The clinical–DWI mismatch

A new diagnostic approach to the brain tissue at risk of infarction

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Abstract—*Objective:* To evaluate the usefulness of a mismatch between the severity of acute clinical manifestations and the diffusion-weighted imaging (DWI) lesion in predicting early stroke outcome and infarct volume. *Methods:* One hundred sixty-six patients with a hemispheric ischemic stroke of <12 hours' duration were studied. The NIH Stroke Scale (NIHSS) score and the volume of DWI lesion were measured on admission and at 72 ± 12 hours. Infarct volume was measured on T2-weighted or fluid-attenuated inversion recovery images at day 30. Early neurologic deterioration (END) was defined as an increase of ≥4 points between the two NIHSS evaluations. Thirty-eight patients received IV thrombolysis or abciximab. Clinical–DWI mismatch (CDM) was defined as NIHSS score of ≥8 and ischemic volume on DWI of ≤25 mL on admission. The adjusted influence of CDM on END, DWI lesion enlargement at 72 hours, and infarct growth at day 30 was evaluated by logistic regression analysis and generalized linear models. *Results:* CDM was found in 87 patients (52.4%). Patients with CDM had a higher risk of END than patients without CDM because NIHSS < 8 (odds ratio [OR], 9.0; 95% CI,1.9 to 42) or DWI lesion > 25 mL (OR, 2.0; 95% CI, 0.8 to 4.9). CDM was associated with an increase of 46 to 68 mL in the mean volume of DWI lesion enlargement and infarct growth in comparison with non-CDM. All the effects were even greater and significant in patients not treated with reperfusion therapies. *Conclusions:* Acute stroke patients with an NIHSS score of ≥8 and DWI volume of ≤25 mL have a higher probability of infarct growth and early neurologic deterioration. The new concept of CDM may identify patients with tissue at risk of infarction for thrombolytic or neuroprotective drugs.

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The mismatch in MRI between the perfusion-weighted imaging (PWI) lesion and the smaller diffusion-weighted imaging (DWI) lesion indicates potentially salvageable ischemic brain tissue and may expand the window for the emergent therapies beyond 3 hours.[1-3] However, PWI is a complex, time-consuming, and not well standardized technique, with availability in only some centers.[4] In fact, the best PWI map and the optimal threshold for the calculation of the volume of the hypoperfused tissue at risk of infarction have not been established.[5,6]

Most of the ischemic brain is clinically symptomatic because the abnormal PWI volume has a higher correlation with the stroke severity, evaluated by the NIH Stroke Scale (NIHSS), than the DWI volume.[7,8] Therefore, because of the potential clinical expression of the ischemic brain, we investigated the usefulness of a mismatch between the severity of the acute clinical manifestations and the DWI lesion (clinical–DWI mismatch [CDM]) in predicting early stroke outcome and final infarct volume.

Subjects and methods. We prospectively studied 166 patients with a hemispheric ischemic stroke admitted into two university hospitals between July 2001 and June 2003. Inclusion criteria were age older than 18, time from the onset of symptoms to inclusion of <12 hours, previous modified Rankin Scale score of <2, absence of coma, and pure lacunar syndromes on admission. The primary aim of this still-ongoing prospective study is to investigate whether the molecular factors associated with early neurologic deterioration (END) correlate to the evolution of the DWI abnormalities in the acute phase of territorial infarctions. The ethical committees approved the protocol in both centers, and the patients or relatives gave informed consent.

At admission, blood pressure, EKG, and body temperature were recorded, and blood samples were taken. Immediately after these tests, MRI was carried out. The NIHSS score was evaluated by a certified neurologist just before the first MRI study, at 24 ± 6 and 72 ± 12 hours.

