EPITHET

Positive Result After Reanalysis Using Baseline Diffusion-Weighted Imaging/Perfusion-Weighted Imaging Co-Registration

Yoshinari Nagakane, MD, PhD; Soren Christensen, PhD; Caspar Brekenfeld, MD; Henry Ma, MBBS; Leonid Churilov, PhD; Mark W. Parsons, PhD, FRACP; Christopher R. Levi, FRACP; Kenneth S. Butcher, MD, PhD; Andre Peeters, MD; P. Alan Barber, PhD; Christopher F. Bladin, PhD; Deidre A. De Silva, MBBS, MRCP, FAMS; John Fink, FRACP; Thomas E. Kimber, PhD, FRACP; David W. Schultz, FRACP; Keith W. Muir, MD; Brian M. Tress, MD, FRANZCR, FRCR; Patricia M. Desmond, MD; Stephen M. Davis, MD, FRACP; Geoffrey A. Donnan, MD, FRACP; for the EPITHET Investigators

Background and Purpose—The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) was a prospective, randomized, double-blinded, placebo-controlled, phase II trial of alteplase between 3 and 6 hours after stroke onset. The primary outcome of infarct growth attenuation on MRI with alteplase in mismatch patients was negative when mismatch volumes were assessed volumetrically, without coregistration, which underestimates mismatch volumes. We hypothesized that assessing the extent of mismatch by coregistration of perfusion and diffusion MRI maps may more accurately allow the effects of alteplase vs placebo to be evaluated.

Methods—Patients were classified as having mismatch if perfusion-weighted imaging divided by coregistered diffusion-weighted imaging volume ratio was >1.2 and total coregistered mismatch volume was ≥ 10 mL. The primary outcome was a comparison of infarct growth in alteplase vs placebo patients with coregistered mismatch.

Results—Of 99 patients with baseline diffusion-weighted imaging and perfusion-weighted imaging, coregistration of both images was possible in 95 patients. Coregistered mismatch was present in 93% (88/95) compared to 85% (81/95) with standard volumetric mismatch. In the coregistered mismatch patients, of whom 45 received alteplase and 43 received placebo, the primary outcome measure of geometric mean infarct growth was significantly attenuated by a ratio of 0.58 with alteplase compared to placebo (1.02 vs 1.77; 95% CI, 0.33–0.99; $P=0.0459$).

Conclusions—When using coregistration techniques to determine the presence of mismatch at study entry, alteplase significantly attenuated infarct growth. This highlights the necessity for a randomized, placebo-controlled, phase III clinical trial of alteplase using penumbral selection beyond 3 hours. **(*Stroke*. 2011;42:59-64.)**

Key Words: magnetic resonance imaging ■ mismatch ■ penumbra ■ tissue plasminogen activator

Reperfusion therapies including intravenous thrombolysis with recombinant tissue plasminogen activator are based on the premise that ischemic penumbral tissue is at risk for infarction but has the potential to be salvaged by reperfusion.[1] With the advent of MRI techniques, the mismatch concept defined by the perfusion-weighted imaging (PWI) lesion exceeding the diffusion-weighted imaging (DWI) lesion was postulated as a penumbral marker.[2] Since then, MR PWI/DWI has become a widely used imaging research technique in the assessment of acute stroke patients.[3]

Mismatch volume (MV) is conventionally calculated using a volumetric method in which the DWI lesion volume is

Received February 4, 2010; accepted July 29, 2010.

From the National Stroke Research Institute (Y.N., C.B., H.M., L.C., G.A.D.), Florey Neuroscience Institutes, Austin Health, University of Melbourne, Australia; Department of Neurology (S.C., D.A.D.S., S.M.D.), Royal Melbourne Hospital, University of Melbourne, Australia; Institute of Interventional and Diagnostic Neuroradiology (C.B.), University of Bern, Switzerland; Department of Mathematics and Statistics (L.C.), University of Melbourne, Australia; Department of Neurology (M.W.P., C.R.L.), Hunter Medical Research Institute, John Hunter Hospital, University of Newcastle, Australia; Department of Neurology (K.S.B.), University of Alberta, Edmonton, Alberta, Canada; University Hospital St Luc (A.P.), Brussels, Belgium; Neurology Department (P.A.B.), Auckland City Hospital, Grafton, Auckland, New Zealand; Eastern Melbourne Neurosciences (C.F.B.), Melbourne, Australia; Department of Neurology (D.A.D.S.), Singapore General Hospital campus, National Neuroscience Institute, Singapore; Department of Neurology (J.F.), Christchurch Hospital, Christchurch, New Zealand; Royal Adelaide Hospital (T.E.K.), Adelaide, Australia; Department of Neurology (D.W.S.), Flinders Medical Centre, Bedford Park, Australia; Division of Clinical Neurosciences (K.W.M.), University of Glasgow, UK; Department of Radiology (B.M.T., P.M.D.), Royal Melbourne Hospital, University of Melbourne, Australia.

The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.580464/DC1.

