doi:10.1093/brain/awt246 Brain 2013: 136; 3554–3560 | 3554

BRAIN
A JOURNAL OF NEUROLOGY

Factors that determine penumbral tissue loss in acute ischaemic stroke

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The goal of acute stroke treatment with intravenous thrombolysis or endovascular recanalization techniques is to rescue the penumbral tissue. Therefore, knowing the factors that influence the loss of penumbral tissue is of major interest. In this study we aimed to identify factors that determine the evolution of the penumbra in patients with proximal (M1 or M2) middle cerebral artery occlusion. Among these factors collaterals as seen on angiography were of special interest. Forty-four patients were included in this analysis. They had all received endovascular therapy and at least minimal reperfusion was achieved. Their penumbra was assessed with perfusion- and diffusion-weighted imaging. Perfusion-weighted imaging volumes were defined by circular singular value decomposition deconvolution maps ($T_{max} > 6$ s) and results were compared with volumes obtained with non-deconvolved maps (time to peak > 4 s). Loss of penumbral volume was defined as difference of post- minus pretreatment diffusion-weighted imaging volumes and calculated in per cent of pretreatment penumbral volume. Correlations between baseline characteristics, reperfusion, collaterals, time to reperfusion and penumbral volume loss were assessed using analysis of covariance. Collaterals ($P = 0.021$), reperfusion ($P = 0.003$) and their interaction ($P = 0.031$) independently influenced penumbral tissue loss, but not time from magnetic resonance ($P = 0.254$) or from symptom onset ($P = 0.360$) to reperfusion. Good collaterals markedly slowed down and reduced the penumbra loss: in patients with thrombolysis in cerebral infarction 2 b-3 reperfusion and without any haemorrhage, 27% of the penumbra was lost with 8.9 ml/h with grade 0 collaterals, whereas 11% with 3.4 ml/h were lost with grade 1 collaterals. With grade 2 collaterals the penumbral volume change was −2% with −1.5 ml/h, indicating an overall diffusion-weighted imaging lesion reversal. We conclude that collaterals and reperfusion are the main factors determining loss of penumbral tissue in patients with middle cerebral artery occlusions. Collaterals markedly reduce and slow down penumbra loss. In patients with good collaterals, time to successful reperfusion accounts only for a minor fraction of penumbra loss. These results support the hypothesis that good collaterals extend the time window for acute stroke treatment.

Keywords: acute stroke; penumbra, tissue loss; time; time window

Abbreviations: DWI = diffusion-weighted imaging; PWI = perfusion-weighted imaging; TICI = thrombolysis in cerebral infarction

Received December 1, 2012. Revised June 27, 2013. Accepted July 13, 2013. Advance Access publication September 24, 2013
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Introduction

The goal of acute stroke treatment with intravenous thrombolysis or endovascular therapy is to rescue the penumbral tissue at risk. The penumbra refers to the severely hypoperfused brain tissue at risk of infarction, but still salvageable if reperfused early enough (Astrup *et al*., 1981; Heiss, 2000). One viable method for approximation of penumbral tissue in clinical practice is applying diffusion-weighted (DWI) and perfusion-weighted imaging (PWI) using MRI and calculation of the PWI-DWI mismatch, although this method cannot define the penumbra with absolute accuracy (Heiss, 2011).

Factors influencing the penumbral evolution are of major interest. Reperfusion success and the elapsed time from symptom onset to reperfusion are known to be critical for the evolution of the penumbra. The impact of collaterals has been addressed by some studies and good collaterals are considered to protect the penumbra (Miteff *et al*., 2009; Zhang *et al*., 2010; Liebeskind *et al*., 2010; Shuaib *et al*., 2011). However, knowing all factors that have an effect on the evolution of the PWI-DWI mismatch is important for stroke therapy, because PWI-DWI mismatch is or has been used for patient selection and treatment decisions both in clinical practice and trials such as DEFUSE 2, MR-RESCUE, EPITHET and DIAS-2 (Davis *et al*., 2008; Hacke *et al*., 2009; Lansberg *et al*., 2012; Kidwell *et al*., 2013).

