Change in Perfusion in Acute Nondominant Hemisphere Stroke May Be Better Estimated by Tests of Hemispatial Neglect Than by the National Institutes of Health Stroke Scale

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Background and Purpose—It has been reported that National Institutes of Health Stroke Scale (NIHSS) scores correlate poorly with hypoperfused tissue measured by perfusion-weighted imaging (PWI) in nondominant hemisphere stroke. We conducted 2 studies to determine whether tests of hemispatial neglect provide a better measure of hypoperfusion and reperfusion than NIHSS in nondominant hemisphere stroke.

Methods—In study 1, 74 patients with acute ischemic, supratentorial stroke were administered the NIHSS, tests of neglect or aphasia, and diffusion-weighted imaging (DWI) and PWI on day 1 (<24 hours from onset) of stroke. Pearson correlations between volumes of PWI/DWI abnormality and functional tests were calculated. In study 2, 10 patients with acute, nondominant hemisphere stroke who were candidates for intervention to restore perfusion underwent PWI, DWI, NIHSS, and a line cancellation test on days 1 and 3. Correlations between change in volumes of PWI/DWI abnormality and change in functional tests were calculated.

Results—In study 1, in nondominant hemisphere stroke, volume of PWI abnormality correlated significantly with neglect scores ($r=0.71; P<0.002$) but not with NIHSS scores ($r=0.39; P=NS$). In dominant hemisphere stroke, volume of PWI abnormality correlated better with aphasia scores ($r=0.50; P=0.0001$) than with NIHSS scores ($r=0.45; P=0.001$). In study 2, change in volume of hypoperfused tissue on PWI correlated with change in line cancellation performance ($r=0.83; P=0.003$) but not with change in NIHSS score ($r=0.26; P=NS$).

Conclusions—Tests of hemispatial neglect may better reflect dysfunction and reperfusion than NIHSS for patients with nondominant hemisphere stroke. (Stroke. 2003;34:2392-2398.)

Key Words: cognition ■ magnetic resonance imaging, perfusion-weighted ■ reperfusion ■ stroke assessment

It has recently been demonstrated that there is a low correlation between National Institutes of Health Stroke Scale (NIHSS) score and volume of hypoperfusion measured by MR perfusion-weighted imaging (PWI) in acute nondominant hemisphere ischemic stroke.1 This finding is not surprising because the NIHSS was not designed to measure functions of a large part of the nondominant cortex, which is prominently involved in spatial attention, integrative or interpretive aspects of cognition, and prosody.2 However, the result has important implications for acute stroke intervention trials, which have used either the change in NIHSS score or change in volume of hypoperfusion as primary outcome measures on the assumption that both NIHSS score and PWI abnormality are measures of severity of stroke or volume of dysfunctional tissue. Some studies have even used NIHSS score as a substitute for volume of PWI abnormality in estimating the tissue at risk in acute stroke because PWI is not readily available or standardized.3 There are 2 possible accounts of the poor correlation between NIHSS score and volume of hypoperfusion on PWI. First, PWI abnormalities might not reflect dysfunctional tissue but might reflect instead benign oligemia.4 Alternatively, the NIHSS might be a poor estimate of dysfunctional tissue because it is not sensitive to cognitive functions of the nondominant cortex. The first explanation is implausible, since several studies have shown a strong correlation between volume of hypoperfusion on PWI and dysfunction, either using the NIHSS and volume of hypoperfusion for all strokes (combining dominant and nondominant hemisphere stroke)5 or using measures of cognition (language for dominant hemisphere stroke; spatial attention for nondominant hemisphere stroke)6. The second
account—that NIHSS is insensitive to nondominant hemisphere cognitive dysfunction—is plausible, since only 1 item on the NIHSS pertains to cognitive function of the nondominant hemisphere, whereas several items reflect cognitive function of the left hemisphere (language) or motor functions. In this article we report results of 2 studies that evaluate the possible accounts of the low correlation between NIHSS and volume of hypoperfusion on PWI in nondominant hemisphere stroke and that evaluate a way to improve measures of function in acute, nondominant hemisphere stroke. In the first study we directly test the hypothesis that volume of hypoperfused tissue on PWI correlates more strongly with dysfunction as measured by tests of cognition (language for dominant hemisphere stroke; spatial attention for nondominant hemisphere stroke) than with dysfunction measured by the NIHSS. In the second study we evaluate the hypothesis that change in volume of hypoperfusion on PWI correlates more strongly with change in scores on a simple test of hemispatial neglect than with change in NIHSS scores in patients with nondominant hemisphere stroke. We discuss implications of these findings for measuring effectiveness of therapy in acute stroke intervention trials.

