

Reperfusion after ischemic stroke is associated with reduced brain edema

Hannah J Irvine^{1,2}, Ann-Christin Ostwaldt^{1,2},
 Matthew B Bevers³, Simone Dixon⁴, Thomas WK Battey^{1,2},
 Bruce CV Campbell^{5,6}, Stephen M Davis⁵, Geoffrey A Donnan⁶,
 Kevin N Sheth⁷, Reza Jahan⁸, Jeffrey L Saver⁹,
 Chelsea S Kidwell⁴ and W Taylor Kimberly^{1,2}

Abstract

Rapid revascularization is highly effective for acute stroke, but animal studies suggest that reperfusion edema may attenuate its beneficial effects. We investigated the relationship between reperfusion and edema in patients from the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) cohorts. Reperfusion percentage was measured as the difference in perfusion-weighted imaging lesion volume between baseline and follow-up (day 3–5 for EPITHET; day 6–8 for MR RESCUE). Midline shift (MLS) and swelling volume were quantified on follow-up MRI. We found that reperfusion was associated with less MLS (EPITHET: Spearman $\rho = -0.46$; $P < 0.001$, and MR RESCUE: Spearman $\rho = -0.49$; $P < 0.001$) and lower swelling volume (EPITHET: Spearman $\rho = -0.56$; $P < 0.001$, and MR RESCUE: Spearman $\rho = -0.27$; $P = 0.026$). Multivariable analyses performed in EPITHET and MR RESCUE demonstrated that reperfusion independently predicted both less MLS (β coefficient = -0.056 ; $P = 0.025$, and β coefficient = -0.38 ; $P = 0.028$, respectively) and lower swelling volumes (β coefficient = -4.7 ; $P = 0.007$, and β coefficient = -10.7 ; $P = 0.009$, respectively), after adjusting for age, sex, NIHSS, admission glucose and follow-up lesion size. Taken together, our data suggest that even modest improvement in perfusion is associated with less brain edema in EPITHET and MR RESCUE.

Keywords

Stroke, reperfusion, brain edema, magnetic resonance imaging, perfusion-weighted imaging

Received 13 February 2017; Revised 10 May 2017; Accepted 25 May 2017

Introduction

In acute stroke, early restoration of blood flow to ischemic brain tissue has repeatedly been shown to improve clinical outcomes. Accordingly, revascularization with intravenous tissue plasminogen activator (IV tPA)^{1,2} or intra-arterial thrombectomy (IAT),³ and spontaneous revascularization^{4–7} lead to reduced long-term disability. Such findings support the penumbra hypothesis, which proposes that early revascularization preserves hypoperfused brain tissue at risk of infarction⁸ by arresting infarct growth surrounding the core stroke lesion.^{9–11}

³Divisions of Stroke, Cerebrovascular and Critical Care Neurology, Brigham & Women's Hospital, Boston, MA, USA

⁴Department of Neurology, University of Arizona College of Medicine, Tucson, AZ, USA

⁵Department of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia

⁶Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria, Australia

⁷Division of Neurocritical Care and Emergency Neurology, Yale New Haven Hospital, New Haven, USA

⁸Department of Radiology, Ronald Reagan – UCLA Medical Center, Los Angeles, CA, USA

⁹Comprehensive Stroke Center and Department of Neurology, Ronald Reagan – UCLA Medical Center, Los Angeles, CA, USA

¹Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA

²Division of Neurocritical Care and Emergency Neurology, Massachusetts General Hospital, Boston, MA, USA

Corresponding author:

W Taylor Kimberly, 55 Fruit Street, Lunder 644, Boston, MA 02114, USA.
 Email: wtkimberly@mgh.harvard.edu

However, several studies have also suggested that revascularization may lead to secondary injury.^{12–14}

Post-ischemic reperfusion edema is one potential form of secondary injury, yet studies on the relationship between revascularization and brain edema have yielded conflicting results. Findings from pre-clinical rodent and primate studies suggest that revascularization may result in the development of edema.^{15–17} In contrast, human studies have shown that persistent proximal occlusion is associated with malignant edema and high mortality.^{18,19} In this study, we sought to characterize the relationship between reperfusion and edema using serial perfusion-weighted magnetic resonance imaging (PWI) compared with two measures brain edema: midline shift (MLS) and swelling volume.²⁰

We focused on two cohorts with relatively prolonged periods of ischemia, an IV tPA study [the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET)]²¹ and an earlier generation IAT study [the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial].²² Because the interventions tested in both cohorts do not reflect current practice, and because our analysis included patients randomized to each study's control arm, reperfusion was assessed as a change in perfusion deficit on PWI regardless of treatment modality. Recovery of perfusion deficit, represented quantitatively as reperfusion percentage, was then evaluated for association with morphometric measures of edema. We sought to determine whether improved tissue perfusion after acute stroke was associated with less brain edema.

Subjects and methods

Patient characteristics

Patients enrolled in EPITHET (NCT00238537) and MR RESCUE (NCT00389467) were retrospectively analyzed. Details of the EPITHET²¹ and MR RESCUE²² cohorts have been previously described. Briefly, subjects were enrolled in the EPITHET study from 2001 to 2007 and were randomized to administration of placebo or IV tPA 3–6 h after stroke onset. Subjects were enrolled in the MR RESCUE study from 2004 to 2011, and randomized to IAT or standard medical care within 8 h of stroke onset. Subjects in each cohort received pre-treatment diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI), with repeat imaging performed three to five days later in EPITHET, and six to eight days later in MR RESCUE. Due to the baseline differences in the cohorts, analyses were performed in each cohort separately; no pooled analyses were conducted.

Subjects included in the present study had a baseline and at least one follow-up MRI examination with DWI or fluid-attenuated inversion recovery (FLAIR)

sequence and PWI. Those with poor quality DWI or PWI (due to motion artifact or technical inadequacy) were excluded if the imaging readers could not delineate a region-of-interest around the DWI lesion or if the concentration curves for PWI sequences could not be generated. All patients enrolled in MR RESCUE had an anterior circulation large-vessel occlusion, while EPITHET included patients without evidence of proximal large-vessel occlusion. This study protocol was reviewed and approved by the Institutional Review Board at Partners Healthcare (protocol 2010P002749) and all subjects or their legally authorized representative originally provided informed consent. This study was carried out according to the guidelines set by the Partners Healthcare Human Research Committee.