Once admitted in the acute stroke unit, patients were treated according to published guidelines.[9] Thirty-eight patients received IV tissue plasminogen activator (n = 32), desmoteplase/placebo (n = 5), or abciximab (n = 1) within the first 6 hours from stroke onset, in 27 cases after or during the MRI examination and in 11 cases prior to the MRI (in 6 patients MRI was performed within 2 hours and in 5 patients >2 hours after treatment). Ten patients were included in negative clinical trials with neuroprotective agents. Following the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, the stroke subtype classification at dis-

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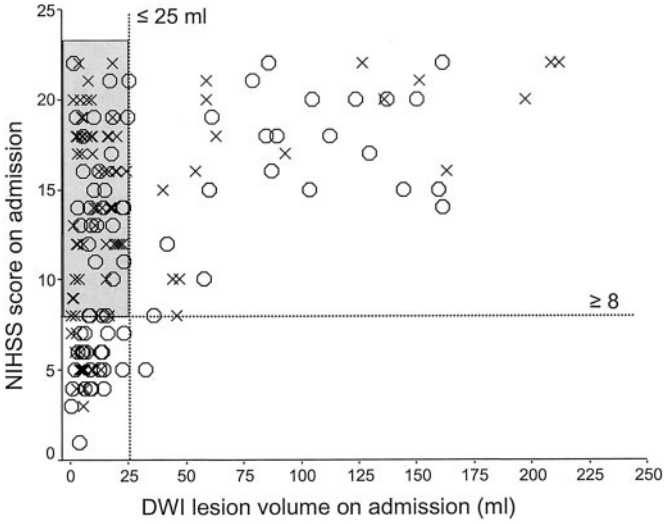

Figure 1. Scatterplot showing the correlation between the NIH Stroke Scale (NIHSS) score and the diffusion-weighted imaging (DWI) lesion volume on admission in the left (X's) and right (O's) hemispheric infarctions. The shaded area corresponds to patients with clinical–DWI mismatch according to the definition of the current study. Note that almost all patients with an NIHSS score of <8 had DWI lesion volumes of <25 mL.

charge was cardioembolic stroke in 76 patients, atherothrombotic stroke in 67, lacunar stroke in 7, and of unknown origin in 16.

Multiparametric MRI study. Two neuroradiologists who were blinded to the clinical data carried out the evaluation of the MRI in each center. All patients had an initial MRI study on admission (<3 hours from onset in 35 patients, 3 to 6 hours in 44, and 6 to 12 hours in 87). A second MRI study at 72 ± 12 hours was carried out in 161 patients who survived the first 3 days, and a third MRI study at day 30 ± 7 was done in 108 patients; CT scan was performed in 33 patients. The third MRI was not carried out in 21 patients who died within the first month and in 4 patients who refused the follow-up examination.

MR images were obtained on a 1.5 T system (Intera, Philips, Best, the Netherlands; or 1.5 Magneton Symphony, Siemens, Erlangen, Germany), with echoplanar capabilities of 25-mT/m gradients and 300- to 350-microsecond rise times. The MRI protocol included DW, T2-weighted, and, in one center, fluid-attenuated inversion recovery (FLAIR) imaging. The DWI sequence was performed with a *b* value of 1,000 and was analyzed in the trace image to avoid anisotropy. The volumetric analysis of the DWI, T2-weighted, and FLAIR lesions was performed with a manual segmentation method after the end of follow-up. First, the perimeter of the area of abnormal signal intensity was traced on each DWI and T2-weighted/FLAIR map, and subsequently, the volumetric software estimated the total volume using the thickness and the traced area on each slice. The window level and window width were chosen to obtain the best contrast between the lesion and the normal surrounding tissue. Each volume calculation was done three times, and the mean value was taken as definitive. The workstation time of this study was on average 30 minutes for each sequence.

CDM. The CDM was defined as an NIHSS score of ≥8 and ischemic volume on DWI of ≤25 mL on admission. The NIHSS score of ≥8 has been associated with a high rate of neurologic deterioration, a low frequency of spontaneous functional recovery, and cortical perfusion deficits in previous reports.[7,10] So, we used this cut-off point as an indirect clinical sign of a large volume of ischemic brain tissue. An exploratory posthoc analysis of our data showed that almost all patients with NIHSS score of <8 had DWI lesion volumes of ≤25 mL (figure 1). Therefore, we used this volume cut-off point as indicative of a mismatch between the tissue that might be irreversibly damaged and the magnitude of the clinical stroke severity.

