Stroke MRI in Intracerebral Hemorrhage
Is There a Perihemorrhagic Penumbra?

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Background and Purpose—Cerebral ischemia has been proposed as a contributing mechanism to secondary neuronal injury after intracerebral hemorrhage (ICH). The search for surrogate parameters that allow treatment stratification for spontaneous ICH continues. We sought to assess the presence and prognostic effect of perihemorrhagic ischemic changes and hypoperfusion in a prospective stroke MRI study.

Methods—We performed stroke MRI in 32 patients with hyperacute ICH (mean, 16.9±17.2 mL) within 6 hours after symptom onset (mean, 3.1±1.3 hours). Clinical data at baseline (National Institutes of Health Stroke Scale) and on day 90 (Barthel Index, modified Rankin Scale) were assessed. Perihemorrhagic perfusion- and diffusion-weighted imaging changes were assessed in a 1-cm-wide area around the clot.

Results—Despite a mild perihemorrhagic mean transit time prolongation of 0.7±1.1 second, there were no significant perihemorrhagic apparent diffusion coefficient or mean transit times changes indicating irreversible ischemia or hypoperfusion. ICH size, time to imaging, or clinical severity at baseline or outcome were not reflected by changes of relative apparent diffusion coefficient or perfusion-weighted imaging. ICH size correlated with baseline clinical severity (r=0.51, P=0.005). There was a significant association (P=0.0494) and a significant negative correlation (r=−0.468, P=0.0103) of perihemorrhagic perfusion change with time from symptom onset not associated with ICH size.

Conclusions—Perihemorrhagic hypoperfusion probably is a consequence of reduced metabolic demand (diaschisis) rather than a sign of ischemia. We found no evidence for a perihemorrhagic and potentially salvageable ischemic penumbra in hyperacute ICH. Further studies should address metabolic, toxic, apoptotic, and microvascular aspects. (Stroke. 2003;34:1674-1680.)

Key Words: intracerebral hemorrhage ■ magnetic resonance imaging, diffusion-weighted ■ magnetic resonance imaging, perfusion-weighted ■ penumbra ■ risk

Although primary intracerebral hemorrhage (ICH) is responsible for up to 15% of all strokes, there is no consensus with regard to its treatment.1,2 A large, international, randomized multicenter trial for surgery versus best medical treatment is currently under way.3 Perihemorrhagic ischemia may be a potential surrogate indicator to identify patients who may profit from surgical hematoma evacuation.4 At present there are only inconsistent information and contradictory findings from animal experiments as well as patient studies.5–8 Multisequence stroke MRI protocols, including diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI), have been used in small patient series of ICH and showed a correlation of perihemorrhagic diffusion impairment with unfavorable clinical outcome.9 We sought to verify these findings in a prospective stroke MRI study of patients with ICH within the first 6 hours after symptom onset in a large set of patients examined with both DWI and PWI.

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Subjects and Methods

Patients
We prospectively examined 32 patients from January 2000 to August 2002 (23 men, 9 women), with a mean age of 65.5±11.1 years (range, 35 to 87 years), who suffered a primary ICH and received stroke MRI within 6 hours after symptom onset (mean, 3.12±1.31 hours; range, 1.30 to 5.75 hours). Stroke onset was defined as the last time the patient was seen to be neurologically intact. Exclusion criteria were age <18 years, a significant preexisting neurological deficit (modified Rankin Scale [mRS] score ≥1), unstable vital signs, and a history or imaging findings of ICH due to other etiologies. We assessed clinical data at baseline with the National Institutes of Health Stroke Scale (NIHSS) and on day 90 with the Barthel Index (BI) and the mRS (continuously and categorized for mRS 0 to 2 versus 3 to 6, ie, independent versus dependent or dead), in analogy to other studies. Patients with hemodynamically relevant
occlusive extracranial carotid artery disease according to ultrasound and patients who underwent surgical evacuation of the hematoma were excluded from the study to prevent a bias with regard to perfusion abnormalities and outcome analysis. Patients requiring external ventricular drainage or a shunt due to an intermittent or persistent malresorptive hydrocephalus were not excluded. Informed consent was obtained from all patients or their next of kin. The study protocol was approved by the local institutional review board. We did not analyze the diagnostic sensitivity of stroke MRI for ICH in this study; however, all ICH were identified as such, albeit not in a randomized or blinded fashion.