Reperfusion measures

Reperfusion has been closely linked to tissue and clinical outcomes.^{23–25} To investigate the association between reperfusion and brain edema, reperfusion was quantified as the percent change between the baseline and follow-up PWI sequences. The PWI assessments and reperfusion percentage calculations were conducted as part of the original EPITHET and MR RESCUE trials, and the post-acquisition PWI data processing procedures employed have been previously described.^{21,22} For all patients, reperfusion percentage was calculated as follows: $[(PWI_{\text{baseline}} \text{ volume} - PWI_{\text{follow-up}} \text{ volume}) / PWI_{\text{baseline}} \text{ volume}] \times 100$. In these analyses, an improvement in reperfusion may be due to (1) resolution of the initial occlusion, (2) distal migration of the occlusion, and/or (3) improvements in collateral blood flow in spite of persistent occlusion. We therefore also conducted sensitivity analyses to evaluate whether recanalization status predicted reperfusion percentage, and to assess the correlation of edema metrics with both “successful recanalization” based on serial MR angiography,²⁴ and separately, “successful reperfusion” dichotomized at >90% reperfusion as originally pre-specified in the EPITHET and MR RESCUE trials^{21,22} (see Supplementary File).

Perfusion-diffusion mismatch definitions were derived from the original respective studies. Mismatch in EPITHET was defined as $[(PWI_{\text{baseline}} \text{ volume} - DWI_{\text{baseline}} \text{ volume}) / DWI_{\text{baseline}} \text{ volume}] \times 100$.^{21,22} The penumbral pattern in MR RESCUE was defined as $PWI_{\text{baseline}} \text{ volume} / DWI_{\text{baseline}} \text{ volume}$ and dichotomized at 70% or less.²²

Analysis of midline shift

Midline shift was measured in each cohort on the axial view of the follow-up FLAIR or DWI sequence. First, the midline was established by laying a straight line

between the anterior and posterior attachment of the falx cerebri. Midline shift was quantified by drawing and measuring a second, perpendicular line at the point of maximal deviation from the midline. In subjects with decompressive craniectomy (DC) for malignant cerebral edema ($n=9$ in MR RESCUE), MLS measurements were imputed with the greatest MLS value measured in the corresponding study cohort. All MLS measurements were generated by readers (A-C.O., H.J.I.) blinded to reperfusion status.

Analysis of infarct growth and swelling volume

Midline shift is used as a marker for edema in large hemispheric strokes.^{26,27} Because EPITHET and MR RESCUE enrolled patients with moderately sized baseline strokes, we also measured brain edema using a second measure, lesional swelling volume.²⁰ Infarct growth and lesional swelling volumes were measured as previously described^{20,28} using region-of-interest

(ROI) methodology in Analyze 11.0 (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN). In brief, stroke lesion ROIs were outlined on the baseline and the follow-up DWI using a semi-automated seed point method to generate lesion volumes, and change in lesion volume between baseline and follow-up DWI (Δ DWI) was calculated. The component volumes of Δ DWI attributable to infarct growth, swelling, and hemorrhage were distinguished according to our previously described methodology.^{20,28} Specifically, the baseline and follow-up DWI sequences were co-registered and were examined in the coronal, sagittal and axial planes. New neuroanatomic areas with restricted diffusion were defined as infarct growth and outlined using Analyze 11.0. Swelling volume was calculated based on the following relationship: swelling volume = Δ DWI – infarct growth volume – parenchymal hemorrhage volume. All swelling volume measurements were performed by independent readers (A-C.O., T.W.K.B.) blinded to reperfusion status.

Table 1. Clinical and imaging characteristics of the study cohorts.

	EPITHET ($n=71$)	MR-RESCUE ($n=67$)	<i>P</i>
Age, years, median [IQR]	75 [64–83]	67 [56–80]	0.005**
Sex, male, n (%)	38 (53)	38 (57)	0.73
Admission blood glucose (mmol/L), median [IQR]	7 [6–8]	7 [6–9]	0.28
History of smoking, yes, n (%)	25 (35)	27 (42)	0.48
Comorbidities, n (%)			
Diabetes mellitus	18 (25)	19 (28)	0.71
Hypertension	48 (68)	52 (78)	0.25
Hyperlipidemia	29 (41)	38 (58)	0.06
Atrial fibrillation	30 (42)	23 (34)	0.38
Received IV tPA, n (%)	31 (44)	23 (34)	0.30
Received IAT, n (%)	–	35 (52)	–
Time to treatment (IV tPA or IAT), h, mean (SD)	4.8 (0.71) ^a	6.7 (1.1) ^b	<0.001**
Baseline NIHSS, median [IQR]	13 [9–17]	17 [12–21]	<0.001*
Baseline DWI volume, mL, median [IQR]	21 [9–45]	36 [14–74]	0.02*
Follow-up DWI volume, mL, median [IQR]	56.1 [17–147]	89 [40–171]	0.02*
Swelling volume, mL, mean \pm SD	25 \pm 28	28 \pm 40	0.60
Infarct growth volume, mL, median [IQR]	5.3 [0–20]	15 [4–47]	0.002*
Midline shift, mm, median [IQR]	1.6 [0–2.6]	2.8 [1.1–6.9]	<0.001*
Reperfusion percentage, median [IQR]	78 [19–98]	91 [52–100]	0.10
Reperfusion > 90%, n (%)	28 (39)	34 (51)	0.23

DWI: diffusion-weighted imaging; IAT: intra-arterial thrombectomy; IV tPA: intravenous tissue plasminogen activator; NIHSS: National Institutes of Health Stroke Scale, reperfusion >90%: greater than 90% reduction in perfusion-weighted imaging deficit between baseline and follow-up imaging.

^aData are for 31 patients randomized to IV tPA.

^bData are for 35 patients randomized to IAT.