Correspondence to Geoffrey A. Donnan, Florey Neuroscience Institutes, University of Melbourne, Level 2 Alan Gilbert Building, 161 Barry Street, Carlton South Victoria 3053, Australia. E-mail gdonnan@unimelb.edu.au

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.110.580464**

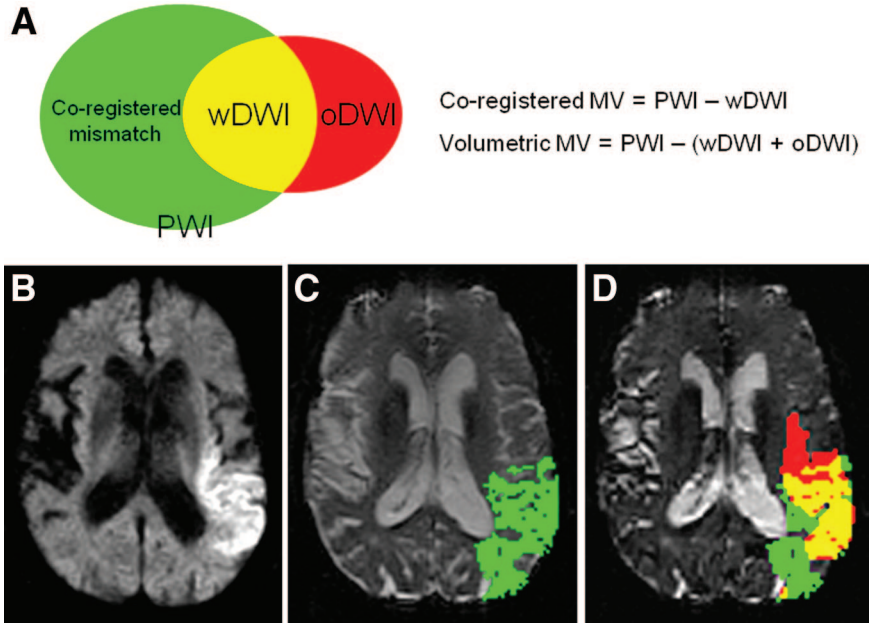

Figure 1. A, Coregistration of perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) allows the DWI lesion to be divided into 2 regions: DWI within (wDWI; yellow) and DWI lying outside the PWI lesion (oDWI; red). Using the volumetric technique, the mismatch volume (MV) is PWI−(wDWI+oDWI), whereas the coregistered MV (green) is defined as PWI−wDWI. An 82-year-old woman with baseline MRI performed 325 minutes after stroke onset. The baseline DWI lesion volume was 65.3 mL (B) and PWI lesion volume was 68.8 mL (C; green areas indicate PWI abnormalities of Tmax 2 seconds or more). In EPITHET using the volumetric technique, she was classified as having no mismatch (3.5 mL); however, while coregistered (D), she was classified as having mismatch (26.2 mL; wDWI in yellow, oDWI in red, and coregistered mismatch areas in green).

simply subtracted from the PWI volume.[2] This method assumes that ischemic core represented by the DWI lesion is surrounded by a hypoperfused area defined by the PWI lesion.[4] However, the region of hypoperfusion fluctuates in the hours after stroke onset attributable to processes such as spontaneous reperfusion and changes in collateral blood flow.[5] Early reperfusion of the infarct core may result in a component of the DWI lesion lying outside the PWI lesion.[6] Coregistration of DWI and PWI images allows a more precise estimate of these spatial relationships, with simple volumetric analysis consistently underestimating the mismatch volume when compared to the coregistration method.[7]

The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) was a phase II, prospective, randomized, double-blinded, placebo-controlled, multinational trial of 101 patients treated between 3 and 6 hours after stroke onset.[8] Importantly, the primary hypothesis was that patients with mismatch (defined by the standard volumetric method) who received alteplase would have attenuation of infarct growth seen on MRI. Although there was a trend toward attenuation of infarct growth, this did not reach statistical significance. Given that the mismatch assessment in EPITHET by the volumetric method may have underestimated the mismatch volume and, hence, the target population in whom the primary hypothesis was tested, we reanalyzed the dataset using coregistration of DWI/PWI images at baseline. We hypothesized that this may have increased the number of patients with eligible mismatch and that this, in turn, may have influenced the effects of alteplase on attenuation of infarct growth.

Patients and Methods

Imaging Protocol

The study design of EPITHET, including patient eligibility, treatment allocation, and imaging protocol, has been previously reported.[8] Briefly, patients with acute hemispheric ischemic stroke who presented 3 to 6 hours after symptom onset were assigned to intravenous alteplase or placebo and had DWI, PWI, and MRA sequences with 1.5-T echoplanar-equipped MRI scanners before treatment and again at days 3 to 5. At day 90, T2-weighted images were obtained to measure final infarct volume.

Imaging Analysis

Baseline DWI was registered to the baseline PWI using MINC software (The McConnell Brain Imaging Centre) by 1 investigator (Y.N.) blinded to treatment assignment but not to time point. First, automatic registration was applied to register baseline DWI to the PWI frame. Second, manual landmark-based registration was used to initialize another automatic registration in cases in which automatic coregistration failed on the first attempt. The quality of coregistration was reviewed by a second investigator (S.C.).

Using these coregistration techniques, the baseline DWI lesion was divided into 2 regions: DWI within and DWI outside of the PWI volume (Figure 1). Regions of interest on DWI and T2-weighted images, Tmax map, and MRA ratings were unaltered from the original trial. Similarly, hypoperfusion volumes were defined using a Tmax delay of ≥2 seconds as previously described. For patients who died or who could not be studied at day 90, the last results at days 3 to 5 were carried forward as a measure of imaging outcome.

Definitions

All definitions were as in the main EPITHET study except for the addition of coregistered mismatch (Table 1).[8]

Outcome Measures

The primary outcome measure was infarct growth attenuation in coregistered mismatch patients between alteplase and placebo, primarily analyzed by geometric mean and secondarily by relative growth, absolute growth, and difference in cube root lesion volumes. Secondary end points included reperfusion, clinical outcomes, recanalization, and symptomatic intracerebral hemorrhage.