The aim of this study was to examine the impact of the quality of collaterals, reperfusion, elapsed time and baseline factors on the evolution of the penumbral volume as defined by PWI-DWI mismatch in patients undergoing endovascular therapy for middle cerebral artery occlusions.

Materials and methods

Patients and treatment

The present study includes patients of the Bernese stroke registry, a prospectively collected database. Some of their aspects have been reported previously (Arnold *et al*., 2007; Jung *et al*., 2011, 2012; Galimanis *et al*., 2012). Patients were included in this analysis if: (i) diagnosis of ischaemic stroke was established; (ii) a proximal occlusion of the middle cerebral artery (M1 or M2 segment) was documented on digital subtraction angiography; (iii) they underwent endovascular therapy and achieved at least minimal reperfusion in control angiography at the end of the endovascular procedure [thrombolysis in cerebral infarction (TICI) score $\geqslant$1; Higashida *et al*., 2003]; (iv) pretreatment DWI and PWI and post-treatment DWI were performed with sufficient quality; and (v) imaging data were recorded into the picture archiving and communication system (as done since 2004). Patients without any reperfusion (TICI score 0) had to be excluded from this study because time to reperfusion, that was needed for our calculations, could not be defined.

Age, gender, medication, National Institutes of Health Stroke Scale (NIHSS), time from symptom onset to treatment, coronary artery disease, atrial fibrillation, hypertension, diabetes, smoking, hypercholesterolaemia, history of transient ischaemic attack or ischaemic stroke, family history of transient ischaemic attack and stroke, treatment details (use of urokinase, mechanical procedures, bridging concept) and complications were recorded as baseline characteristics. Collaterals were classified as suggested by Higashida *et al*. (2003). Both collaterals and reperfusion were scored retrospectively by two examiners blinded for clinical data (J.G., C.Z.). Disagreements in scoring were resolved by discussion. The study was performed according to the ethical guidelines of the Canton of Bern and with approval of our institutional review board.

Magnetic resonance imaging and image analysis

All patients had pre- and post-treatment magnetic resonance scans. MRI was performed using a 1.5 T or 3 T MRI system (Magnetom, Siemens). The MRI protocol included whole brain DWI (b = 1000t, 24 slices, thickness 5 mm, repetition time 3200 ms, echo time 87 ms, number of averages 2, matrix 256 $\times$ 256) yielding isotropic b0 and b1000 as well as apparent diffusion coefficient maps that were calculated automatically. Apparent diffusion coefficient (ADC) maps were calculated according to the exponential relation $S(b) = S(0)\ \exp(-b \times ADC)$, where S(b) is the signal intensity using diffusion weighting with the value b, and S(0) is the signal intensity with b = 0. For PWI the standard dynamic-susceptibility contrast enhanced perfusion MRI (gradient-echo echo-planar imaging sequence, repetition time 1410 ms, echo time 30 ms, field of view 230 $\times$ 230 mm, voxel size: 1.8 $\times$ 1.8 $\times$ 5.0 mm, slice thickness 5.0 mm, 19 slices, 80 acquisitions) was acquired. PWI images were acquired during the first pass of a standard bolus of 0.1 mmol/kg gadobutrol (Gadovist, Bayer Healthcare). Contrast medium was injected at a rate of 5 ml/s followed by a 20 ml bolus of saline at a rate of 5 ml/s.

Symptomatic and asymptomatic intracerebral haemorrhage was graded according to the definition of the PROACT II Study (Kase *et al*., 2001).

Segmentation of the DWI lesion volumes was performed with the in-house developed Java software SCANalyze Version 5.1.r637 (Slotboom *et al*., 2008). DWI volumes were calculated using semi-automated thresholding with adjustable standard deviation of pixel values to identify hyperintense regions of interests.