**t-test, *Wilcoxon rank sum test.

Statistical analysis

Patients included in the present study were compared using Wilcoxon rank sum or the Student's *t* test for continuous variables, and the Fisher's exact test for binary variables. Spearman's rank-order correlation was performed to evaluate the association between reperfusion percentage and infarct growth volume, MLS, and swelling volume. Wilcoxon rank sum and the Student's *t* test were employed to investigate the association of successful reperfusion with infarct growth volume, MLS, and swelling volume, as appropriate. To evaluate the correlations between recanalization status and reperfusion percentage, MLS, and swelling volume, Kruskal–Wallis or analysis of variance tests were used, as appropriate. Multivariable linear regression models were developed to assess the independent effect of reperfusion on MLS and swelling volume. To account for skewed distributions of covariates in these models, the following variables were log transformed: baseline blood glucose, follow-up DWI

volume, baseline DWI volume, MLS, and reperfusion percentage. Variance inflation factor (VIF) values were generated for all multivariable models in order to evaluate for multicollinearity, and all VIF were <1.8 . A LOESS local regression line was fit for the relationships between reperfusion percentage and midline shift, swelling volume and infarct growth volume, given the skewness of the data. All tests were two-sided and performed with the threshold for significance set at $P < 0.05$. Because this was an exploratory study, no further adjustment for multiple comparisons was made. Statistical analyses were conducted using JMP Pro 12.0 (SAS Institute, Cary, NC).

Results

Study population

Of 101 subjects enrolled in the EPITHET study, 71 were included in the present analysis. Seventeen subjects were excluded because they lacked DWI or PWI of

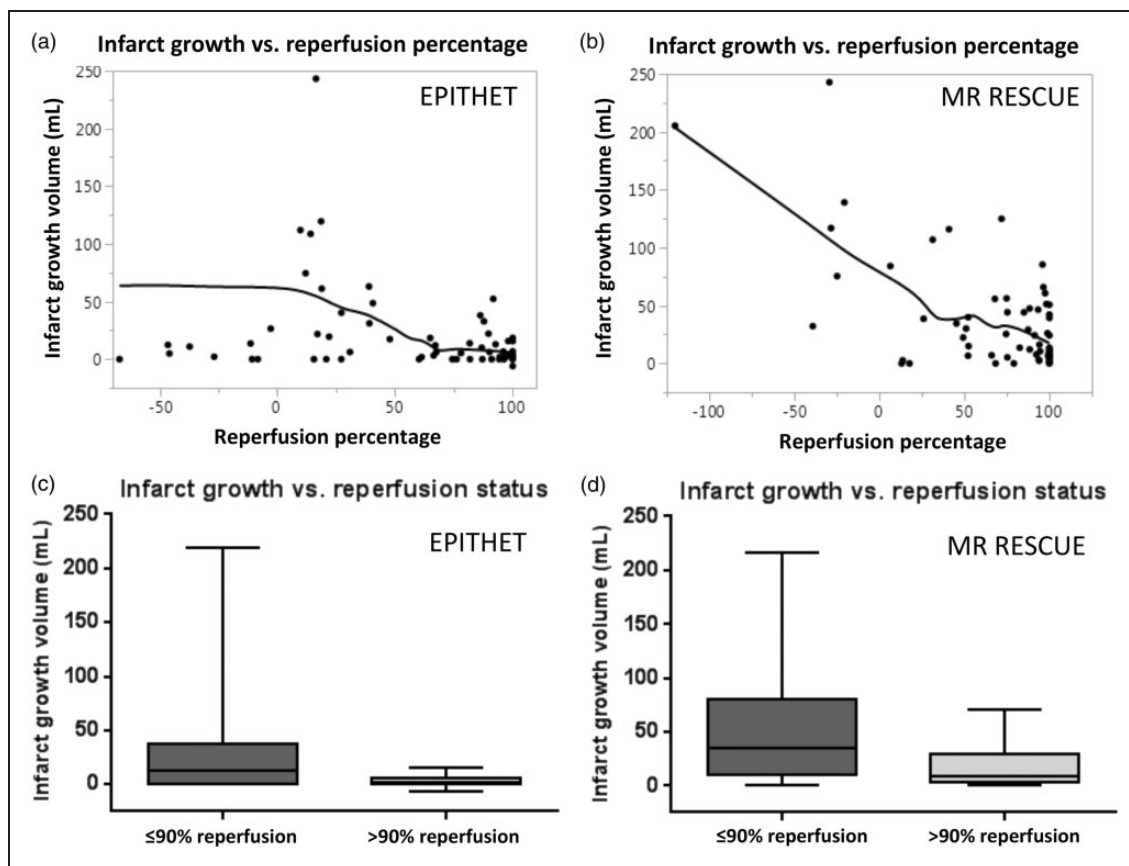


Figure 1. Reperfusion is associated with less infarct growth. Increasing percentage of reperfusion is associated with lower infarct growth volume in the EPITHET cohort ($n = 71$; Spearman $\rho = -0.37$, $P = 0.002$) (a), and in the MR RESCUE cohort ($n = 67$; Spearman $\rho = -0.42$, $P < 0.001$) (b). The line corresponds to a smoothing spline fit to the data. In Wilcoxon rank sum testing, successful reperfusion (dichotomized at $> 90\%$) was also associated less infarct growth in EPITHET ($n = 71$; $P = 0.003$) (c), and in MR RESCUE ($n = 67$; $P = 0.008$) (d).

sufficient quality for analysis; 12 subjects were excluded because they had no follow-up MRI. One subject had no available imaging. Of 118 subjects enrolled in MR RESCUE, 67 were included in the present analysis. Twenty-four were excluded because they lacked baseline MRI. Twenty-seven subjects lacked follow-up MRI or PWI, or had follow-up imaging of insufficient quality for analysis. The clinical characteristics of EPITHET and MR RESCUE subjects included in this study are shown in Table 1. Subjects in MR RESCUE were younger ($P=0.005$), had a higher admission NIHSS ($P<0.001$), larger baseline DWI stroke volumes ($P=0.02$), larger follow-up DWI stroke volumes ($P=0.02$), and a longer time to treatment ($P<0.001$). MR RESCUE subjects also had greater infarct growth ($P=0.002$) and MLS ($P<0.001$) as compared to subjects enrolled in EPITHET. The cohorts were similar

with regard to reperfusion percentage and proportion experiencing $>90\%$ reperfusion.