Outcome variables. Four outcome variables were evaluated: 1) END, as a potential clinical sign of enlarging brain injury; 2) absolute volume of DWI lesion expansion between admission and day 3; 3) growth of infarct volume, defined as the absolute difference between the DWI volume on admission and the lesion volume on T2-weighted or T2/FLAIR sequences at day 30; and 4) poor functional outcome, defined as a modified Rankin Scale score of >2 at 3 months. Early neurologic deterioration was defined as an increase of ≥4 points in the NIHSS score between admission and 72 hours.[11]

Statistical analyses. The results are presented in three groups: in patients with CDM (Group A) and in patients without CDM because DWI lesion volume > 25 mL (Group B) or NIHSS < 8 (Group C). The results are expressed as percentages for categorical variables and as means ± SD or medians (quartiles) for the continuous variables depending on their normal distribution or not. Proportions were compared using the χ^2 test, and analysis-of-variance or Kruskal–Wallis tests were used to compare continuous variables among groups. The odds ratios (ORs) and 95% CI of END for CDM were calculated by logistic regression analysis after adjustment for covariates, using the enter approach and a probability for entry of 0.05. The influence of CDM on DWI volume enlargement at 72 hours and on infarct growth at day 30 was evaluated by general factorial linear models.

Results. CDM was found in 87 patients (52%; Group A). Among the patients without CDM, 41 (25%) patients had an NIHSS score of ≥8 and DWI lesion volume of ≥25 mL (Group B) and 38 (23%) had an NIHSS score of <8 (all but 1 with a DWI lesion volume of <25 mL; Group C) (see figure 1). The frequency of CDM was higher in the 89 patients with left hemispheric infarcts than in the 77 with right hemispheric infarcts (65 vs 38%; $p = 0.001$) due to a higher frequency of small DWI lesions (DWI lesion ≤ 25 mL; 82 vs 68%) and severe strokes (NIHSS ≥ 8; 83 vs 70%) occurring in the left hemisphere.

Baseline clinical characteristics and neuroimaging findings in patients with and without CDM are shown in table 1. The time interval from symptom onset to the baseline MRI was longer in patients without CDM. The frequency of CDM was 74% within 3 hours, 48% from 3 to 6 hours, and 46% from 6 to 12 hours after the onset of symptoms. In line with the more severe strokes, body temperature and serum glucose were higher in Groups A and B than in Group C.[12] According to the definition of CDM, median NIHSS score and the initial DWI lesion volume were different between groups. A final diagnosis of lacunar infarction was established in seven patients of Group C, but the frequency of the other stroke subtype was similar in all groups.

Clinical and neuroimaging outcomes were different in patients with and without CDM. Five patients died before the NIHSS and MRI evaluation at 72 hours, four patients had a prior NIHSS worsening of ≥4 points due to brain herniation and were classified as END, and one patient died after a cardiac arrest. END was more frequent in patients with CDM than in those without (Group A 37%, Group B 29%, and Group C 5%; $p = 0.001$), and this difference was even greater among patients who did not receive reperfusion therapies (47, 28, and 3%, respectively; $p < 0.001$). Interestingly, the higher frequency of END in patients with CDM was significant in the left-side infarctions (45, 31, and 0%; $p = 0.005$) but not in the right ones (21, 28, and 9%; $p = 0.236$). Patients with CDM had a significantly higher risk of END in comparison with Group C (OR, 9.0; 95% CI, 1.9 to 42) and a nonsignificant higher risk of END in comparison with Group B (OR, 2.0; 95% CI, 0.8 to 4.9). These effects were even higher and significant