PWI lesion volumes were obtained by block-circular singular value decomposition deconvolution maps and generated with the Perfusion Mismatch Analyzer (PMA, from Acute Stroke Imaging Standardization Group ASIST) Ver.3.4.0.6 (Wu *et al*. 2003; Kudo *et al*. 2009). The maps were segmented with Slicer 3D with a time to maximum (T_{max}) cut-off value of 6 s.

In addition, PWI lesion volumes were obtained by non-deconvolved maps with the in-house developed java software SCANalyze Version 5.1.r645 (H.S.) with a time to peak (time to peak) threshold of $>$4 s to distinguish the penumbra from benign oligemia (Supplementary material).

Volume measurements were performed by one author (M.G.) and checked by another (M.E.), both blinded for the clinical data and outcomes.

Statistical analysis

Statistical analysis was performed using SPSS 21 (SPSS Inc.). Reperfusion was dichotomized into poor (TICI 1-2a) and good (TICI 2b-3).

The ratio of penumbral tissue loss was defined as:

$$100\,x\,\frac{\text{post treatment DWI volume} - \text{pretreatment DWI volume}}{\text{pretreatment PWI volume} - \text{pretreatment DWI volume}}$$

The following factors were examined for correlations with the

penumbral tissue loss in univariate analysis: collaterals, reperfusion, PWI-DWI mismatch volume, time from symptom onset to reperfusion, time from MRI to reperfusion, age, gender, atrial fibrillation, diabetes, smoking, hypertension, hypercholesterolaemia, asymptomatic intracerebral haemorrhage and NIHSS score on admission. All variables with a *P*-value of <0.2 were then examined for correlations with the penumbral tissue loss in analysis of covariance.

After exclusion of all non-significant factors the final analysis of covariance was performed for the dependent variable penumbral tissue loss. Covariates were time from symptom onset to reperfusion or time from MRI to reperfusion, and factors were collaterals (five levels) and reperfusion (two levels: TICI 1-2a and TICI 2b-3). A *P*-value of <0.05 was considered significant. For subgroup analysis reperfusion had the two levels TICI 2b and TICI 3.

Because DWI and PWI volumes were not normally distributed, the consistency of the results was verified after square root transformations of the volumes.

Results

Altogether, 356 patients were treated for M1 or M2 occlusions with endovascular therapy from 2004 to April 2012. In 56 patients a technically sufficient pre- and post-treatment MRI scan was performed and in 44 of these at least a minimal reperfusion (TICI score $\geqslant 1$) was achieved. Baseline characteristics of the 44 patients with proximal middle cerebral artery occlusions analysed in this study (Table 1) were similar to all patients with anterior circulation occlusion and endovascular treatment in our centre (Galimanis *et al.*, 2012). Median time from symptom onset to reperfusion was 323 min (range: 237–492 min) and from MRI to reperfusion 173 min (range: 91–288 min). Occlusion site as seen in angiography was M1 in 36 of 44 patients (81.8%) and M2 in eight patients (18.2%).

Collaterals before treatment and reperfusion success on control angiography at the end of the endovascular procedure was graded by two examiners in consensus reading (inter-rater variability kappa = 0.636 for collaterals and 0.809 for reperfusion). Collaterals were graded as 0 in eight patients (18.2%), as 1 in 12 patients (27.3%) and as 2 in 24 patients (54.5%, two patients borderline grade 3). Reperfusion was graded as TICI 1 in two patients (4.5%), TICI 2a in six patients (13.6%), TICI 2b in 22 patients (50%), and TICI 3 in 14 patients (31.8%). Post-treatment MRI was performed on Day 1 in 38 patients (86.4%), Day 2 in two patients (4.5%), and Days 5, 7, 8 and 10 in one patient each (each 2.3%).

