered, but it caused at least one of the terms and some of the observations to drop out of the model due to the model predicting outcomes perfectly.

To further illustrate the combined effects of good collateral status and major reperfusion upon favourable outcome in CTP mismatch patients, we designed a 'decision tree' based upon these three variables (Fig. 3). We choose a mismatch ratio cut-point of ⩾3.0 as this was the ratio where there was the largest number of patients with no favourable outcomes below the cut-point. Thus, all 37 patients below a mismatch ratio of 3.0 had an unfavourable outcome, consequently collateral status and major reperfusion were irrelevant in predicting outcome (Fig. 3). In those with a mismatch ratio ⩾3.0, 27 of 55 had a favourable outcome. Of these 55 patients, 36 had good collateral status, and all 17 with good collaterals and major reperfusion had a favourable outcome, whereas only 7 of 19 with good collaterals but without major reperfusion had a favourable outcome. Of the 19 patients with mismatch ratio ⩾3.0 and with reduced collaterals, only three had a favourable outcome, and all three had major reperfusion. Thus, in patients with a mismatch ratio ⩾3.0, the presence of good collaterals and major reperfusion predicted a favourable outcome perfectly and the absence of good collaterals and major reperfusion predicted an unfavourable outcome perfectly (Fig. 3).

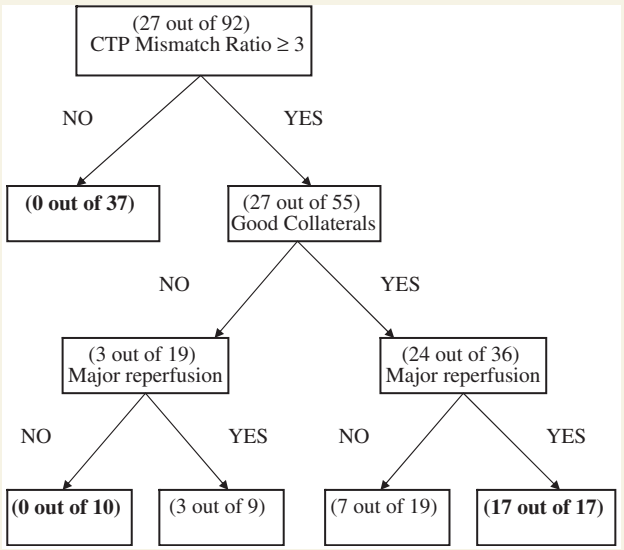

Figure 3 Decision tree showing the variable used to classify subjects into sub-groups at high and low risk of having a good outcome as measured by mRS of 0–2 at Day 90 (proportion with mRS of 0–2 in brackets for each decision step).

Collateral status and relationship with other variables

Collateral status was good in 51 patients (56%), moderate in 24 (26%) and poor in 17 (18%). There was a significant difference in median acute NIHSS between the good and reduced collateral status groups (NIHSS 16 versus 18, $P = 0.012$). Left and right hemisphere strokes were equally distributed between the good (26 left versus 25 right) and reduced collaterals (20 left versus 21 right) groups. Median mismatch volume in the good collateral status group was higher compared with the reduced collaterals group (102 cm^3 versus 73 cm^3, $P = 0.002$). Median baseline infarct core volume in the good collateral status group was

Table 3 Differences in baseline and outcome variables between groups defined by collateral status

Collateral status	Good ($n=51$)	Reduced (moderate and poor combined) ($n=41$)	Moderate ($n=4$)	Poor ($n=17$)
Acute NIHSS	16 (14–20)*	18 (17–20)	18 (15–19)**	20 (19–22)
Mismatch volume (cm^3)	102 (86–125)*	73 (IQR 49–103)	70 (43–113)	77 (50–94)
Baseline infarct core volume (cm^3)	23 (7–62)*	57 (27–92)	47 (17–90)	65 (IQR 32–97)
Time to CT (h)	2 (1.5–3)	2.5 (1.8–3.5)	3 (1.8–3.5)	2.5 h IQR 1.8–3.5
Absolute infarct expansion (cm^3)	4 (0–21)*	42 (28–61)	32 (20–43)	59 (46–77)**
mRS 0–2, *n* (%)	24/51 (47)*	3/41 (7)	3/24 (13)	0/17

Data represented in median (IQR) values, unless otherwise mentioned.
*Significant difference between good and reduced collaterals group ($P<0.05$).
**Significant difference between moderate and poor collateral sub-groups ($P<0.05$).

smaller compared with the reduced collaterals group (23 cm^3 versus 57 cm^3, $P=0.003$). Median infarct expansion was greater in the reduced collaterals group (4 cm^3 versus 42 cm^3, $P<0.001$). Favourable 90-day outcome (mRS 0–2) was seen in only 27 patients (29%), this comprised 24 of the 51 patients with good collateral status and only 3 of 41 patients with reduced collaterals ($P<0.001$). Time between symptom onset and imaging was not significantly different between the good collaterals group compared with the reduced collaterals groups (2 h versus 2.5 h, $P=0.10$) and similarly between patients with a mismatch ratio $\geqslant 3.0$ compared with those without (2 h versus 2.8 h, $P=0.01$). Within the reduced collaterals group, there were minimal differences between patients with moderate compared with poor collateral status (Table 3).