Magnetic Resonance Imaging

Our imaging protocol has been described in detail elsewhere. The stroke MRI protocol included axial T2-weighted imaging, fluid-attenuated inversion recovery imaging (FLAIR), isotropic DWI, MR angiography, and PWI with an axial T2*-weighted imaging echo-planar image sequence (40 data sets with a time resolution of 1.2 seconds during and after injection of 0.1 mmol/kg body wt gadolinium-DTPA with a power injector [5 mL/s]). The T2*-weighted images were used to identify ICH. Perfusion maps were calculated from the concentration-time curves as the normalized first moment of the concentration-time curve, i.e., the time that divides the area under the concentration curve (relative cerebral blood volume [rCBV]) into 2 equal parts. The MR images were postprocessed with the use of commercial image analysis software and a workstation (Philips VISTAR). Lesion volumes were measured in analogy to CT according to the procedure of Kothari et al. For the calculation of perihemorrhagic changes of the apparent diffusion coefficient (ADC), we manually outlined a ring on the ADC map with a width of 1 cm around the hematoma on the 3 adjacent slices with the maximum ICH diameter in analogy to and for comparative purposes with other groups. Then we calculated ADC ratios using the ADC of the individual patient’s healthy hemisphere as the denominator. In addition to analysis of the absolute ratios, we categorized relative ADC (rADC) ratios into ≤0.9 and >0.9, indicating cytotoxic edema (ischemia), and into <1.1 and ≥1.1, indicating vasogenic edema. In those cases in which the ICH was directly adjacent to the ventricles, we outlined only the lateral part of the perihemorrhagic area. In analogy to ADC maps, we analyzed an equivalent area on mean transit time (MTT) maps and calculated the time difference in seconds between the perihemorrhagic area and the healthy hemisphere, which is a semiquantitative assessment at best. In some centers, instead of the MTT, phenomenological (summary) parameters such as the time from bolus injection to bolus maximum, i.e., time to peak (TTP), or maximum of signal loss are used. These parameters have the following disadvantages: they do not have a direct physiological correlate; they are influenced by multiple physiological parameters; without a fitted model function, they can be assessed only with wide error margins; and they do not represent a robust measure of perfusion. In addition to the absolute time difference ΔMTT (=MTT perihemorrhagic rim–MTT healthy hemisphere), we arbitrarily categorized the time difference into 2 seconds (absence of perihemorrhagic hypoperfusion) and >2 seconds (presence of perihemorrhagic hypoperfusion). Because hypoperfusion in ICH has been described in the immediate proximity of ICH as well as diffusely in the affected hemisphere, we further assessed a mild hemispheric hyperintensity on MTT on the lesion side as being present or not. All sequences could be analyzed in all patients but 1, in whom the PWI was not diagnostic because of infusion pump failure. All imaging data were postprocessed by coauthors blinded to clinical data; all clinical follow-ups were performed by coauthors blinded to the MRI data. See Figure 1.

Statistical Analysis

We used a standard software package (StatView 4.5, Abacus Concepts) for statistical analysis. Demographic data, time intervals of examinations, and descriptive statistics of scores are given as mean or median values with SD or median absolute deviation and range as appropriate. Because our data are not normally distributed, we applied the following nonparametric tests: Spearman rank corre-

Results

All patients had proof of ICH on the susceptibility-weighted T2*-weighted images of stroke MRI. The mean size of ICH was 16.86 ± 17.16 mL (median, 9.65 ± 5.65 mL; range, 1 to 61.9 mL) and did not differ between men and women (P = 0.98, Mann-Whitney U test). Most ICH were located or originated in the deep subcortical gray and white matter (n = 27), whereas only 5 hematomas were lobar; 18 ICH were in the left hemisphere, and 14 ICH were in the right hemisphere. Five patients had partial ventricular hemorrhage, and 2 subsequently required ventricular drainage. Median clinical severity of the ICH at baseline according to the NIHSS was 10.5 ± 4.5 points; the median outcome at 90 days was 3 ± 1 points on the mRS and 75 ± 25 points on the BI. Five of the 32 patients died as a direct result of the ICH; 13 patients were independent at day 90 (mRS 0 to 2).

Role of Time

Patients who were imaged in the first 3 hours had worse NIHSS scores at presentation and worse mRS and BI scores at outcome; this slightly missed being of statistical significance (P = 0.06, P = 0.08, and P = 0.06, respectively, Mann-Whitney U test). This was not due to hematoma size (r = 0.43, Mann-Whitney U test), although there was a general correlation between hematoma size and baseline NIHSS (r = 0.51, P = 0.005, Spearman rank correlation). Additionally, time to imaging was associated with neither the presence of an ADC reduction (P = 0.59, Mann-Whitney U test) nor a diffuse MTT prolongation (P = 0.49, Fisher exact test) but was associated with an absolute MTT prolongation (r = 0.049, Mann-Whitney U test). Time to stroke MRI correlated inversely and moderately but significantly with MTT prolongation (r = −0.47, P = 0.01, Spearman rank correlation) but not with the ADC ratio (r = 0.11, P = 0.55, Spearman rank correlation). Perihemorrhagic edema (categorized as rADC <1.1 or >1.1) was not associated with time from symptom onset to imaging (P = 0.87, Mann-Whitney U test; P = 0.99, Fisher exact test). See Figure 2.