The pre- and post-treatment DWI volumes, penumbral volumes and the penumbral tissue loss in dependence of the degree of collaterals are listed in Table 2 and demonstrated in Fig. 1.

Covariance analysis of the ratio of penumbra loss for the two factors collaterals and reperfusion success (dichotomized into levels 1-2a and 2b-3) and controlling for the covariate time interval from MRI to reperfusion showed significant main effects (quality of collaterals $P = 0.021$, reperfusion success $P = 0.003$) and a significant interaction between both factors ($P = 0.031$). The effect of time as covariate was not significant ($P = 0.254$). Tissue loss was

Table 1 Baseline characteristics and therapy of 44 patients

		P-value in analysis of covariance
Occlusion location M1	36/44 (81.8%)	
Occlusion location M2	8/44 (18.2%)	
Age, years (SD)	60.1 (17.2)	0.851
Female sex	21/44 (47.7%)	0.550
Vascular risk factors		
Diabetes mellitus	8/44 (18.2%)	0.052
Hypertension	25/44 (56.8%)	0.962
Current smoking	10/44 (22.7%)	0.141
Hypercholesterolaemia	27/44 (61.4%)	0.669
Atrial fibrillation	17/38 (44.7%)	0.501
Baseline NIHSS score, median (range)	12 (3–36)	0.888
Thrombolysis		
Endovascular with/without mechanical procedures	28/44 (63.6%)	
Endovascular mechanical only	7/44 (15.9%)	
Bridging	9/44 (20.5%)	
Minutes from symptom onset to reperfusion, median (range)	323 (237–492)	0.360
Minutes from MRI to reperfusion, median (range)	173 (91–288)	0.254
Reperfusion TICI 2b-3	36/44 (81.8%)	**0.003**
Collaterals		**0.021**
Grade 0	8/44 (18.2%)	
Grade 1	12/44 (27.3%)	
Grade 2	24/44 (54.5%)	
Asymptomatic intracerebral haemorrhage	10/44 (22.7)	0.199
Symptomatic intracerebral haemorrhage	0/44	

The centre column shows the results of analysis of covariance with penumbral tissue loss as dependent variable.

Table 2 Clinical and radiological data in dependence of quality of collaterals of 44 patients

	Collaterals grade 0 ($n = 8$)	Collaterals grade 1 ($n = 12$)	Collaterals grade 2 ($n = 24$)
Baseline NIHSS score, median (range)	11 (3–17)	12 (5–36)	13 (5–22)
Pretreatment DWI volume (cm^3), mean (SD)	34.4 (31.4)	28.7 (21.4)	29.3 (43.3)
Pretreatment penumbral volume (cm^3), mean (SD)	98.4 (44.9)	107.3 (47.9)	126.5 (50.9)
Post-treatment DWI volume (cm^3), mean (SD)	68.8 (73.1)	42.2 (29.7)	32.5 (41.1)
Penumbral tissue loss, %, mean (SD)	25 (52)	14 (18)	3 (17)
Asymptomatic intracerebral haemorrhage	5/8 (62.5%)	1/12 (8.3%)	4/24 (16.7%)

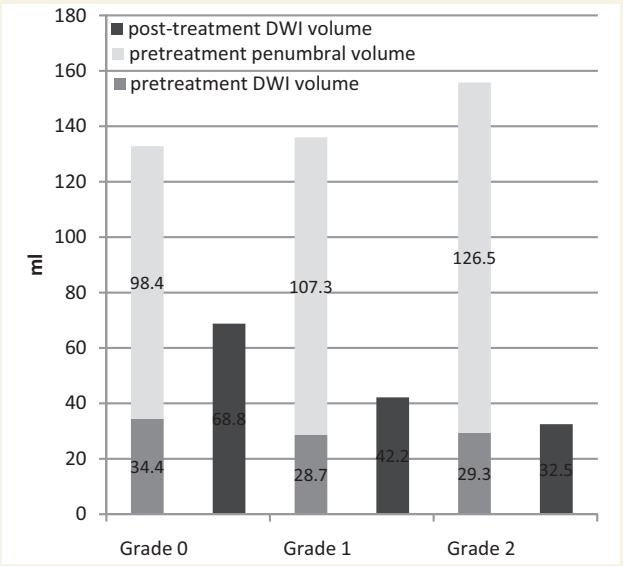

Figure 1 Collateral quality dependent mean values of pretreatment DWI and PWI volumes and post-treatment DWI volumes.