Subjects and Methods

Study 1: Correlations Between Volume of Hypoperfusion and NIHSS Score Versus Volume of Hypoperfusion Cognitive Tests

Study 1: Subjects
A consecutive series of adults with acute, ischemic, supratentorial stroke, who consented to the study and had none of the following exclusion criteria, were enrolled. Exclusion criteria were as follows: contraindication for MRI; allergy to gadolinium; impaired level of consciousness; hemorrhage on initial CT or MRI; intubation; known prior history of uncorrected hearing loss, visual loss, or cognitive impairment; or lack of proficiency in English. Consent was obtained from each patient and from the closest living relative for patients with aphasia or neglect resulting from the stroke, with forms and procedures approved by the Johns Hopkins Institutional Review Board.

Study 1: Methods
All patients had imaging, including diffusion-weighted imaging (DWI) and PWI (protocol described below) and a battery of cognitive tests within 24 hours of onset of stroke symptoms. For patients with dominant hemisphere stroke symptoms (sensory or motor deficits affecting the dominant limbs and/or language deficits), a battery of aphasia tests was administered at bedside 1 to 22 (mean=10.7) hours after onset. For patients with nondominant hemisphere stroke symptoms (sensory or motor deficits affecting the nondominant limbs and/or contralesional hemispatial neglect without aphasia), a battery of tests for hemispatial neglect was administered 1 to 23 (mean=11.2) hours after onset. One patient in each group was tested and imaged within 3 hours; 2 left hemisphere and 1 right hemisphere patients were tested 3 to 6 hours after onset. These tests are described below.

Aphasia Battery
Tests included the following: (1) oral and written naming of 34 pictured objects; (2) oral naming of 17 objects with tactile input; (3) oral reading of 34 words and 25 pseudowords; (4) spelling to dictation of 34 words and 25 pseudowords; (5) spoken word/picture verification with 17 semantic foils, 17 phonological foils, and 17 correct matches; (6) written word/picture verification with 17 semantic foils, 17 visual foils, and 17 correct matches; and (7) repetition of 34 words and 25 pseudowords. Additionally, each patient was asked 10 yes/no questions, 5 with simple sentence structure and 5 with reversible sentence structure (eg, Does Monday come after Tuesday?). The battery was scored by total errors divided by total items.

Neglect Battery
Tests included the following: (1) oral reading of 20 words and 5 sentences; (2) line cancellation,7 in which a page of 48 lines is presented directly in front of the patient, and he or she is instructed to cross out all of the lines; (3) the bells test,8 in which a page of figures (eg, bells, horses) is presented with instructions to circle all of the bells; (4) direct copying of the “Ogden scene”9 (a house, a fence, and 2 trees); (5) drawing a clock; and (6) a gap detection task,10 in which patients are asked to detect gaps in 60 circles (20 with left gaps, 20 with right gaps, and 20 with no gap) in 3 different locations with respect to the body (midsagittal line; 45 degrees to the right, and 45 degrees to the left). Each segment of the stimulus figures for copying and each part of the clock were assigned 1 point. Omission of any point was considered an error. The battery was scored by total errors divided by total number of items/points.

To obtain norms, we administered these batteries to 46 hospitalized control subjects without any evidence of cognitive impairment who were awaiting surgical repair of asymptomatic, unruptured intracerebral aneurysms or awaiting cardiac bypass surgery. These subjects were comparable in age, education, and sex ratio to the stroke subjects. Of these 46 control subjects, 22 also had DWI and PWI before their surgery. Control subjects scored 94.9% correct or better on each subtest of the batteries. Mean scores for each subtest ranged from 98.0% (SD=3.1) correct in oral reading to 100% (SD=0) correct in tactile naming. Only 1 subject showed any DWI abnormality (tiny left subcortical infarct, after cardiac catheterization); none showed any PWI abnormality. For subjects and controls whose highest education was below 10th grade or who reported premorbid impairment of reading or writing, reading and writing subtests were not scored. Interjudge reliability in scoring each of the subtests of each battery was >90% point-to-point percent agreement.