Table 1 *Baseline clinical characteristics, neuroimaging findings, and stroke subtype*

Parameter	Clinical–DWI mismatch			*p* Value
	Yes: Group A, n = 87	No: Group B, n = 41	No: Group C, n = 38	
Sex, male; %	48	41	53	0.600
Age, y	70.3 ± 8.4	71.1 ± 9.8	67.3 ± 10.1	0.142
Risk factors, %				
Hypertension	57	54	53	0.852
Diabetes	36	49	34	0.297
Atrial fibrillation	34	32	39	0.763
Ischemic heart disease	21	24	18	0.803
Systolic blood pressure, mm Hg	164 ± 31	162 ± 33	163 ± 25	0.929
Diastolic blood pressure, mm Hg	90 ± 17	86 ± 20	91 ± 13	0.326
Body temperature, °C	36.7 ± 0.5	36.8 ± 0.5	36.4 ± 0.4	0.002
Serum glucose, mg/dL	171 ± 58	188 ± 58	138 ± 54	0.001
Baseline NIHSS score	14 (12,18)	18 (15,20)	5 (4,6)	<0.001
Time from onset to MRI, h	5.5 (2.8,8.8)	7.0 (5.2,10.5)	7.1 (4.3,9.9)	0.015
Initial DWI lesion volume, mL	10.1 (4.8,17.3)	90 (58,141)	5.9 (3.5,12.4)	<0.001
Stroke subtype classification at discharge, %				0.001
Large-artery disease	40	49	32	
Cardioembolic	48	46	40	
Lacunar	—	—	18	
Undetermined	11	5	10	
Specific therapies				
Thrombolysis or abciximab	29	12	21	0.110

Continuous variables are expressed as means ± SD or medians (quartiles).

DWI = diffusion-weighted imaging; NIHSS = NIH Stroke Scale.

after exclusion of patients treated with reperfusion therapies (table 2) and did not change when patients with the final diagnosis of lacunar infarction were removed from the analysis.

The median absolute DWI lesion enlargement at 72 hours was greater in patients with CDM, and the difference was even higher in patients who were not treated with reperfusion therapies (figure 2). Regarding location, DWI lesion enlargement was greater in patients with CDM in both cerebral hemispheres (left, $p < 0.001$; right, $p = 0.023$). Generalized linear models showed that patients with CDM had a 68-mL increase in the estimated mean infarct volume in comparison with Group C and a 48-mL increase in comparison with Group B. These values were even higher in patients who did not receive reperfusion therapies (table 3).

Table 2 *Adjusted odds ratios (95% CI) of END for CDM on admission*

CDM group	Total series, n = 166	*p* Value	Patients without reperfusion therapies, n = 128	*p* Value
Group A vs C	9.0 (1.9, 42)	0.005	22 (2.6, 183)	0.004
Group A vs B	2.0 (0.8, 4.9)	0.109	2.9 (1.1, 7.3)	0.028

All models were adjusted for time interval from symptom onset to baseline MRI, body temperature, and serum glucose on admission. See the text for group definitions.

END = early neurologic deterioration; CDM = clinical–diffusion-weighted imaging mismatch.

MRI on day 30 was carried out in 64 patients with CDM and in 44 patients without CDM on admission. The absolute median infarct volume increase between the baseline DWI and the outcome T2-weighted or FLAIR imaging was greater in patients with CDM (figure 3). The same significant effect was observed in the left and right hemispheres. Generalized linear models showed that patients with CDM had a mean increase in infarct growth of 59 mL in comparison with Group C and of 46 mL in comparison with Group B. These values were even higher in patients not treated with reperfusion therapies (see table 3).