Statistical Analysis

Statistical analyses were performed using Stata/IC 10 (StataCorp). The comparisons between volumetric and coregistration methods were made with Wilcoxon signed-rank test for continuous variables and with McNemar exact test for categorical variables. The agreement between the original DWI volumes and the coregistered DWI volumes was assessed by Lin's concordance coefficient and intraclass correlation coefficient. As per the original protocol of EPITHET, the difference in means of log-relative growth between patients treated

Table 1. Definitions

Coregistered mismatch: PWI÷wDWI volume >1.2, and PWI−wDWI volume ≥10 mL
Volumetric mismatch: PWI÷DWI volume >1.2, and PWI−DWI volume ≥10 mL
Infarct growth: expansion between baseline DWI and day-90 T2-weighted lesion
Geometric mean: exponential of mean log relative growth
Relative growth: final lesion volume÷baseline DWI lesion volume
Absolute growth: final lesion volume−baseline DWI lesion volume
Difference in cube root volumes: (final lesion volume)$^{1/3}$−(baseline DWI lesion volume)$^{1/3}$
Any growth: relative growth >0%
Malignant profile: DWI volume and/or PWI volume with Tmax ≥8 seconds ≥100 mL
Reperfusion: >90% reduction between baseline and day-3 PWI volumes
Recanalization: improvement from baseline to day 3 to 5 in arterial obstruction by ≥2 points, based on an adaptation of the thrombolysis in myocardial infarction grading on MRA (0=complete occlusion, 1=severe stenosis, 2=mild to moderate stenosis, and 3=normal arterial caliber)
Symptomatic ICH: ICH with significant clinical deterioration of ≥4 NIHSS points within 36 hours of treatment and parenchymal hemorrhage of grade 2 on CT (blood clots in >30% of the infarcted area with substantial space-occupying effect) adjudicated by a blinded committee (SITS-MOST definition)[9]
Good neurological outcome: NIHSS at day 90 of 0 or 1 or improvement ≥8 from baseline
Good functional outcome: modified Rankin scale at day 90 of 0 to 2

DWI indicates diffusion-weighted imaging; ICH, intracerebral hemorrhage; PWI, perfusion-weighted imaging; wDWI, diffusion-weighted imaging within the perfusion-weighted imaging lesion.

with alteplase and with placebo was tested by *t* test. The 2-sample Wilcoxon rank-sum test was used for the comparison of relative growth, absolute growth, and the difference of cube root transformed volume change. Hodges-Lehman shift parameter was used to estimate effect sizes for the comparisons when the Wilcoxon rank-sum test was used. Fisher exact test was used to compare patients treated with alteplase and with placebo in respect to the presence or absence of growth (any), reperfusion, and recanalization status, as well as for clinical outcomes. As per the original EPITHET analysis, no adjustments for multiple comparisons were made.

Results

Ninety-nine of 101 patients enrolled in EPITHET had baseline DWI and PWI and were included in this study. Automatic coregistration of baseline DWI and PWI succeeded in 95 of 99 patients, with 5 patients requiring initialization by manual landmarks. Coregistration failed in 4 (4%) patients because of artifact (3 had severe ghost artifacts of PWI and 1 had DWI motion artifacts), and these patients were excluded from subsequent analysis.

Table 2 shows baseline imaging variables for the 95 patients. Transformation of DWI into PWI space during the coregistration process resulted in baseline DWI volume increasing slightly from 20 mL (range, 0–197) to 21 mL (range, 0–204), and the agreement on the DWI volumes between original and after coregistration was confirmed by both intraclass correlation coefficient of 1.00 (95% CI, 0.98–1.00) and Lin concordance coefficient of 0.996 (0.995–0.998). After coregistration, median baseline DWI within and DWI outside the PWI lesion volumes were 13 mL (range, 0–152) and 5 mL (range, 0–119), respectively. Median baseline coregistered MV was significantly larger than baseline volumetric MV (128 mL vs 118 mL), with median difference of 5 mL (interquartile range, 3–12; 95% CI, 4–6; $P<0.0001$). Because 7 patients with no mismatch by the volumetric method had mismatch by the coregistration method (Figure 1B), the prevalence of mismatch increased from 85% (81/95) by the volumetric method to 93% (88/95) by the coregistration method ($P=0.0156$).

Table 2. Baseline Imaging Variables for 95 Patients

	Alteplase (n=49)	Placebo (n=46)
Median baseline DWI volume (mL)	20 (0–188)	21 (0–204)
Median baseline wDWI volume (mL)	10 (0–152)	16 (0–150)
Median baseline PWI volume (mL)	142 (0–558)	192 (0–428)
Median baseline mismatch volume (mL)		
Volumetric method	95 (−10–455)	136 (−93–422)
Coregistration method	99 (0–466)	152 (0–422)
Mismatch		
Volumetric method	40 (82)	41 (89)
Coregistration method	45 (92)	43 (93)

DWI indicates diffusion-weighted imaging; PWI, perfusion-weighted imaging; wDWI, diffusion-weighted imaging within the perfusion-weighted imaging lesion.

Data are median (range) or N (%) of patients.

Figure 2 shows the study profile and Table 3 shows baseline characteristics for mismatch patients with valid imaging outcomes. Of the 101 enrolled patients, 91 patients had baseline PWI and DWI with a day-90 T2-weighted image or with a surrogate day-3 to day-5 DWI for the final lesion. Because of coregistration failure in 4 patients (2 each in the alteplase and placebo groups), 87 patients were assessed for mismatch between PWI and DWI and 80 had mismatch (38 received alteplase and 42 received placebo). Baseline variables of patients with mismatch did not significantly differ ($P\geq0.1$) between alteplase and placebo groups (Table 3), and no statistical correction was needed.