Reperfusion is associated with reduced infarct growth

We next sought to confirm that the degree of reperfusion (i.e., reperfusion percentage) was associated with a smaller volume of infarct growth. As demonstrated in Figure 1(a) and (b), increasing reperfusion percentage was associated with less infarct growth in patients enrolled in both the EPITHET (Spearman $\rho = -0.37$, $P=0.002$) and MR RESCUE (Spearman $\rho = -0.42$, $P<0.001$) cohorts.

We also analyzed the relationship of infarct growth and reperfusion dichotomized as successful ($>90\%$) or unsuccessful ($\leq 90\%$) using Wilcoxon rank sum testing. In EPITHET (Figure 1(c)), successful reperfusion was

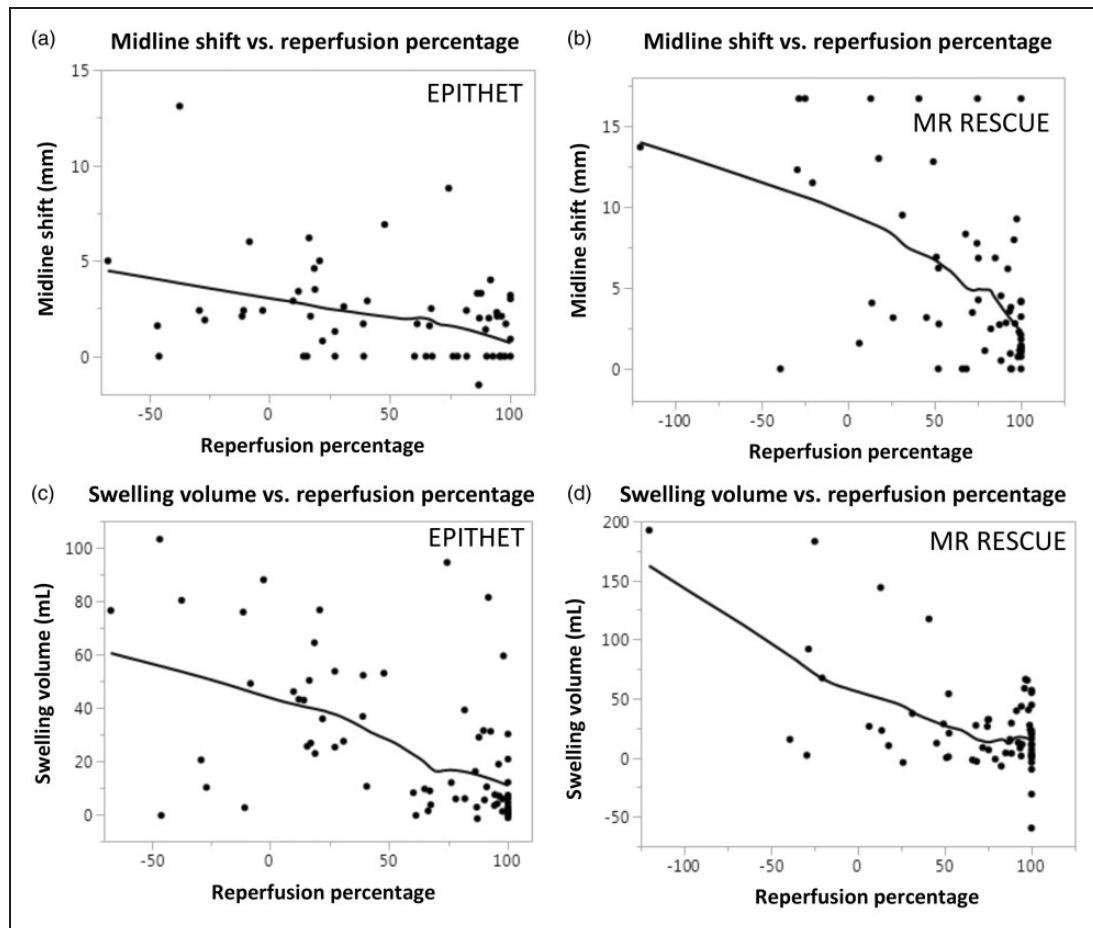


Figure 2. Reperfusion is associated with less brain edema. Greater degree of reperfusion is associated with less MLS in EPITHET ($n=71$; Spearman $\rho = -0.46$, $P<0.001$) (a), and MR RESCUE ($n=67$; Spearman $\rho = -0.49$, $P<0.001$) (b). Increasing reperfusion percentage predicts lower swelling volume in the EPITHET cohort ($n=71$; Spearman $\rho = -0.56$, $P<0.001$) (c), and in the MR RESCUE cohort ($n=67$; Spearman $\rho = -0.27$, $P=0.026$) (d). Each line corresponds to a smoothing spline fit to the data; the reported P values were generated from non-parametric analysis.

associated with a median infarct growth of 2 mL (IQR 0–7 mL), compared to unsuccessful reperfusion which was associated with a median infarct growth of 12 mL (IQR 0–38 mL; $P=0.003$). In the MR RESCUE cohort (Figure 1(d)), successful reperfusion was also associated with less infarct growth (median 8 mL, IQR 3–29 mL) compared to unsuccessful reperfusion (median 35 mL, IQR 10–80 mL; $P=0.008$).

Reperfusion is associated with reduced brain edema

Next, we evaluated the association of reperfusion percentage with two separate measures of brain edema: MLS and swelling volume. Increasing reperfusion percentage was associated with less MLS in both EPITHET (Figure 2(a), Spearman $\rho=-0.46$, $P<0.001$) and MR RESCUE (Figure 2(b), Spearman $\rho=-0.49$, $P<0.001$). Higher reperfusion percentage was also associated with lower swelling volume in both EPITHET (Figure 2(c), Spearman $\rho=-0.56$; $P<0.001$) and MR RESCUE (Figure 2(d), Spearman $\rho=-0.27$, $P=0.026$). An example of the measurements of edema in a patient with successful reperfusion is shown in Figure 3, and Figure 4 illustrates an example

of unsuccessful reperfusion. We also found similar results when recanalization was used instead of reperfusion (see Supplementary Figure 1) or when reperfusion was dichotomized into successful versus unsuccessful reperfusion (see Supplementary Figure 2). Accordingly, reperfusion percentage was tightly correlated with recanalization status (see Supplementary Figure 3).