Two patients were lost to follow-up at 3 months. Poor functional outcome was recorded in 47% of patients with CDM, in 64% of patients of Group B and in 8% of Group C, according to the different stroke severity at baseline in each group ($p < 0.001$). In patients who did not receive reperfusion therapies, poor outcome was observed in 55, 62, and 10%, respectively. END was associated with poorer functional outcome. Among the patients with the most severe strokes at baseline (NIHSS score ≥ 8), a Rankin score

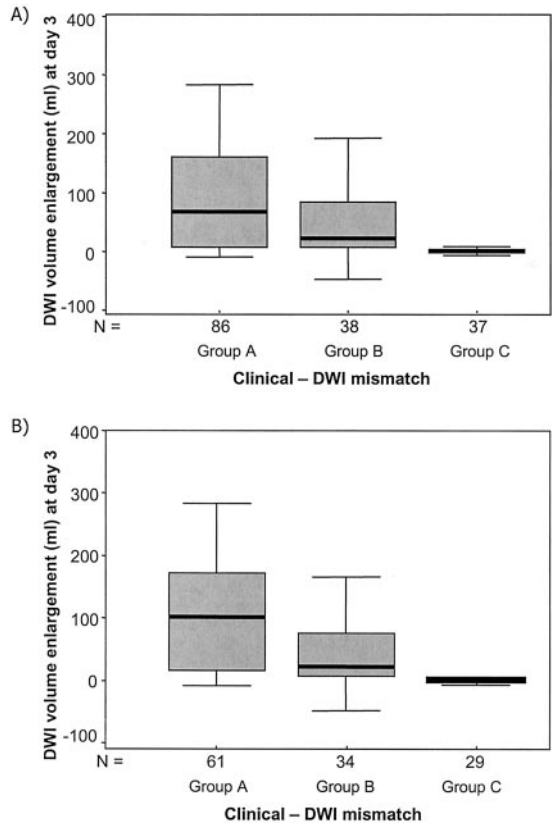

*Figure 2. Boxplots showing median values (horizontal line inside the box), quartiles (box boundaries), and the largest and smallest observed values (lines drawn from the end of the box). Diffusion-weighted imaging (DWI) lesion volume enlargement between day 0 and 3 in patients with clinical–DWI mismatch (Group A) and in patients without because DWI > 25 mL (Group B) or NIH Stroke Scale score < 8 on admission (Group C) in the total series (A) (*p *< 0.001) and in patients who did not receive reperfusion therapies (B) (*p *< 0.001).*

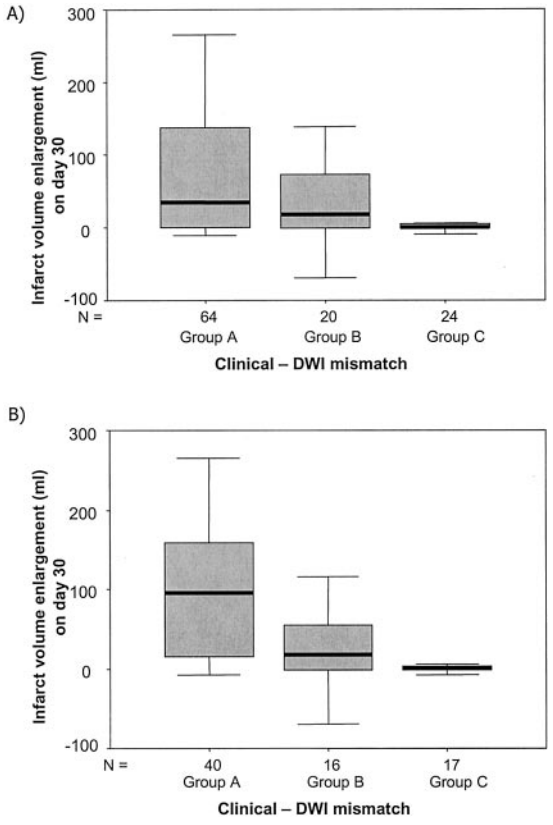

*Figure 3. Boxplots showing median values (horizontal line inside the box), quartiles (box boundaries), and the largest and smallest observed values (lines drawn from the end of the box). Infarct volume enlargement between diffusion-weighted imaging (DWI) on day 0 and T2-weighted or fluid-attenuated inversion recovery imaging on day 30 in patients with clinical–DWI mismatch (Group A) and in patients without because DWI > 25 mL (Group B) or NIH Stroke Scale score < 8 on admission (Group C) in the total series (A) (*p *< 0.001) and in patients who did not receive reperfusion therapies (B) (*p *< 0.001).*

of >2 at 3 months was recorded in 70% of patients with END and in 43% of those without END ($p = 0.005$), although the baseline stroke severity was equal in the two groups (median NIHSS score = 15).