Imaging Protocol
MRI scans, including axial DWI, PWI, T2, and fluid-attenuated inversion recovery (FLAIR) scans, were obtained on a GE Sigma 1.5-T echo-planar imaging—capable system. For DWI, trace images were obtained with a multislice, isotropic, single-shot echo-planar imaging sequence, with bmax=1000 s/mm². Imaging parameters were repetition time/echo time of 10 000/120 ms. For PWI, single-shot, gradient-echo, echo-planar perfusion images were obtained with 20 mL GdDTPA (gadolinium) bolus power injected at 5 mL/s. Imaging parameters for PWI were repetition time/echo time of 2000/60 ms; 17 slices were recorded.

To determine total lesion volumes (in cubic centimeters) on DWI and PWI, a technologist, blinded to the results of NIHSS and cognitive testing, outlined borders of abnormality on each slice of DWI or PWI on the computer monitor, then calculated volumes using Scion Image program (Scion Corporation, 1998). Areas of abnormality in cubic centimeters on each slice were summed, and the sum was multiplied by the width of each slice for the volume in cubic millimeters. Scans were analyzed with the use of 20-color maps to identify areas with >2.5 seconds of delay relative to the normal side.

Data Analyses
Pearson correlations (with the use of Microstat-II, Ecosoft, 1988) were calculated for (1) volume of DWI abnormality and NIHSS score; (2) volume of PWI abnormality and NIHSS score; (3) volume of DWI abnormality and total score on the cognitive battery; and (4) volume of PWI abnormality and total score on the cognitive battery.

Study 2: Correlation Between Change in Volume of Hypoperfusion and Change in Hemispatial Neglect Score Versus Change in NIHSS Score
Study 1 results indicated that volume of hypoperfused tissue is not adequately estimated by NIHSS but is well estimated by tests of hemispatial neglect in patients with nondominant hemisphere stroke. However, administration of a battery of tests (taking up to 45
minutes) is impractical in the setting of acute stroke intervention because the effectiveness of most interventions to restore blood flow depends on rapid initiation. Therefore, in study 2 we evaluated the hypothesis that change in performance on a single test of hemispatial neglect that can be administered in <5 minutes is more strongly correlated with change in volume of hyperperfusion measured with PWI than is change in NIHSS, in patients with acute nondominant hemisphere stroke undergoing intervention to improve perfusion.

**Study 2: Subjects**

The population consisted of a consecutive series of 10 patients who (1) had stroke affecting the nondominant hemisphere; (2) were candidates for intervention aimed at restoring perfusion (and enrolled in an intervention trial or received intervention); and (3) had repeated MRI, including DWI, FLAIR, and PWI, after intervention or day 3. Other inclusion and exclusion criteria and consent procedures were identical to those of study 1.

**Study 2: Methods**

All patients had MRI and were administered the NIHSS and a single test of hemispatial neglect at day 1 (within 24 hours of onset, before intervention) and at day 3 after onset (within 48 hours after initiation of intervention). Potential interventions to improve perfusion included the following: urgent carotid endarterectomy, carotid stenting, intravenous or intra-arterial thrombolysis, and induced blood pressure elevation. The last intervention has been described as a method for improving perfusion in ischemic tissue (which has lost autoregulation) due to large-vessel stenosis.11–13 None of the patients received thrombolyis since only 1 presented within 6 hours of onset, and this patient had other contraindications to thrombolysis. We selected line cancellation as the measure of hemispatial neglect because it is easily quantified, rapid to administer (<5 minutes), has a high interjudge reliability in scoring (100% point-to-point percent agreement by 2 judges on 25 tests), and revealed hemispatial neglect in 93% of patients who showed neglect on any of the tests in our neglect battery in study 1.

Imaging methods and analyses were the same as described for study 1. A technician blinded to the results of line cancellation and NIHSS scores measured volume of abnormality on DWI and PWI. Correlations between change in volume of hyperperfusion and change in NIHSS, as well as change in volume of hyperperfusion and change in line cancellation performance (defined as percentage of lines omitted), were calculated. In addition, correlations between change in volume of infarct/dense ischemia (defined as bright on DWI and dark on apparent diffusion coefficient maps) and change in NIHSS, as well as change in volume of infarct/dense ischemia and change in line cancellation performance, were calculated.