Reperfusion independently predicts reduced brain edema

To assess the independent effect of reperfusion on brain edema, we performed multivariable regression analyses for MLS and swelling volume in both EPITHET and MR RESCUE. In each model, we adjusted for baseline clinical variables including age, admission blood glucose, baseline NIHSS, treatment assignment (IV tPA in EPITHET or IAT in MR RESCUE), and follow-up DWI stroke volume. In both cohorts, reperfusion percentage remained independently associated with less MLS (EPITHET: β coefficient = -0.056 ; $P=0.025$; Table 2 and MR RESCUE: β coefficient = -0.38 ; $P=0.03$; Table 3), and lower swelling volume (EPITHET: β coefficient = -4.7 ; $P=0.007$;

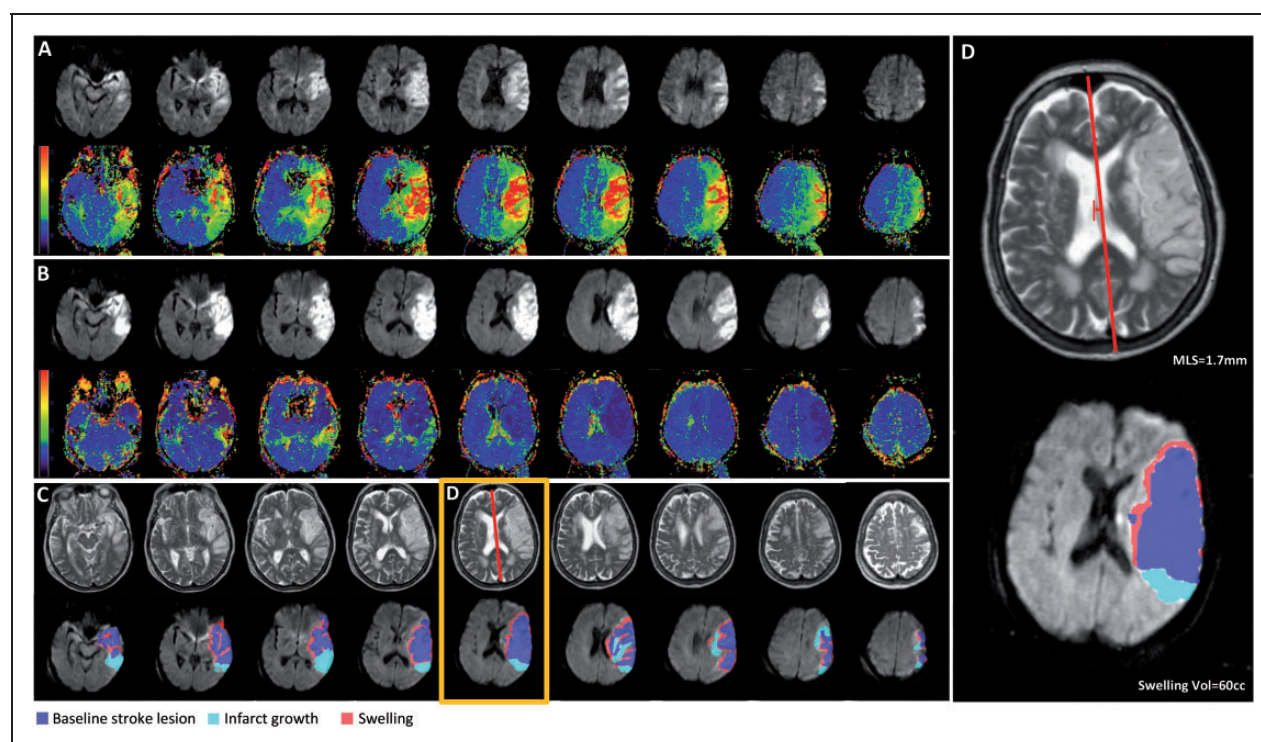


Figure 3. Reduced edema in a patient with successful reperfusion. Example images from a patient enrolled in EPITHET. (a) The baseline DWI and perfusion map reveals the infarct and associated region of hypoperfusion. (b) The follow-up DWI and perfusion map shows the infarct volume and restoration of cerebral blood flow in the region of the infarct. (c) Example of midline shift measurement on T2 sequence and the measurement of infarct growth and swelling volume on co-registered follow-up DWI scan. (d) An individual slice highlighted by the orange box in (c) demonstrates a maximum midline shift of 1.7 mm. The total swelling volume was 60 cc.

Table 2 and MR RESCUE: β coefficient = -10.7 ; $P=0.009$; Table 3). All VIF values generated for these multivariable models were below 1.8, suggesting no multicollinearity.

To assess the robustness of these findings, we substituted the follow-up DWI stroke volume with baseline DWI volume and found that reperfusion percentage remained independently associated with reduced MLS and swelling volume (Supplementary Table 1). We also performed additional sensitivity analyses to examine the role of perfusion–diffusion mismatch. Incorporating mismatch percentage in EPITHET did not alter the independent association between reperfusion and reduced brain edema using either MLS or lesional swelling volume (Supplementary Table 2). An analogous model in MR RESCUE did not alter the association between reperfusion and lesional swelling volume, although it did diminish the association with MLS (Supplementary Table 2). Finally, we evaluated whether the relationship between reperfusion percentage and brain edema was time dependent. Although the sample size had limited power, we nevertheless found that reperfusion remained an independent predictor of MLS and swelling volume in each cohort (Supplementary Table 3).

Discussion

In this study, we investigated the relationship between the degree of reperfusion and brain edema in patients enrolled in EPITHET and MR RESCUE. We investigated two quantitative metrics of brain edema (MLS and lesional swelling volume) since MLS may be less sensitive to edema in smaller strokes as compared to large hemispheric infarction.²⁰ Nonetheless, we found a consistent relationship between reperfusion percentage and each edema metric. In both cohorts, greater reperfusion percentage was associated with decreased infarct growth, MLS, and swelling volume. Multivariable analyses confirmed independent associations, after controlling for other variables, including age, baseline stroke severity, treatment type, and stroke volume.