Discussion. The current study shows that the mismatch between the severity of the neurologic deficit (NIHSS ≥ 8) and the reduced DWI lesion volume (≤25 mL) is a common finding in the acute phase of

Table 3 *Adjusted increase in mean volume (95% CI) of DWI lesion enlargement and infarct growth for CDM*

CDM group	Total series	*p* Value	Patients without reperfusion therapies	*p* Value
DWI lesion enlargement	n = 161		n = 124	
Group A vs C	68 (39, 98)	<0.001	87 (53, 120)	<0.001
Group A vs B	48 (21, 76)	0.001	70 (41, 98)	<0.001
Infarct growth	n = 108		n = 73	
Group A vs C	59 (26, 92)	0.001	79 (38, 119)	<0.001
Group A vs B	46 (13, 80)	0.007	71 (32, 108)	<0.001

All models were adjusted for time interval from symptom onset to baseline MRI, body temperature, and serum glucose on admission. See the text for group definitions. Values are in cm^3.

DWI = diffusion-weighted imaging; CDM = clinical–DWI mismatch.

ischemic stroke. According to this retrospective definition, CDM was observed in 52% of our patients admitted within 12 hours after symptom onset. This proportion is somewhat lower than that of the PWI/DWI mismatch in patients studied within the same time interval.[13]

Our results prove the concept that the CDM indicates the existence of a large volume of tissue at risk of infarction in most patients. The greater expansion of the acute DWI lesion within the first 3 days in patients with CDM and the greater increase in infarct size on day 30, particularly in patients who did not receive reperfusion therapies, confirm this hypothesis. The current findings also support the notion that the initial NIHSS score reflects the volume of the ischemic brain, as has been suggested by others. A good correlation ($r = 0.75$) between the pretreatment NIHSS score and the penumbral brain volume with mild to moderate perfusion deficit that could be salvaged after recanalization has been recently found in 14 patients who were submitted to intra-arterial thrombolytic therapy.[6] In this context, the CDM might be a new diagnostic approach to indicate viable ischemic brain and to select candidates for reperfusion therapies.

An interesting finding of this study is that the CDM was associated with a higher frequency of END. This effect might be related to a greater DWI lesion growth toward paucity-symptomatic ischemic areas, because we can reasonably rule out a different outcome due to noncerebral factors as the results were adjusted for physiologic variables and clinical characteristics at baseline. We have recently described that DWI lesion growth at day 3 was the most important factor associated with END in all three groups combined.[14] From day 0 to 3, for every 10-mL increase in DWI volume, there was a 0.5-point worsening in the NIHSS ($p < 0.001$) after adjustment for covariates. Hyperacute large DWI lesions after internal carotid artery or middle cerebral artery occlusion have also been related to END as a consequence of massive postischemic edema.[15] This effect was not found at baseline in the current series because we studied patients with less severe strokes and before the maximal growth of the DWI lesion volume.

The association between CDM and END may have also prognostic consequences. As has been previously reported,[16] poor functional outcome was more frequent in patients with END, although Group A was not in worse functional conditions at 3 months than Group B, probably owing to a greater baseline stroke severity in the latter.