Inter-observer agreement

The two observers agreed in grading of collateral status correlated in 88 of 92 patients ($\kappa=0.93$) when assessing good, moderate or poor collateral status. When comparing grading of good collateral status there was agreement in 50 of 51 patients ($\kappa=0.98$).

Discussion

This study provides the first description of a complementary interaction between CTA collateral status and the ischaemic penumbra delineated on CTP. Good collateral status is significantly, but not invariably, associated with a larger baseline penumbra, and also appears to maintain penumbra by limiting infarct core expansion until reperfusion takes place. The results emphasize that in patients with a proximal intracranial vessel occlusion, the presence of a large CTP mismatch ratio is a pre-requisite for achieving a favourable clinical outcome, while the probability of a favourable outcome in such patients is further independently influenced by concurrence of good collateral status.

Collateral status not only influenced the likelihood of subsequent penumbral salvage with reperfusion, but was also strongly associated with infarct core volumes at baseline. Reduced collateral status on DSA has been shown to correlate with more severe hypoperfusion on MRI and this may explain in the current study why reduced collateral status was strongly associated with both greater baseline infarct core volumes and subsequent infarct core expansion (Bang *et al*., 2008*a, b*). Although we used validated CTP thresholds for at-risk tissue, those with reduced collateral status may thus have had regions with far worse hypoperfusion than the penumbral threshold, and hence experienced more rapid infarction (Jones *et al*., 1981). Importantly, therefore, we can imply from our results that collateral status influences how rapidly CTP penumbral tissue progresses to infarction.

Major reperfusion substantially increased the chances of a favourable outcome, however, a quarter of patients with CTP mismatch and without major reperfusion still had a favourable outcome (Fig. 3). All these patients had good collateral status, and their outcome presumably reflected the fact that they had significantly less infarct expansion than the other patients without major reperfusion. In turn, the reduced infarct expansion was probably explained by the partial reperfusion seen in these patients despite lack of complete vessel recanalization. This data suggests that even in the absence of major reperfusion or complete vessel re-canalization, there is some potential for good collateral status to improve cerebral perfusion and hence limit penumbral incorporation into the infarct core (Supplementary Fig. 2A and B).

The strong interaction seen between good collateral status and major reperfusion indicates a synergistic effect of the two variables in predicting favourable outcome in patients with significant CTP mismatch. As hypothesized, this interaction probably reflects good collaterals preserving penumbra until reperfusion occurs. Another explanation that might partially explain the interaction is that good collateral status may have enhanced major reperfusion (Roberts *et al*., 2002). In view of most patients (31 of 38) with major reperfusion having received thrombolytic therapy, enhanced reperfusion with good collaterals may relate to improved delivery of thrombolytic to both sides of the thrombus and limiting extension of the occlusion.

Our study also highlights how poorly time to imaging correlates with both good collateral status and the presence of large mismatch ratio, reinforcing the importance of these variables in future more sophisticated assessments of the therapeutic window for stroke thrombolysis. Although significant CTP mismatch indicates the possibility of a favourable response to reperfusion, the added predictive utility of good CTA collateral status highlights the need for future acute stroke imaging trials to move beyond a simplistic single-imaging measure to select patients for acute reperfusion therapy (Hacke *et al*., 2009). Indeed, the clinical utility of CTP mismatch (or its absence) appears most important in

identifying patients with very low probability of benefit from reperfusion therapy. Furthermore, this is the first CTP based study to confirm the recent MR finding that a larger 'mismatch' ratio predicts a more favourable clinical response to reperfusion than the commonly used (but unproven) mismatch ratio of >1·2 (Kakuda *et al*., 2008). It is particularly notable that in our study population no patient with a CTP mismatch ratio of <3 had a favourable outcome. This likely reflects larger baseline infarct core volume in this group pre-determining ultimate outcome (Fig. 3).

It is important to note that this study selected a population of large anterior circulation strokes, a relatively treatment resistant stroke subtype, as reflected by the low rates of favourable outcomes, even in those patients given intravenous thrombolysis. The utility and value of our collateral grading requires further validation and is likely to be significantly lower in those with more distal anterior circulation lesions, as well as posterior circulation strokes. Nonetheless, we did independently confirm (on dynamic CTP source image review) that contrast visualized distal to a complete CTA occlusion in 92 of 97 patients was in fact due to retrograde flow (the remaining five excluded due to CTP slice coverage limitations preventing confirmation of retrograde flow). This has the important clinical implication that retrograde flow and collateral status can be reliably and simply assessed on CTA in patients with proximal intracranial anterior circulation occlusion.

In conclusion, CTP and CTA provide independent, but complementary prognostic information in patients with proximal anterior circulation vessel occlusion, with collateral status providing a unique insight into penumbral 'life expectancy'. Further verification of these findings would support the concept that imaging algorithms to help identify patients with the highest chance of benefit from thrombolytic therapy should incorporate CTA collateral status along with a large CTP mismatch ratio.

Supplementary material

Supplementary material is available at *Brain* online.

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