Taken together, our analyses reaffirm that reperfusion prevents infarct expansion, and also suggests that reperfusion is associated with less brain edema. These data add another dimension to the well-described penumbra hypothesis, wherein reperfusion prevents infarct growth by rescuing hypoperfused tissue.^{8–11} Our data also raise the possibility that reperfusion may rescue brain tissue by limiting edema-associated

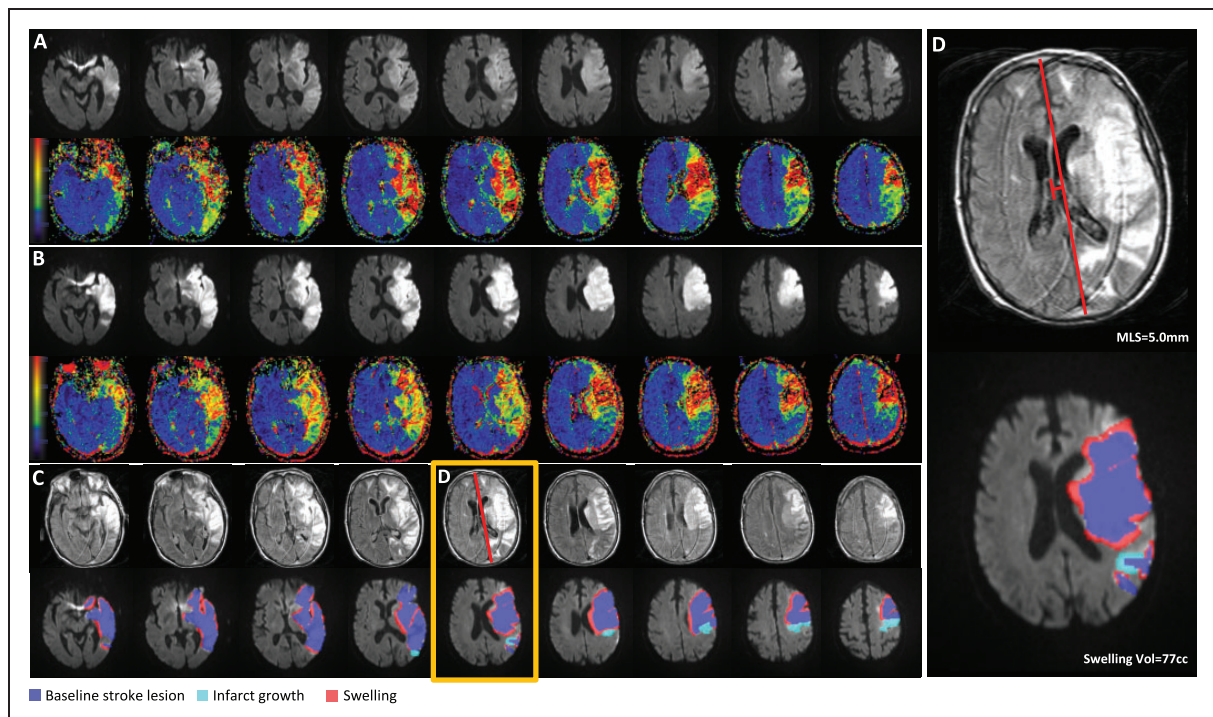


Figure 4. Greater edema in a patient with unsuccessful reperfusion. Example images from a patient enrolled in EPITHET with a similar infarct size as in Figure 3. (a) The baseline DWI and perfusion map reveals the infarct and associated region of hypoperfusion. (b) The follow-up DWI and perfusion map show the infarct volume and persistent perfusion deficit. (c) Example of midline shift measurement on T2 fluid-attenuated inversion recovery sequence and the measurement of infarct growth and swelling volume on co-registered follow-up DWI scan. (d) An individual slice highlighted by the orange box in (c) demonstrates a midline shift of 5.0 mm. The total swelling volume was 77 cc.

Table 2. Univariable and multivariable predictors of midline shift and swelling volume in EPITHET.

	Midline shift						Swelling volume					
	Univariable			Multivariable			Univariable			Multivariable		
	β	95% CI	P	adjusted β	95% CI	P	β	95% CI	P	adjusted β	95% CI	P
Age	-0.0049	-0.010 – 0.0002	0.06	-0.0013	-0.0060 – 0.0035	0.59	-0.46	-0.96 – 0.037	0.07	0.012	-0.31 – 0.34	0.92
Admission glucose	0.0062	-0.23 – 0.24	0.96	-0.10	-0.31 – 0.11	0.34	14.6	-7.5 – 36.8	0.19	3.6	-10.6 – 17.9	0.61
Admission NIHSS	0.014	0.0013–0.026	0.03	0.0024	-0.01 – 0.015	0.71	2.1	0.95 – 3.2	<0.001	0.23	-0.65 – 1.1	0.60
Received IV tPA	-0.0066	-0.075 – 0.062	0.85	-0.029	-0.089 – 0.031	0.33	0.95	-5.7 – 7.6	0.78	-0.88	-5.0 – 3.2	0.67
Follow-up DWI	0.26	0.16–0.36	<0.001	0.21	0.084–0.33	0.001	38.2	30.9 – 45.4	<0.001	33.8	25.2–42.4	<0.001
Reperfusion percentage	-0.076	-0.12 – -0.029	0.002	-0.056	-0.10 – -0.0074	0.025	-9.1	-13.5 – -4.8	<0.001	-4.7	-8.0 – -1.4	0.007

Note: Admission glucose, follow-up DWI volume, reperfusion percentage, and midline shift were log transformed before inclusion in each model. Data are from the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) cohort.

CI: confidence interval; DWI: diffusion-weighted imaging; IV tPA: intravenous tissue plasminogen activator; NIHSS: National Institutes of Health Stroke Scale.

Table 3. Univariable and multivariable predictors of midline shift and swelling volume in MR RESCUE.