greater in patients with TICI 1-2a reperfusion and even greater for those with grade 0 collaterals. A *post hoc* comparison of the three collateral levels showed no differences between grades 0 and 1 or between 1 and 2, but between grades 0 and 2 ($P = 0.018$). When controlling for time from symptom onset to reperfusion as covariate, almost the same main and interaction effects were observed, but 'time' was not significant ($P = 0.360$).

Subgroup analyses were performed in patients with TICI 2b or 3 reperfusion and without any intracerebral haemorrhage ($n = 30$). The results for the mean penumbra loss and mean hourly penumbral tissue loss according to the collateral quality are given in Table 3. Covariance analysis of the ratio of penumbra loss showed a significant main effect only for the quality of collaterals ($P = 0.017$). The effects of reperfusion (levels TICI 2b and 3) and time were not significant (reperfusion $P = 0.386$, time from MRI to reperfusion $P = 0.147$, time from symptom onset to reperfusion $P = 0.329$). When collaterals were excluded from the model time from MRI to reperfusion was the only significant factor ($P = 0.013$). There was a linear relationship between the quality of collaterals and penumbra loss per hour in regression analysis ($P = 0.008$). Only in the subgroup of patients with grade 2 collaterals we found a trend for a linear relationship between time from MRI to reperfusion and penumbra loss in regression analysis ($P = 0.068$).

Table 3 Penumbral tissue loss depending on collateral quality in patients with TICI 2b-3 reperfusion and without any haemorrhage ($n = 30$)

Collateral quality	*n*	Total penumbral tissue loss (%), mean (SD)	Penumbral tissue loss per hour (ml/h), mean (SD)
Grade 2	18	−2 (13)	−1.5 (6.9)
Grade 1	9	11 (19)	3.4 (4.4)
Grade 0	3	27 (29)	8.9 (11.3)

With non-deconvoluted time to peak maps for penumbra definition the results were comparable (Supplementary material). The above described trend for linearity between time and penumbra loss in patients with TICI 2b or 3 reperfusion and grade 2 collaterals was significant with this definition of the penumbra ($P = 0.018$).

Discussion

This study shows that the loss of MRI-defined penumbral tissue in patients with proximal middle cerebral artery occlusions who receive endovascular therapy is mainly influenced by the quality of collaterals, the quantity of successful reperfusion and an interaction between these two factors. Good collaterals markedly slow down and reduce the penumbra loss. Accordingly the elapsed time accounts only for a minor fraction of penumbral volume loss in patients with good collaterals but influences penumbra loss in larger scale in patients with poor collaterals. These results indicate that collaterals have a major impact on penumbral evolution and support the hypothesis that good collaterals extend the time window for acute stroke treatment by slowing down the tempo of penumbral tissue loss.

The final infarct volume correlates with functional outcome and has been used as a marker for success of acute stroke treatment (Yoo *et al*., 2012). The location of the vessel occlusion, reperfusion success and the elapsed time to reperfusion are considered as the main factors determining the final infarct volume. From a clinical point of view the knowledge of factors contributing to the evolution of the MRI defined penumbra is of major interest

because the primary goal of acute stroke treatment is to rescue penumbral tissue. In addition, penumbral volumes have been and are being used for patient selection in clinical studies and treatment decisions in clinical practice.