For the primary outcome measure using the originally prespecified analytic method (geometric mean growth), the coregistered mismatch patients showed significant infarct growth attenuation with alteplase compared to placebo (1.02 vs 1.77; ratio, 0.58; 95% CI, 0.33–0.99; $P=0.0459$; Table 4). When the geometric mean growth was compared among the volumetric mismatch patients without coregistration, infarct growth attenuation did not differ between the treatment groups (1.06 vs 1.79; ratio, 0.59; 95% CI, 0.32–1.06; $P=0.0779$). This was confirmed by significant attenuation in infarct growth by the secondary analytical methods: relative growth ($P=0.0139$), absolute growth ($P=0.0332$), and difference in cube root lesion volume ($P=0.0204$). Further additional analytical methods including the proportion of patients who had any growth ($P=0.0216$), ratio of geometric mean ($P=0.0113$), and median relative growth ($P=0.0038$)

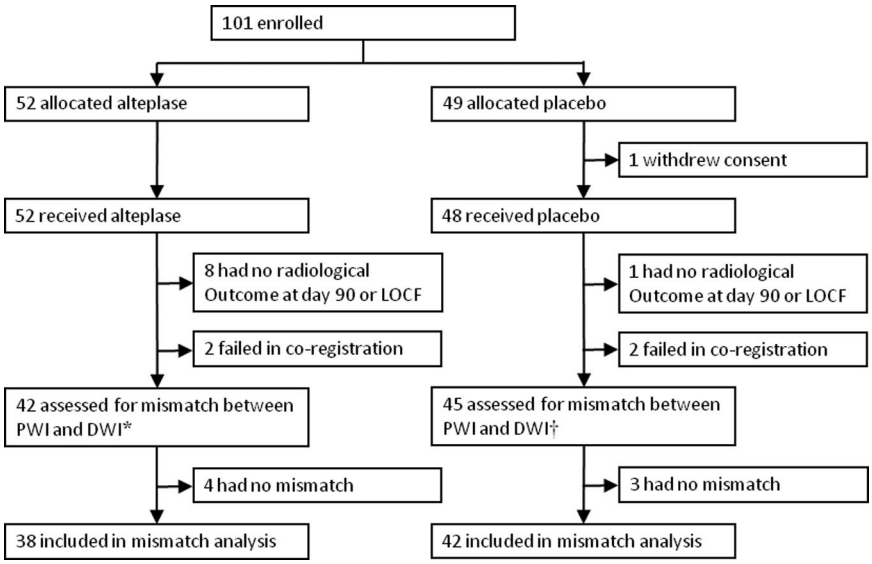

Figure 2. Trial profile. *Last observation carried forward (LOCF) data were used in 11 patients. †LOCF data were used in 7 patients.

in patients with a baseline lesion of >5 mL (33 patients in the alteplase group and 36 in the placebo group) also showed a positive effect of alteplase compared to placebo.

For secondary outcome measures, 76 of the 88 coregistered mismatch patients had a valid PWI volume at days 3 to 5 to assess reperfusion, and all 88 had assessment of clinical outcome (Tables 4 and the online-only supplemental Table, available at http://stroke.ahajournals.org). Both the incidence of reperfusion (≥90%) and the median percentage of reperfusion were significantly higher in patients with coregistered mismatch who received alteplase. Reperfusion was significantly associated with infarct growth attenuation, good neurological outcome, and good functional outcome in patients with coregistered mismatch. As with the original EPITHET analysis, which was not powered for a clinical outcome, the difference in good neurological and functional outcomes between the alteplase and placebo groups was not significant in patients with coregistered mismatch. Recanalization could be assessed with adequate MRA scans in 43 patients with coregistered mismatch, and it occurred in 27 (63%) of these patients (Table 4). The proportion of recanalization did not differ between treatment arms.

Table 3. Baseline Characteristics for Patients With Coregistered Mismatch

	Alteplase (n=38)	Placebo (n=42)	*P*
Age (y)			0.7835
Mean	71.7 (14.1)	71.3 (13.6)	
Median	75 (23–87)	74 (39–92)	
Male	15 (39%)	20 (48%)	0.505
Hypertension	29 (76%)	27 (64%)	0.329
Diabetes mellitus	9 (24%)	10 (24%)	>0.999
Hyperlipidemia	18 (47%)	14 (33%)	0.255
Atrial fibrillation	17 (45%)	15 (36%)	0.495
Current or past smoker	11 (29%)	19 (45%)	0.168
Median NIHSS at presentation	13 (4–23)	11 (5–25)	0.4778
Time to treatment (min)			0.9041
Mean	296 (44)	294 (49)	
Median	303 (187–365)	306 (195–365)	
Median baseline DWI volume (mL)	21 (2–188)	21 (0–204)	0.8059
Median baseline PWI volume (mL)	147 (13–558)	199 (40–428)	0.3353
Median baseline mismatch volume (mL)			
Volumetric method	105 (−10–455)	157 (−93–422)	0.3702
Coregistration method	110 (11–466)	162 (26–422)	0.3163
Malignant profile*	12 (32%)	16 (38%)	0.641

DWI indicates diffusion-weighted imaging; PWI, perfusion-weighted imaging. Data are mean (SD), median (range), or N (%) of patients.

*DWI volume ≥100 mL, PWI volume ≥100 mL, or both, with Tmax delay ≥8 sec.