**Results**

**Study 1**

A total of 74 patients (48 dominant, 26 nondominant hemisphere), all with anterior circulation stroke, enrolled in the study. Demographic data are given in the Table. There were no significant differences between patients with dominant hemisphere versus nondominant hemisphere stroke with respect to age, education, sex, NIHSS scores, scores on the aphasia or neglect battery, volume of DWI abnormality, or volume of PWI abnormality (Table).

For patients with nondominant hemisphere stroke, there was a significant correlation between volume of PWI abnormality and neglect battery scores (r=0.71; P<0.002) but not a significant correlation between volume of PWI abnormality and NIHSS scores (r=0.39; P=NS). DWI abnormality correlated with neither neglect scores (r=0.21; P=NS) nor NIHSS (r=−0.09; P=NS). For patients with dominant hemisphere stroke, there was a higher correlation between volume of PWI abnormality and aphasia battery scores (r=0.50; P=0.0001) than between volume of PWI abnormality and NIHSS scores (r=0.45; P=0.001). DWI abnormality correlated with neither language scores (r=0.16; P=NS) nor NIHSS scores (r=0.18; P=NS).

Examples of scans of patients with various degrees of hemispatial neglect are shown in Figure 1.

**Study 2**

Of the 10 patients, 9 were right-handed and had right hemisphere strokes; 1 was left-handed and had a left hemisphere stroke with right neglect and no aphasia (with normal performance on our aphasia battery). Fifty percent were female. Mean initial NIHSS score was 9 (range, 1 to 16). Mean initial score on the line cancellation test was 55.5%
errors (range, 12% to 93%). Mean volume of DWI abnormality was 8.9 cm³ (range, 3 to 31 cm³). Mean volume of PWI abnormality was 156 cm³ (range, 55 to 284 cm³). All patients had a large DWI-PWI mismatch and were considered candidates for intervention to improve perfusion. All patients had stenosis or occlusion of the middle cerebral artery and/or internal carotid artery on the symptomatic side, confirmed with MR angiogram or conventional angiogram. Intervention consisted of urgent endarterectomy (1 patient), carotid stenting (1 patient), and induced blood pressure elevation (5 patients). An additional 3 patients were randomized to conventional management (ie, served as controls) in a trial of induced blood pressure elevation; these 3 patients and 3 of the patients treated with induced blood pressure elevation participated in that study. Therefore, patients with various degrees of reperfusion were included.

Mean change in NIHSS score was −1.7 (range, −5 to 0). Mean change in line cancellation score was −1.3 (range, −39.6 to +14.6). Mean change in DWI abnormality was 4.3 cm³ (range, −4 to 32 cm³). Mean change in PWI abnormality was −70.2 cm³ (range, −209 to 0 cm³). There was a significant correlation between change in volume of hypoperfused tissue on PWI and change in line cancellation performance ($r = 0.83; r^2 = 0.69; P = 0.003$). In contrast, there was not a significant correlation between change in volume of hypoperfusion and change in NIHSS score ($r = 0.26; r^2 = 0.07; P = NS$). There was also not a significant correlation between change in volume of infarct/densely ischemic tissue on DWI and change in either line cancellation performance ($r = 0.10; r^2 = 0.01; P = NS$) or NIHSS score ($r = −0.48; r^2 = 0.23; P = NS$) in these patients, since none showed substantial change in DWI abnormality.

Examples of MR scans before and after intervention in patients with hemispatial neglect before intervention are shown in Figure 2. It is not the case that all patients improved in both perfusion and line cancellation. The case in Figure 3 illustrates MR scans and line cancellation tests in patients who did not significantly improve in either line cancellation or volume of hypoperfusion.