The goal of the present study was to identify factors contributing to the evolution of the penumbra. In our analysis of covariance we considered baseline factors, time, collaterals and reperfusion. It turned out that the ratio of penumbra loss was influenced by the quality of collaterals ($P = 0.021$), the quantity of reperfusion ($P = 0.003$) and an interaction between these two factors ($P = 0.031$). This interaction indicates that the effect size of collaterals depends on the quality of reperfusion and the effect of collaterals to save penumbra is larger in case of poor reperfusion. None of the baseline factors influenced penumbra loss. We found only one study that made a similar analysis with inclusion of multiple factors. In the study of Bang *et al*. (2008) recanalization instead of reperfusion and infarct growth instead of loss of penumbra were used. They found the quality of collaterals and the volume of PWI-DWI mismatch to influence infarct growth, but not recanalization. In our study collaterals had a significant effect on the ratio of penumbra loss: in patients with TICI 2b-3 reperfusion and without any haemorrhage 27% [standard deviation (SD) 29%] of the penumbra had been lost with grade 0 collaterals, but only 11% (SD 19%) with grade 1 collaterals and −2% (SD 13%) with grade 2 collaterals. The results of our study are in line with studies that found good collaterals associated with smaller final infarct volumes (Roberts *et al*., 2002; Christoforidis *et al*., 2005; Miteff *et al*., 2009; Zhang *et al*., 2010). Instead of analysing final infarct volume or infarct growth, we preferred the ratio of penumbral tissue loss, because it includes pre- and post-treatment volumes and adjusts for the variability of pretreatment infarct and penumbral volumes.

Randomized trials using intravenous recombinant tissue plasminogen activator show unequivocally that time to treatment is crucial for outcome (Lees *et al*., 2010). Unlike in these trials, penumbra loss in our patients with proximal middle cerebral artery occlusions and endovascular therapy was not influenced in analysis of covariance by the time from symptom onset to reperfusion ($P = 0.360$) nor by the time from MRI to reperfusion ($P = 0.254$). To exclude any confounding effects, additional subgroup analyses were performed in patients with TICI 2b-3 reperfusion and without any haemorrhage. Patients with TICI 1-2a reperfusion were excluded from the subgroup analysis, because after poor reperfusion tissue loss probably continues and time to reperfusion may differ from the time until final infarct size. Patients with acute intracerebral haemorrhage were also excluded to avoid any confounding effect due to haemorrhage induced infarct growth (outliers with acute intracerebral haemorrhage are illustrated in Fig. 2B). The subgroup analysis in the remaining 30 patients confirms our main results: only the quality of collaterals influenced penumbra loss ($P = 0.017$). Reperfusion success (levels TICI 2b or 3) ($P = 0.386$), time from symptom onset ($P = 0.329$) and time from MRI to reperfusion ($P = 0.147$) did not influence penumbra loss. The main results and results of subgroup analyses were also consistent when penumbral volumes were obtained by non-deconvoluted time to peak maps (Supplementary material) and after square root transformation of the volumes.

According to our findings the quality of collaterals and success of reperfusion seem to be more important than the time elapsing from stroke onset to reperfusion among all factors determining penumbra loss. Remarkably, time from MRI to reperfusion turned out as significant predictor of penumbra loss after exclusion of the factor collaterals from the model ($P = 0.013$). This was also the case in our recent analysis of 623 patients with anterior circulation strokes who had received endovascular treatment. Time to treatment turned out to be a predictor of clinical outcome only when collaterals were excluded from multivariable analysis (Galimanis *et al*., 2012).