Symptomatic intracerebral hemorrhage was seen in 8.0% (4/50) of patients treated with alteplase. All patients had mismatch by the coregistration method, whereas 3 out of 4 had mismatch by the volumetric method. Median baseline DWI volume did not differ between patients with symptomatic intracerebral hemorrhage (43 mL; interquartile range, 31–101) and those without symptomatic intracerebral hemorrhage (15 mL; interquartile range, 7–37; $P=0.058$).

Primary outcome could be assessed in 7 patients without coregistered mismatch. Infarct growth did not differ significantly between the alteplase and placebo groups (geometric mean growth 0.93 vs 1.03; ratio, 0.91; 95% CI, 0.31–2.66; $P=0.8283$). Between mismatch and nonmismatch patients in the alteplase group, infarct growth, reperfusion rate, and clinical outcomes did not differ significantly.

Discussion

The efficacy analysis in EPITHET, although negative on the prespecified primary outcome, provided strong support for further investigation of the use of PWI/DWI mismatch in the identification of favorable reperfusion outcomes with alteplase. By applying the coregistration method to assess MV

Table 4. Trial Outcomes for Patients With Coregistered Mismatch

	Alteplase	Placebo	Difference or Ratio (95% CI)*	*P*
Infarct growth	n=38	n=42		
Primary analytical method				
Geometric mean	1.02	1.77	0.58† (0.33–0.99)	0.0459
Secondary analytical methods				
Median relative growth	1.00 (0.50–1.80)	1.70 (1.00–3.10)	0.57† (0.36–0.88)	0.0139
Median absolute growth (mL)	−0.2 (−5.7–32.1)	27.4 (−0.2–55.6)	−12.2‡ (−31.8–0.7)	0.0332
Mean difference in cube root volumes (cm)	0.27 (1.19)	0.71 (1.06)	−0.43 (−0.94–0.06)	0.0855
Median difference in cube root volumes (cm)	0.0 (−0.4–0.7)	0.5 (0.0–1.2)	−0.5‡ (−0.9 to −0.1)	0.0204
Additional analytical methods				
Growth >0%	18 (47%)	31 (74%)	−26% (−47% to −6%)	0.0216
Baseline DWI lesions >5 mL				
Geometric mean growth§	1.04	2.01	0.52† (0.31–0.86)	0.0113
Median relative growth§	1.00 (0.50–1.80)	1.85 (1.30–3.20)	0.53† (0.33–0.77)	0.0038
Reperfusion assessed	n=34	n=42		
Reperfusion ≥90%	20 (59%)	11 (26%)	33% (11%–54%)	0.0052
Median percentage reperfusion	93% (68–100)	53% (16 to 93)	18% (3%–53%)	0.0088
Recanalization assessed	n=17	n=26		
Recanalization	13 (76%)	14 (54%)	22% (−5%–50%)	0.1994
Clinical outcomes	n=45	n=43		
Good neurological outcome	23 (51%)	16 (37%)	14% (−7%–34%)	0.2056
mRS 0–2	20 (44%)	17 (40%)	5% (−16%–26%)	0.6712
mRS 0–1	16 (36%)	9 (21%)	15% (−4%–33%)	0.1591

DWI indicates diffusion-weighted imaging; mRS, modified Rankin Scale.
Data are mean (SD), N (%) of patients, or median (interquartile range).
*Difference of average or percentage for alteplase minus that for placebo, unless indicated as a ratio or median difference.
†Ratios.
‡Median difference estimated by Hodges-Lehman shift parameter (95% CI).
§Data for patients with baseline lesion >5 mL: 33 (87%) in the alteplase group and 36 (86%) in the placebo group.

at study entry, we found that the prevalence of mismatch patients was increased and resulted in a positive outcome of EPITHET for the primary end point of infarct growth attenuation with alteplase in mismatch patients. As in EPITHET, we also found a strongly positive relationship between reperfusion and both attenuation of infarct growth and good clinical outcome in the coregistered mismatch group. These results emphasize the concept that selecting patients with PWI/DWI mismatch beyond 3 hours might be a useful approach to extend the time window for thrombolytic therapy.[10,11] Our findings can now be put in the context of EPITHET, in which there was a borderline significant attenuation in relative infarct growth with alteplase in patients with standard volumetric mismatch. Interestingly, the coregistered mismatch definition appears to be a more sensitive selection criterion, with all measures of infarct growth showing significant attenuation with alteplase in patients included in EPITHET using this approach.

The great advantage of coregistration of PWI and DWI is that it allows a more precise estimate of the spatial relationship between these imaging modalities to occur and, hence, a better understanding of the dynamic nature of the evolving ischemia and reperfusion process. In particular, it becomes clear that portions of the DWI lesions have already reperfused at the time of imaging and, under these circumstances, the volumetric method does underestimate the true proportion of mismatch.[7] This is illustrated in Figure 1A, in which the coregistered MV is greater than the volumetric MV by the amount of the DWI outside volume (the volume of the DWI portion lying outside the PWI lesion). Already reperfused DWI tissue has previously been labeled by reversible acute diffusion lesion already reperfused.[6] This particular region is most likely to recover if reperfusion occurs within 6 hours of symptom onset. Overall, in the current study, MV calculated by the coregistration method was a median of 5 mL (95% CI, 4–6) larger than that calculated by the volumetric method.

Interestingly, using a higher Tmax threshold instead of Tmax 2-second delay may cause an even larger difference between volumetric and coregistered MV. For example, when using Tmax 6-second threshold, PWI lesion volumes were smaller than those using Tmax 2 seconds (median, 82 vs 162 mL); this made DWI within smaller (10 vs 13 mL) and DWI outside larger (8 vs 5 mL). Although median MV were 48 mL and the prevalence of mismatch was 76% (72/95) by the volumetric method, median MV were 63 mL and the prevalence of mismatch was 85% (81/95) by the coregistration method. In other words, this confirms that the differences between the volumetric and coregistration methods were greater when using Tmax 6 seconds rather than Tmax 2 seconds. It is worth noting that the same central processing and data analysis

techniques as the original EPITHET were used, apart from the addition of the coregistration components.