The crucial point is whether the CDM may be a reliable method to identify patients with tissue at risk of infarction in clinical routine. The NIHSS is a widely used tool to measure stroke severity, which has a low interobserver variability among experienced neurologists.[17] It has been shown to be a good predictor of poor outcome after stroke and is a powerful measure of the effectiveness of stroke treatment.[18] However, the NIHSS underestimates the infarct volume in right hemispheric infarctions,[19] particularly in patients with a score from 0 to 5.[20] In this context, the CDM definition might not be sensitive enough for the diagnosis of ischemic penumbra in right-sided lesions owing to larger infarct volumes for a given score in comparison with the left hemispheric infarctions. Accordingly, we found a lower frequency of CDM in right hemispheric infarctions and a lack of association between the CDM and END in patients with a right-side stroke. Despite this limitation, CDM was associated with an equally large volume of infarct growth in both hemispheres.

Because the neurologic examination cannot fully differentiate the status of the tissue, some type of rapid and accurate technique is needed to distinguish potentially reversible from irreversible ischemia, which in turn may aid in the decision to undertake risky but potentially life-saving therapies. CT is widely available, and a score based on early ischemic changes on CT identifies stroke patients unlikely to make an independent recovery despite thrombolytic treatment.[21] However, the CT score is not a validated technique to measure the hyperacute ischemic volume. In contrast, DWI has a better sensitivity and accuracy than CT to detect ischemic tissue within minutes of onset and is a good predictor of poorer outcome.[22,23] It is generally accepted that most DWI lesion volume represents the core of the early infarction.[1] However, DWI lesions have been shown to reverse with successful early recanalization,[24] so DWI overestimates the amount of irreversibly infarcted tissue. In fact, 25% of our patients without CDM due to a DWI lesion volume of >25 mL showed some degree of DWI lesion reduction within the first 3 days and of the ultimate infarct volume on day 30 in comparison with the initial DWI ischemic lesion, but interestingly, this effect was not so evident in patients with CDM (see figures 2 and 3).

Perfusion imaging in acute cerebral ischemia is valuable. The demonstration of a normal perfusion map suggests that reperfusion has occurred spontaneously.[25] However, the main limiting factor in the use of DWI/PWI mismatch for clinical routine is the lack of availability of PWI in all centers, the lack of online PWI analysis, and the lack of a standardized method to measure the PWI lesion volume.[4,25] Furthermore, some reports have suggested that hypoperfused PWI areas below a particular threshold are not viable despite early recanalization,[6] so perfusion thresholds that distinguish the irreversibly infarcted core from penumbral regions have not been delineated. In this context, we think that the CDM may be an alternative to estimate the tissue at risk in centers without these capabilities.

This study has a number of methodologic limitations. First, the definition of the CDM was established retrospectively in a single database within a highly selected population, so it needs to be tested in a new and larger series of patients and in other data sets in which the volume of cerebral infarction has

been carefully measured. The manual segmentation method for the measurement of the DWI lesion volume is rather time consuming, so a semiautomatic method or a quick volume calculation, like the Cavalieri direct estimator, should be used.[26] Manual volumetric analysis may also be limited by interobserver and intraobserver variability. However, this variability was lower than 2% in our experience[27] and was partially controlled by using the mean value of three different estimations. Second, a different effect on the enlargement of the infarcted tissue in patients with and without CDM could be due to systemic factors. To partially control for such effect, we used multivariate analyses adjusting for baseline variables that were different between groups. Third, several patients received reperfusion therapies or were included in clinical trials of neuroprotection, so we may not completely rule out the influence of these drugs in our findings. However, we have no evidence of a clinical benefit of the used neuroprotectants, and our results were even more consistent for patients not treated with thrombolytic agents. Last, a number of patients without CDM might have some volume of salvageable ischemic brain and consequently might obtain some benefit from reperfusion therapies, whereas some patients with CDM might have no perfusion deficits owing to an early recanalization. So, the usefulness of this tool should be compared with the PWI/DWI mismatch.

If these results are replicated by others, CDM might be used in future trials to explore the potential benefit of thrombolytic agents and new neuroprotective drugs in patients with a large volume of cerebral tissue at risk of infarction.

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