	Midline Shift						Swelling Volume					
	Univariable			Multivariable			Univariable			Multivariable		
	β	95% CI	P	adjusted β	95% CI	P	β	95% CI	P	adjusted β	95% CI	P
Age	-0.00034	-0.0075 – 0.0069	0.93	-0.00045	-0.0097 – 0.0007	0.09	0.23	-0.42 – 0.88	0.49	-0.061	-0.54 – 0.41	0.80
Admission glucose	-0.07	-0.44 – 0.30	0.71	-0.1	-0.40 – 0.20	0.50	28.9	-4.5 – 62.3	0.09	24.8	-1.9 – 51.5	0.07
Admission NIHSS	0.031	0.012 – 0.049	0.001	0.018	0.0084 – 0.035	0.04	2.2	0.42 – 3.9	0.02	0.25	-1.3 – 1.8	0.75
Received IAT	-0.031	-0.14 – 0.077	0.57	0.025	-0.054 – 0.10	0.53	-2.8	-12.6 – 7.0	0.57	5	-2.2 – 12.3	0.17
Follow-up DWI	8.0	6.0 – 10.1	<0.001	0.48	0.24 – 0.72	<0.001	59.2	42.7 – 75.8	<0.001	49.3	28.6 – 70.0	<0.001
Reperfusion percentage	-0.16	-0.24 – -0.068	<0.001	-0.38	-0.72 – -0.044	0.03	-18.8	-26.1 – -11.4	<0.001	-10.7	-18.6 – -2.8	0.009

Note: Admission glucose, follow-up DWI volume, reperfusion percentage, and midline shift were log transformed before inclusion in each model. Data are from the Mechanical Retrieval and Recanalization of Stroke Clots Using Thrombectomy Trial (MR RESCUE) cohort.

CI: confidence interval; DWI: diffusion-weighted imaging; IAT: intra-arterial thrombectomy; NIHSS: National Institutes of Health Stroke Scale.

tissue injury, and supports the notion that there may be multiple beneficial effects of reperfusion.

Prior studies on the relationship of revascularization and edema in patients have yielded variable or inconclusive results. For example, in large stroke, persistent proximal vessel occlusion has been linked to clinically significant edema.¹⁹ A more recent study reported that large core lesions were associated with edema, but an association with TICI reperfusion and edema was not evident, perhaps because a qualitative approach to edema measurement was employed.²⁹ Here we report that in two cohorts with relatively delayed time to treatment (EPITHET treatment was initiated at ~5 and MR RESCUE at ~7 h), a greater degree of reperfusion was associated with lower brain edema. We hypothesize that our quantitative approach to edema measurement revealed a relationship not captured by prior methods.

Our findings are in apparent contradiction with rodent and primate models, which have shown that revascularization can accentuate brain edema.^{15–17,30} Several possibilities may explain the discrepancy in these studies. First, our analysis of reperfusion percentage may reflect several physiological phenomena. An increase in reperfusion percentage may derive from several processes, including: (1) resolution of the occlusion, (2) migration of the occlusion to more distal vessels, and/or (3) improvements in collateral blood flow. As such, reperfusion percentage, although highly correlated with recanalization status (Supplementary Figure 3), may not solely represent restored blood flow from revascularization. Second, the rate of ischemia and progression to infarction is likely different in humans as compared to animal models.³¹ This may result in differing propensities for reperfusion edema. Third, prior animal studies had measured edema shortly after revascularization,^{15–17} whereas available patient imaging data correspond to substantially later time points, when edema has reached a plateau. Finally, it is likely that reperfusion injury proceeds differently in rodent compared to human brain due to neuroanatomical differences. For example, rodent lissencephaly or disparate collateral flow patterns may be key mediators of the discordant findings between clinical and preclinical studies.

There also are also several potential explanations for the variable findings in clinical studies. One important possibility is that reperfusion edema may be a substantial risk in only select circumstances, perhaps only after late revascularization or in the setting of severe infarction (conditions that are less commonly treated with IV tPA and/or IAT). It is likely that such patients were excluded from enrollment in both EPITHET and MR RESCUE, and as such, our study results may not be generalizable to severe infarction. It is also possible that our study was underpowered to detect the

uncommon, but clinically meaningful event of reperfusion edema in late revascularization and/or severe infarction. Additional identification of clinical risk factors for reperfusion edema may help to further clarify the discrepancies among rodent models and clinical studies.

Our study has limitations. Our results may have limited generalizability because the present analyses were performed in a cohort of patients with moderate-to-severe stroke, in the context of two clinical trials. EPITHET patients were randomized to IV tPA 3–6 h after stroke onset, and MR RESCUE patients were randomized to thrombectomy using early generation clot retrieval devices. While these cohorts do not reflect current clinical practice, analysis of these cohorts would tend to bias towards the null hypothesis, suggesting that there may be a robust association between reperfusion and reduced brain edema. Our study does not answer whether or not thrombolysis or thrombectomy directly attenuates brain edema. However, in sensitivity analysis using reperfusion or recanalization dichotomized into successful or unsuccessful categories, each was associated with a smaller amount of edema. Such findings raise the hypothesis that therapeutic reperfusion may mitigate brain edema. Future studies in contemporary thrombectomy cohorts are needed to address this unresolved issue. Finally, the imaging requirements for our analyses necessitated the exclusion of subjects who lacked follow-up MRI or PWI, potentially introducing bias. These individuals may have had more severe strokes making them unstable during each study's follow-up period, or they may have expired prior to imaging acquisition. While we anticipate, this may have excluded the most severe strokes that would be prone to reperfusion edema, it does not change our main finding that reperfusion leads to decreased brain swelling in most circumstances.

Summary

Taken together, our findings suggest that a greater degree of reperfusion is associated with less brain edema after ischemic stroke. While our data do not exclude the possibility of worse edema in some circumstances, our findings raise the possibility that favorable outcome with IV tPA and IAT may, in part, be linked to less brain edema.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The funding for EPITHET was from the National Health and Medical Research Council, Australia (S.M.D., G.A.D.) and the funding for the MR RESCUE trial was from the NIH P50NS044378 (C.S.K.). The analysis was

funded in part by NIH K23NS076597, NIH R01NS099209, and the Andrew David Heitman Neurovascular Research Foundation (W.T.K.). Dr. Kimberly has received research support from Remedy Pharmaceuticals, NIH grants K23NS076597 and R01NS099209, the Andrew David Heitman Neurovascular Research Foundation and AHA 14GRNT19060044.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' contributions

Study concept and design: HJI, ACO, MBB, WTK.