There are some limitations to this study. First, some patients were excluded from the analysis because of coregistration failure, mainly attributable to inadequate imaging quality. Therefore, the altered trial results cannot be attributed exclusively to the inclusion of additional patients. There is a constant improvement occurring in the quality of DWI and PWI imaging techniques with software and MR hardware developments. In the clinical trial setting, imaging quality is better-controlled and may allow the support of successful coregistration procedures (including manual adjustment when required), whereas in a clinical setting, volumetric mismatch would seem to be a realistic "fall-back" option in cases in which registration fails. Second, the coregistration method here was only used to select patients and not to assess infarct growth, which requires the presence of follow-up MR images. Coregistration is possible but less reliable at later time points because of the structural changes associated with later infarct volumes, hemorrhagic transformation, and shrinkage. Although it seems likely that automated coregistration software without manual quality control may become a reality in the near future, its clinical use is likely to be restricted to the acute assessment only as it was in the current study. Third, this study was a post hoc analysis and, therefore, does not provide any change in interpretation of the original results of EPITHET. Despite these limitations, this study provided a more ideal mismatch analysis approach for selecting eligible candidates for thrombolytic therapy beyond the 3-hour time window. This suggests that there is a need to develop appropriate software to provide rapid coregistered image analysis.

Sources of Funding

National Health and Medical Research Council, Australia; National Stroke Foundation, Australia; and Heart Foundation of Australia.

Disclosures

None.

References

1. Donnan GA, Baron JC, Davis SM, Sharp FR. The Ischemic Penumbra. New York: Informa Healthcare; 2007.
2. Baird AE, Benfield A, Schlaug G, Siewert B, Lövblad KO, Edelman RR, Warach S. Enlargement of human cerebral ischemic lesion volumes measured by diffusion-weighted magnetic resonance imaging. *Ann Neurol*. 1997;41:581–589.
3. Donnan GA, Davis SM. Neuroimaging, the ischaemic penumbra, and selection of patients for acute stroke therapy. *Lancet Neurol*. 2002;1:417–425.
4. Darby DG, Barber PA, Gerraty RP, Desmond PM, Yang Q, Parsons M, Li T, Tress BM, Davis SM. Pathophysiological topography of acute ischemia by combined diffusion-weighted and perfusion MRI. *Stroke*. 1999;30:2043–2052.
5. Harris AD, Kosior RK, Chen HS, Andersen LB, Frayne R. Evolution of hyperacute stroke over 6 hours using serial MR perfusion and diffusion maps. *J Magn Reson Imaging*. 2009;29:1262–1270.
6. Olivot JM, Mlynash M, Thijs VN, Purushotham A, Kemp S, Lansberg MG, Wechsler L, Bammer R, Marks MP, Albers GW. Relationships between cerebral perfusion and reversibility of acute diffusion lesions in DEFUSE: insights from RADAR. *Stroke*. 2009;40:1692–1697.
7. Ma H, Zavala JA, Teoh H, Churilov L, Gunawan M, Ly J, Wright P, Phan T, Arakawa S, Davis SM, Donnan GA. Penumbral mismatch is underestimated using standard volumetric methods and this is exacerbated with time. *J Neurol Neurosurg Psychiatry*. 2009;80:991–996.
8. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, Barber PA, Bladin C, De Silva DA, Byrnes G, Chalk JB, Fink JN, Kimber TE, Schultz D, Hand PJ, Frayne J, Hankey G, Muir K, Gerraty R, Tress BM, Desmond PM, EPITHET investigators. 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.
9. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G, SITS-MOST investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet.* 2007;369:275–282.
10. Parsons MW, Barber PA, Chalk J, Darby DG, Rose S, Desmond PM, Gerraty RP, Tress BM, Wright PM, Donnan GA, Davis SM. Diffusion- and perfusion-weighted MRI response to thrombolysis in stroke. *Ann Neurol*. 2002;51:28–37.
11. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, Bammer R, Kakuda W, Lansberg MG, Shuaib A, Coplin W, Hamilton S, Moseley M, Marks MP, DEFUSE Investigators. 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.

Stroke
Journal of the American Heart Association

EPITHET: Positive Result After Reanalysis Using Baseline Diffusion-Weighted Imaging/Perfusion-Weighted Imaging Co-Registration

Yoshinari Nagakane, Soren Christensen, Caspar Brekenfeld, Henry Ma, Leonid Churilov, Mark W. Parsons, Christopher R. Levi, Kenneth S. Butcher, Andre Peeters, P. Alan Barber, Christopher F. Bladin, Deidre A. De Silva, John Fink, Thomas E. Kimber, David W. Schultz, Keith W. Muir, Brian M. Tress, Patricia M. Desmond, Stephen M. Davis and Geoffrey A. Donnan
for the EPITHET Investigators

Stroke. 2011;42:59-64; originally published online December 2, 2010;
doi: 10.1161/STROKEAHA.110.580464
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENTAL DATA

(Online-only) Table. Effect of reperfusion on radiological, neurological, and functional outcomes for co-registered mismatch patients