**Discussion**

Animal studies of acute stroke intervention have generally used final infarct size or imaging characteristics as the final outcome measure. In contrast, in human acute stroke intervention trials, outcome has most often been measured by the NIHSS score (often along with the Glasgow Outcome Scale, Rankin Scale, and/or Barthel Index) because function is considered a more important outcome than imaging characteristics or because imaging is less standardized or less commonly available. However, none of these functional scales is sensitive to degrees of hemispatial neglect, which is among the most disabling impairments in patients with nondominant hemisphere stroke (see Azouvi et al for review of assessment and outcome of neglect). Furthermore, although changes in these measures of function such as NIHSS have been assumed to reflect the volume of “salvaged” tissue, results of the present study challenge this assumption. Consistent with a previous study, we found no significant correlation between the NIHSS score and volume of hypoperfused tissue on PWI for patients with nondominant hemisphere stroke, although we did find a strong correlation between volume of hypoperfused tissue estimated by PWI and cognitive performance in both dominant and nondominant hemisphere stroke. Results of study 1 suggest that volume of hypoperfused tissue may reflect dysfunctional tissue (as measured by aphasia or neglect tests or by NIHSS for dominant hemisphere stroke), but NIHSS does not reflect dysfunctional tissue in patients with nondominant hemisphere stroke. This conclusion is further corroborated by the results of study 2, which demonstrated that change in volume of hypoperfused tissue was associated with change in a test of hemispatial neglect but not associated with change in NIHSS score.

One caveat in our conclusion from study 2 is that patients were selected for intervention to restore perfusion on the basis of a large diffusion-perfusion mismatch. Therefore, all of these patients had a large area of cortical hypoperfusion associated with hemispatial neglect. Although hemispatial neglect has been well described after subcortical stroke (see Karnath et al for review), a recent study indicated that neglect after nondominant subcortical stroke is due to cortical hypoperfusion. Thus, the test of line cancellation would be a poor measure of the volume of dysfunctional tissue in patients with nondominant subcortical stroke without cortical hypoperfusion because change in volume of subcortical tissue dysfunction might not be reflected at all in line cancellation...
performance. In patients with strictly subcortical stroke, NIHSS may be an adequate measure of tissue dysfunction, although this hypothesis has not yet been tested. A second caveat is that study 2 included a small number of patients, indicating the need to confirm results with a larger population.

The implication of our results is straightforward. The NIHSS score alone does not provide a good estimate of the volume of hypoperfused tissue or change in hypoperfused tissue in nondominant stroke affecting the cortex. One previous group tried to improve the “lateralization bias” (more points for dominant hemisphere stroke) and to improve the reliability and validity of the NIHSS by dropping items concerning facial weakness and dysarthria. While this change may improve interjudge reliability, the authors’ claim that omitting the dysarthria item improves the lateralization bias is not supported because dysarthria occurs after stroke in either hemisphere or more commonly after brain stem stroke or bilateral strokes. The implication from the present study is that volume of tissue with restored blood flow in patients with nondominant hemisphere stroke in acute intervention trials would be better measured either with a combination of NIHSS and some measure of hemispatial neglect or with imaging (eg, PWI, in conjunction with DWI and FLAIR images). We have demonstrated that a very simple, bedside test of hemispatial neglect (line cancellation), which takes 5 minutes to administer, may be a good estimate of volume of hypoperfusion, or dysfunctional tissue, in patients with acute nondominant stroke affecting cortical perfusion.

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References


Editorial Comment

Measurement of Cognitive Deficits in Acute Stroke

Whereas diffusion-weighted imaging (DWI) identifies areas of metabolic failure and cellular injury that are often, but not invariably, irreversible,1 perfusion-weighted imaging (PWI) depicts areas of hypoperfusion that, when not matched by a diffusion abnormality, constitute the potentially reversible ischemic penumbra.2 Early neurological deficits correlate with core and penumbral lesion volume rather than with the diffusion abnormality.3 These new imaging techniques are powerful tools that provide insights into the pathophysiology of the deficits and the effects of therapeutic interventions in patients with acute stroke.