The quality of collaterals competes with the elapsed time in logistic regression models because good collaterals both reduce and slow down penumbra loss ($P = 0.008$): in patients with grade 0 collaterals 8.9 ml (SD 11.3) penumbra was lost per hour, with grade 1 collaterals 3.4 ml/h (SD 4.4) and with grade 2 collaterals −1.5 ml/h (SD 6.9). With grade 2 collaterals the penumbra volume change is probably linear ($P = 0.068$ for T_{max}-based maps and $P = 0.018$ for time to peak-based maps in linear regression analysis, see Fig. 2A–C). The negative values indicate an overall DWI lesion reversal in patients with grade 2 collaterals, although it took a median time of 3 h to reperfusion in these patients. Our patients with grade 2 and 1 collaterals showed a slower and those with grade 0 collaterals a faster penumbra loss than the 5.4 ml/h calculated for a typical non reperfused large vessel stroke in a theoretical model (Saver, 2006). Accordingly the elapsed time accounts only for a minor fraction of penumbra loss in patients with good collaterals but influences penumbra loss in large scale in patients with poor collaterals.

Our study has several limitations. The relatively large standard deviations of the mean values of penumbra loss in our patients sound a note of caution for the interpretation of these values. Because only 44 of our 356 patients with proximal middle cerebral artery occlusions had technically adequate pre- and post-treatment magnetic resonance scans and at least TICI grade 1 reperfusion, we cannot exclude a selection bias. Another limitation relates to the assessment of the penumbra. It is known that DWI magnetic resonance scans tend to overestimate the real infarct core volume and PWI magnetic resonance scans overestimate the real tissue at risk compared to the golden standard PET (Heiss *et al*., 2004; Sobesky *et al*., 2005; Olivot and Marks, 2008; Takasawa *et al*., 2008; Zaro-Weber *et al*., 2010; Campbell *et al*., 2012). It is controversial which MRI based definition of the penumbra and which thresholds most accurately approximate the PET-defined penumbra. Three studies found similar performance of maps of T_{max} ($\geqslant 5.5$ s) and maps of deconvolved time to peak ($\geqslant 4.2$ s respectively $\geqslant 4.8$ s) compared with a PET derived penumbra definition (Takasawa *et al*., 2008; Zaro-Weber *et al*., 2010). Also our results obtained with a T_{max} (>6 s) based definition of the penumbra were consistent with those obtained with a time to peak (>4 s) based definition of the penumbra. The wide range of time from MRI to reperfusion and that 14% of follow-up scans were performed >1 day after the stroke may represent another limitation. Finally, our results are only valid in our selected patients with proximal middle cerebral artery occlusions and reperfusion within 8 h. We do not