	Reperfusion	No reperfusion	Difference or ratio (95% CI)*	p
Infarct growth	n=31	n=45		
Geometric mean	0.79	1.99	0.40† (0.23 to 0.69)	0.0013
Median relative growth	0.80 (0.30 to 1.70)	1.70 (1.20 to 3.30)	0.38† (0.23 to 0.65)	0.0003
Median absolute growth (mL)	–2.2 (–8.7 to 9.9)	40.1 (1.4 to 76.7)	–36.9‡ (–57.5 to –18.2)	<0.0001
Mean difference in cube root volumes (cm)	–0.13 (0.77)	0.95 (1.16)	–1.07 (–1.55 to –0.60)	<0.0001
Median difference in cube root volumes (cm)	–0.1 (–0.7 to 0.5)	0.7 (0.2 to 1.5)	–1.0‡ (–1.4 to –0.5)	<0.0001
Clinical outcomes	n=31	n=45		
Good neurological outcome	23 (74%)	13 (29%)	45% (25 to 66%)	0.0002
Good functional outcome	20 (65%)	15 (33%)	31% (9 to 53%)	0.0101

Data are mean (SD), number (%) of patients, or median (IQR).

*Difference of average or percentage for reperfusion minus that for no reperfusion, unless indicated as a ratio or median difference. †Ratios.

‡Median difference estimated by Hodges-Lehman shift parameter (95%CI).

Abstract

EPITHET — ベースラインの拡散強調画像／灌流強調画像のコレジストレーションによる再分析で得られた肯定的な結果

EPITHET — Positive Result After Reanalysis Using Baseline Diffusion-Weighted Imaging/Perfusion-Weighted Imaging Co-Registration

Yoshinari Nagakane, MD, PhD[1]; Soren Christensen, PhD[2]; Caspar Brekenfeld, MD[1,3]; Henry Ma, MBBS[1]; Leonid Churilov, PhD[1,4]; Mark W. Parsons, PhD, FRACP[5]; Christopher R. Levi, FRACP[5]; Kenneth S. Butcher, MD, PhD[6]; Andre Peeters, MD[7]; P. Alan Barber, PhD[8]; Christopher F. Bladin, PhD[9]; Deidre A. De Silva, MBBS, MRCP, FAMS[2,10]; John Fink, FRACP[11]; Thomas E. Kimber, PhD, FRACP[12]; David W. Schultz, FRACP[13]; Keith W. Muir, MD[14]; Brian M. Tress, MD[15], FRANZCR, FRCR; Patricia M. Desmond, MD[15]; Stephen M. Davis, MD, FRACP[2]; Geoffrey A. Donnan, MD, FRACP[1]; for the EPITHET Investigators

[1] National Stroke Research Institute, Florey Neuroscience Institutes, Austin Health, University of Melbourne, Australia; [2] Department of Neurology, Royal Melbourne Hospital, University of Melbourne, Australia; [3] Institute of Interventional and Diagnostic Neuroradiology, University of Bern, Switzerland; [4] Department of Mathematics and Statistics, University of Melbourne, Australia; [5] Department of Neurology, Hunter Medical Research Institute, John Hunter Hospital, University of Newcastle, Australia; [6] Department of Neurology, University of Alberta, Edmonton, Alberta, Canada; [7] University Hospital St Luc, Brussels, Belgium; [8] Neurology Department, Auckland City Hospital, Grafton, Auckland, New Zealand; [9] Eastern Melbourne Neurosciences, Melbourne, Australia; [10] Department of Neurology, Singapore General Hospital campus, National Neuroscience Institute, Singapore; [11] Department of Neurology, Christchurch Hospital, Christchurch, New Zealand; [12] Royal Adelaide Hospital, Adelaide, Australia; [13] Department of Neurology, Flinders Medical Centre, Bedford Park, Australia; [14] Division of Clinical Neurosciences, University of Glasgow, UK; [15] Department of Radiology, Royal Melbourne Hospital, University of Melbourne, Australia

背景および目的：Echoplanar Imaging Thrombolytic Evaluation Trial（EPITHET）は，脳卒中発症から3～6時間後にアルテプラーゼを投与して行われた前向き無作為二重盲検プラセボ対照第II相試験である。主要評価項目は，アルテプラーゼを投与したミスマッチ例に観察されるMRI上の梗塞増大抑制効果であったが，コレジストレーションを行わずに通常の体積測定を行った結果，ミスマッチ体積が少なく見積もられ，主要評価項目に関する結果は否定的であった。我々は，MRI灌流画像と拡散画像のコレジストレーションによってミスマッチの程度を評価することで，プラセボと比較したアルテプラーゼの効果をより正確に評価できるのではないかと仮定した。

方法：灌流強調画像と，重ね合わせた拡散強調画像の体積比が1.2より大きく，コレジストレーションによって測定した総ミスマッチ体積が10 mL以上の場合をミスマッチ例とみなした。主要評価項目は，アルテプラーゼを投与したミスマッチ例の梗塞増大をプラセボ投与例と比較することであった。

結果：ベースライン時に拡散強調画像と灌流強調画像が得られた99例のうち，両画像のコレジストレーションが可能だったのは95例であった。コレジストレーションによるミスマッチ例は全体の93%（95例中88例）であったのに対し，標準的な体積測定によるミスマッチ例は85%（95例中81例）であった。コレジストレーションによるミスマッチ例のうち，アルテプラーゼ投与群は45例，プラセボ投与群は43例であり，主要評価項目である梗塞増大の幾何平均の値は，アルテプラーゼ群の方が有意に小さく，アルテプラーゼ群とプラセボ群の比は0.58であった（1.02対1.77，95% CI：0.33～0.99，$p = 0.0459$）。