Acquisition, analysis or interpretation of data: HJI, ACO, MBB, SD, TWKB, BCVC, SMD, GAD, KNS, RJ, JLS, CSK, WTK.

Drafting of the manuscript: HJI, WTK.

Critical revision of the manuscript for important intellectual content: HJI, ACO, MBB, SD, TWKB, BCVC, SMD, GAD, KNS, RJ, JLS, CSK, WTK.

Study supervision: SMD, GAD, CSK, WTK.

Supplementary material

Supplementary material for this paper can be found at the journal website: <http://journals.sagepub.com/home/jcb>

References

1. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004; 363: 768–774.
2. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014; 384: 1929–1935.
3. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; 387: 1019–1030.
4. Rha JH and Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke* 2007; 38: 967–973.
5. Zaidat OO, Suarez JJ, Sunshine JL, et al. Thrombolytic therapy of acute ischemic stroke: correlation of angiographic recanalization with clinical outcome. *Am J Neuroradiol* 2005; 26: 880–884.
6. del Zoppo GJ and Koziol JA. Recanalization and stroke outcome. *Circulation* 2007; 115: 2602–2605.
7. Eilaghi A, Brooks J, d'Esterre C, et al. Reperfusion is a stronger predictor of good clinical outcome than recanalization in ischemic stroke. *Radiology* 2013; 269: 240–248.
8. Astrup J, Siesjö BK and Symon L. Thresholds in cerebral ischemia – the ischemic penumbra. *Stroke* 1981; 12: 723–725.
9. Heiss WD, Huber M, Fink GR, et al. Progressive derangement of periinfarct viable tissue in ischemic stroke. *J Cereb Blood Flow Metab* 1992; 12: 193–203.
10. Ginsberg MD and Pulsinelli WA. The ischemic penumbra, injury thresholds, and the therapeutic window for acute stroke. *Ann Neurol* 1994; 36: 553–554.
11. Albers GW, Thijs VN, Wechsler L, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Ann Neurol* 2006; 60: 508–517.
12. Hallenbeck JM and Dutka AJ. Background review and current concepts of reperfusion injury. *Arch Neurol* 1990; 47: 1245–1254.
13. Kidwell CS, Saver JL, Starkman S, et al. Late secondary ischemic injury in patients receiving intraarterial thrombolysis. *Ann Neurol* 2002; 52: 698–703.
14. Li F, Silva MD, Liu KF, et al. Secondary decline in apparent diffusion coefficient and neurological outcomes after a short period of focal brain ischemia in rats. *Ann Neurol* 2000; 48: 236–244.
15. Pillai DR, Dittmar MS, Baladranov D, et al. Cerebral ischemia-reperfusion injury in rats – a 3 T MRI study on biphasic blood-brain barrier opening and the dynamics of edema formation. *J Cereb Blood Flow Metab* 2009; 29: 1846–1855.
16. Bell BA, Symon L and Branston NM. CBF and time thresholds for the formation of ischemic cerebral edema, and effect of reperfusion in baboons. *J Neurosurg* 1985; 62: 31–41.
17. Gartschore G, Patterson J and Macrae IM. Influence of ischemia and reperfusion on the course of brain tissue swelling and blood-brain barrier permeability in a rodent model of transient focal cerebral ischemia. *Exp Neurol* 1997; 147: 353–360.
18. Hacke W, Schwab S, Horn M, et al. “Malignant” middle cerebral artery territory infarction clinical course and prognostic signs. *Arch Neurol* 1996; 53: 309–315.
19. Thomalla G, Hartmann F, Juettler E, et al. Prediction of malignant middle cerebral artery infarction by magnetic resonance imaging within 6 hours of symptom onset: a prospective multicenter observational study. *Ann Neurol* 2010; 68: 435–445.
20. Battey TWK, Karki M, Singhal AB, et al. Brain edema predicts outcome after nonlacunar ischemic stroke. *Stroke* 2014; 45: 3643–3648.
21. Davis SM, Donnan GA, Parsons MW, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol* 2008; 7: 299–309.
22. Kidwell CS, Jahan R, Gornbein J, et al. MR RESCUE: a trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med* 2013; 368: 914–923.
23. Cho T-HH, Nighoghossian N, Mikkelsen IK, et al. Reperfusion within 6 hours outperforms recanalization in predicting penumbra salvage, lesion growth, final infarct, and clinical outcome. *Stroke* 2015; 46: 1582–1589.

24. Khatri P, Neff J, Broderick JP, et al. Revascularization end points in stroke interventional trials: recanalization versus reperfusion in IMS-I. *Stroke* 2005; 36: 2400–2403.
25. De Silva DA, Fink JN, Christensen S, et al. Assessing reperfusion and recanalization as markers of clinical outcomes after intravenous thrombolysis in the echoplanar imaging thrombolytic evaluation trial (EPITHET). *Stroke* 2009; 40: 2872–2874.
26. Ropper AH. Lateral displacement of the brain and level of consciousness in patients with an acute hemispherical mass. *N Engl J Med* 1986; 314: 953–958.
27. Pullicino PM, Alexandrov AV, Shelton JA, et al. Mass effect and death from severe acute stroke. *Neurology* 1997; 49: 1090–1095.
28. Kimberly WT, Battey TWK, Pham L, et al. Glyburide is associated with attenuated vasogenic edema in stroke patients. *Neurocrit Care* 2014; 20: 193–201.
29. Cheripelli BK, Huang X, Macisaac R, et al. Interaction of recanalization, intracerebral hemorrhage, and cerebral edema after intravenous thrombolysis. *Stroke* 2016; 47: 1761–1767.
30. Nour M, Scalzo F and Liebeskind DS. Ischemia-reperfusion injury in stroke. *Interv Neurol* 2013; 1: 185–199.
31. Carmichael ST. Rodent models of focal stroke: size, mechanism, and purpose. *NeuroRx* 2005; 2: 396–409.