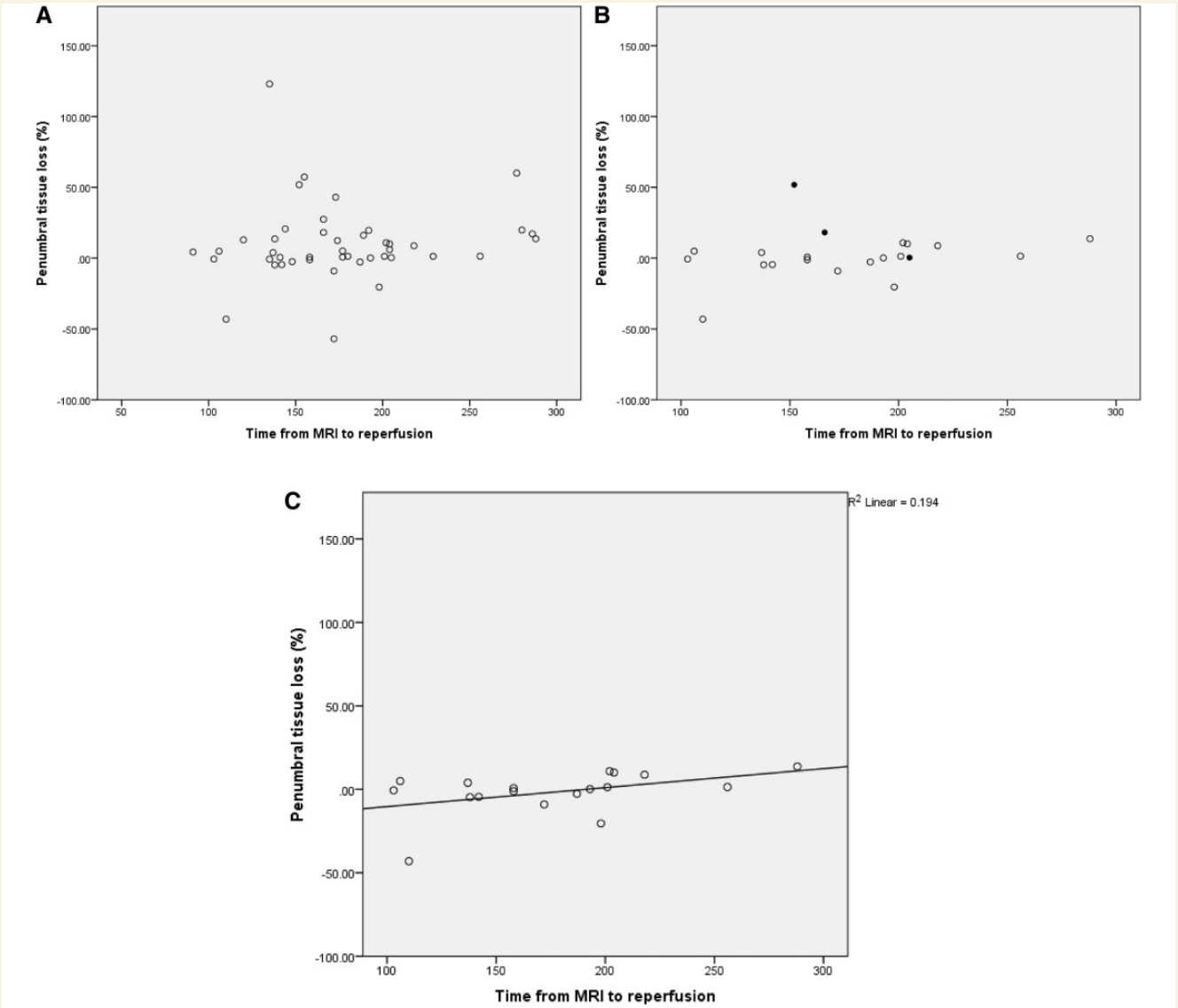

Figure 2 (**A**) Percentage of penumbral tissue loss in dependence of the elapsed time from MRI to reperfusion ($n = 44$). (**B**) Percentage of penumbral tissue loss in dependence of time in patients with both good collaterals and TICI 2b/3 reperfusion ($n = 21$), Filled circles = patients with asymptomatic intracerebral haemorrhage. Open circles = patients without asymptomatic intracerebral haemorrhage. (**C**) Percentage of penumbral tissue loss in dependence of time in patients with good collaterals and TICI 2b/3 reperfusion but without asymptomatic intracerebral haemorrhage ($n = 18$).

know whether the evolution of the penumbra is similar in patients with occlusions of other cerebral vessels, during the first hour or after 8 h of symptom onset.

In conclusion, the quality of collaterals and the quantity of reperfusion are the major factors determining the penumbra loss as assessed with PWI and DWI in patients with proximal middle cerebral artery occlusions. Good collaterals both markedly reduce and slow down penumbra loss. The elapsed time accounts only for a minor fraction of penumbra loss in patients with good collaterals but influences penumbra loss in large scale in patients with poor collaterals. Thus, good collaterals seem to extend the time window by slowing down the tempo of penumbral tissue loss. Our study confirms that 'time is brain', but the collaterals set the pace.

Acknowledgements

We thank Pietro Ballinari for statistical advice.

Funding

S.J. is supported by the Swiss National Science Foundation (SNSF; SPUM-Grant 140340).

Supplementary material

Supplementary material is available at *Brain* online.

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