結論：コレジストレーションの技術を用いて試験組入れ時のミスマッチの存在を判定した場合には，アルテプラーゼ投与により梗塞増大が有意に抑制された。このことから，ベナンブラ選択に基づき，発症後3時間以上が経過してからアルテプラーゼを投与する無作為プラセボ対照第III相試験が必要である。

Stroke 2011; 42: 59-64

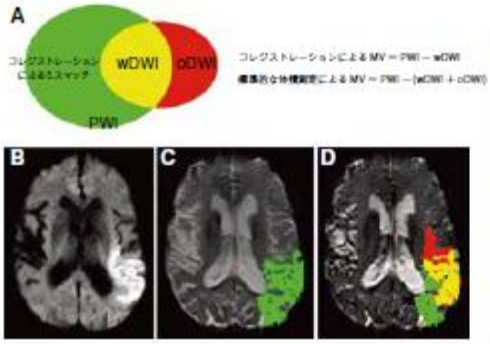

図1 A：灌流強調画像（PWI）と拡散強調画像（DWI）のコレジストレーションにより，DWI病変は，PWI病変内のDWI（wDWI，黄色部分）とPWI病変外のDWI（oDWI，赤色部分）の2領域に分類できる。標準的な体積測定では，ミスマッチ体積（MV）＝PWI－（wDWI＋oDWI）として計算されるが，コレジストレーションによる測定では，MV（緑色部分）＝PWI－wDWIと定義される。脳卒中発症から325分後にベースラインのMRIを実施した82歳の女性では，ベースラインのDWI病変の体積は65.3 mL（B），PWI病変の体積は68.8 mL（C，緑色の部分はTmaxが2秒以上の異常領域を示す）であった。EPITHETの体積測定方法では，ミスマッチなし（3.5 mL）と判定されたが，コレジストレーションによる測定（D）では，ミスマッチあり（26.2 mL）と判定された（黄色部分はwDWI，赤色部分はoDWI，緑色部分はコレジストレーションによるミスマッチ領域）。

EPITHET: resultado positivo tras un reanálisis utilizando un registro basal conjunto de RM con ponderación de difusión/RM con ponderación de perfusión

Se cree que la discrepancia de difusión-perfusión en las imágenes de RM aporta una aproximación de la penumbra isquémica, que se considera el objetivo de las estrategias actuales de reperfusión, incluida la trombolisis con activador de plasminógeno tisular (tPA). El estudio *Echoplanar Imaging Thrombolytic Evaluation Trial* (EPITHET) fue un ensayo multinacional de fase II, prospectivo, aleatorizado, doble ciego y controlado con placebo, en el que se evaluó la hipótesis de que la trombolisis con tPA en un plazo de 3 a 6 horas tras el inicio del ictus pudiera atenuar el crecimiento del infarto observado en la RM. Aunque se observó una tendencia a la atenuación del crecimiento del infarto, ésta no alcanzaba significación estadística. Nagakane y colaboradores presentan un reanálisis de los datos del EPITHET utilizando técnicas de registro conjunto de las imágenes de ponderación de difusión-imágenes de ponderación de perfusión (DWI-PWI) para mejorar la identificación de los pacientes con una discrepancia elegible, así como los efectos posteriores de tPA sobre la atenuación del crecimiento del infarto. El registro conjunto indicó una prevalencia significativamente superior de la discrepancia en comparación con la evaluación volumétrica simple (93% frente a 85%, $p = 0{,}0156$). La media geométrica del crecimiento (variable de valoración primaria) se vio atenuada de forma significativa en el grupo de tPA en comparación con el grupo control al utilizar el método de registro conjunto ($p = 0{,}0459$) pero no en el análisis volumétrico simple ($p = 0{,}0799$). Se obtuvieron resultados similares con el empleo de diversos métodos analíticos secundarios y adicionales (en los pacientes con una lesión basal < 5 mL en las imágenes de DWI). Con el empleo del conjunto de datos de registro conjunto, los parámetros de valoración secundarios indicaron una incidencia más elevada de reperfusión $\geq 90\%$ ($p = 0{,}0052$), así como de la mediana de porcentaje de reperfusión ($p = 0{,}0088$). La reperfusión se asoció significativamente a la atenuación del crecimiento del infarto, una buena evolución neurológica y un buen resultado funcional en los pacientes con una discrepancia en el registro conjunto. El estudio EPITHET no tuvo la potencia estadística suficiente para la evaluación de resultados clínicos, y no hubo una diferencia significativa entre el grupo de alteplasa y el grupo placebo en cuanto a la buena evolución neurológica y funcional. Con el empleo de técnicas sofisticadas de registro conjunto puede obtenerse una delimitación más sensible y exacta de la penumbra isquémica. Es de esperar que esto se traduzca en una selección adecuada mediante RM de los pacientes en los que es más probable la obtención de un efecto beneficioso con estrategias de perfusión después de la ventana temporal establecida para el tratamiento. (**Comentario al artículo EPITHET: Positive Result After Reanalysis Using Baseline Diffusion-Weighted Imaging/Perfusion-Weighted Imaging Co-Registration**. Yoshinari Nagakane, Soren Christensen, Caspar Brekenfeld, Henry Ma, Leonid Churilov, Mark W. Parsons, Christopher R. Levi, Kenneth S. Butcher, Andre Peeters, P. Alan Barber, Christopher F. Bladin, Deidre A. De Silva, John Fink, Thomas E. Kimber, David W. Schultz, Keith W. Muir, Brian M. Tress, Patricia M. Desmond, Stephen M. Davis, Geoffrey A. Donnan for the EPITHET Investigators. *Stroke.* **2011;42:59-64.**)