Earlier SPECT observations showed that patients with subcortical stroke and aphasia or neglect had decreased cortical perfusion that was attributed to the interruption of neural connections (diascisiss).4 Using neuropsychological tests and PWI, however, Hillis and colleagues have shown that patients with subcortical strokes have aphasia and neglect because of the cortical hypoperfusion,5 and that these deficits improve when blood flow to the cortex is restored.6 In this issue of Stroke, Hillis et al demonstrate that a battery of neurobehavioral tests that assess language and attention correlates well with the volume of hypoperfused cortex but that the National Institute of Health Stroke Scale (NIHSS) score correlates poorly when the left hemisphere is involved and not at all when right hemisphere is injured. Neither neurobehavioral nor NIHSS scores correlated with DWI
abnormalities, regardless of which hemisphere was affected.\textsuperscript{7} Furthermore, in a second experiment, they found that among patients with right-sided stroke, treatment-induced changes in perfusion correlate with changes in performance on the line cancellation task but not with changes in the NIHSS score.\textsuperscript{7}

Attention depends on a complex neuroanatomically distributed modular network that includes the dorsolateral prefrontal lobes, the posterior and superior temporal and inferior parietal lobes, the cingulate gyrus, and portions of the diencephalic and mesencephalic reticular activating system. Lesions anywhere in this network, particularly—in the right hemisphere, can lead to attention abnormalities including extinction, hemispatial neglect, personal neglect, and anosognosia. Attention deficits are found in 20\% to 40\% of patients 3 months after a stroke.\textsuperscript{9,10} While these deficits do not always precisely localize the lesion, it is important to identify them because they are disabling and negatively impact rehabilitation. They are, however, rarely elicited or recorded by neurologists in the acute stage, particularly when a standardized scale is not used.\textsuperscript{11}

The findings reported in this issue by Hillis and colleagues highlight some issues regarding the NIHSS that have been previously identified.\textsuperscript{12,13} This scale is used to select acute stroke patients for treatment with pharmacological and mechanical agents, and is a measure of stroke severity in many prospective stroke databases. The scale, however, is biased toward left hemisphere strokes, since 7 out of 42 possible points are assigned to language dysfunction while only 2 are given for neglect. As a result, for a given NIHSS score the volume of acute diffusion-weighted (DWI) abnormality\textsuperscript{13} and of infarction on CT\textsuperscript{12} is larger when the stroke is in the right, particularly if the deficits are mild.\textsuperscript{13} This bias has significant implications. Patients with low NIHSS scores are seldom treated with tissue plasminogen activator, even though one third of the untreated patients die or are dependent at discharge.\textsuperscript{14} In addition, higher NIHSS score and stroke volume are associated with worse outcomes,\textsuperscript{15,16} and when strokes of similar size in both hemispheres are compared, those in the right lead to worse outcomes.\textsuperscript{17}

Hillis et al demonstrate that a battery of cognitive tests that takes about 45 minutes to administer correlates with PWI abnormalities.\textsuperscript{5–7} We need a shorter instrument for use in clinical care and research in the acute setting. Hillis et al chose the line cancellation task for the second experiment for its sensitivity and reliability. However, different tests assess separate components of the neglect syndrome, and patients may perform well on one test but not on the other.\textsuperscript{18} Binder and colleagues did not find a correlation between the scores in the line bisection and the letter cancellation tasks.\textsuperscript{19} Perhaps a measure that combines elements of both tests, such as one recently proposed by Na and coworkers, will be useful.\textsuperscript{20} This test consists of horizontally aligned strings of characters and the subject’s task is to mark a target character that is at, or closest to, the true midpoint of the simulated line. The sensitivity and specificity of this task in the setting of acute stroke, however, still need to be established.

More than 60\% of patients have deficits in at least one cognitive domain 3 months after a stroke,\textsuperscript{10} yet cognitive disorders are often either overlooked or underestimated in the assessment of acute stroke. Clinical trials inadequately assess cognitive status as an outcome measure. In their second experiment, Hillis and colleagues demonstrate the value of using cognitive outcomes—the treatment associated change in perfusion correlated with changes in performance of line cancellation task but not with changes in the NIHSS.\textsuperscript{7} Thus, there is a need for a cognitive scale that can be used in conjunction with the NIHSS both to select patients for acute stroke treatment and to be used as baseline and outcome measure in clinical trials. Such a scale must allow prompt evaluation of the domains that are most often affected by stroke and must be simple to administer by physicians who are not familiar with neurobehavioral testing. Like the NIHSS it should provide an overall numeric score, but should also provide subscores that can be used to track changes in individual domains over time. The scale can have a brief multicognitive domain screening section that can be applied in a few minutes before treatment, and more detailed components to address domains where the patient performed abnormally. Data such as those presented by Hillis et al in this issue should be the basis for such a scale.

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