MRI and Scores

In the healthy hemisphere, mean ADC values were 1153 ± 227 × 10−6 mm²/s (range, 711 to 1901 × 10−6 mm²/s), and mean MTT values were 23.79 ± 5.52 seconds (range, 13.8
to 33.3 seconds). In the affected hemisphere, mean ADC values were $1155 \pm 251 \times 10^{-6}$ mm$^2$/s (range, 778 to 1916 $\times 10^{-6}$ mm$^2$/s), and mean MTT values were $24.47 \pm 5.88$ seconds (range, 13.8 to 34.3 seconds). In 32 patients there was a mean rADC surrounding the ICH of 1.029 $\pm$ 0.205 and a mean MTT prolongation of 0.682s $\pm$ 1.126 seconds. Nineteen patients were categorized as dependent or dead and 13 as independent. Four patients had a large MTT prolongation of >2 seconds, 14 patients had a diffuse MTT prolongation, and 7 patients had a rADC ratio of <0.9. Presence of MTT prolongation was not associated with a categorized outcome (mRS, 0 to 2 versus 3 to 6) according to the mRS ($P=0.67$, Mann-Whitney U test), nor was rADC ($P=0.45$, Mann-Whitney U test). The same is true for death (MTT, $P=0.36$; rADC, $P=0.48$, Mann-Whitney U test). Fourteen patients had a diffuse hemispheric PWI prolongation, and 18 did not; 7 patients had a rADC of <0.9, and 25 did not. Additionally, when categorical tests were applied (rADC <0.9 or >0.9 and MTT prolongation <2 or >2 seconds), there was no significant association of rADC or diffuse hemispheric MTT prolongation with death ($P=0.30$ and $P=0.35$, Fisher exact test) and only a trend toward an association of perihemorrhagic MTT prolongation with death ($P=0.07$, Fisher exact test). However, in absolute numbers, the 4 patients with MTT prolongation >2 seconds had a bad outcome. The association of the same categories with an independent versus dependent or dead outcome assessment with the mRS also rendered nonsignificant results. There was no correlation for MTT prolongation with either mRS or BI or with rADC. Finally, although 2 patients with rADC ratios <0.9 died, 2 others had mRS scores of 1 and 2, respectively, and another 3 were moderately or severely disabled (mRS 3, 4, and 5). Presence of perihemorrhagic vasogenic edema as indicated by rADC values >1.1 was not associated with MTT prolongation ($P=0.36$, Mann-Whitney U test; $P=0.99$,}

**Figure 2.** Time course of perihemorrhagic MTT (top) and rADC (bottom). There is a moderate ($r=-0.468$) but significant ($P=0.01$) negative correlation of MTT with time, ie, perfusion abnormality is at its highest early after symptom onset (SO) and diminishes thereafter.
Fisher exact test) or diffuse MTT lesion ($P=0.27$, Fisher exact test). In addition, baseline stroke severity and outcome were not associated with the presence or absence of vasogenic edema (Table).

**Role of ICH Size**
Hematoma size was significantly correlated with baseline clinical severity ($r=0.51$, $P=0.005$, Spearman rank correlation). Furthermore, ICH size showed a moderately low but nonsignificant association with MTT prolongation but not with rADC ($r=0.32$, $P=0.08$, and $r=-0.03$, $P=0.86$, respectively, Spearman rank correlation). Size did not correlate with outcome (mRS, $r=0.3$, $P=0.12$; BI, $r=-0.22$, $P=0.2$, Spearman rank correlation) and did not predict death ($P=0.14$, Mann-Whitney $U$ test). In addition, a categorical test did not reveal an association between outcome and ICH size ($P=0.17$, Fisher exact test). Perihemorrhagic vasogenic edema was not associated with ICH size.

**Discussion**
After decades of research, neurologists and neurosurgeons still face the therapeutic dilemma that there is no effective therapy for spontaneous ICH that could be established in a large trial. 1,2 Prognostic factors such as hematoma size and location, clinical status, age, and comorbidity have been proposed to facilitate decision making, but these factors have had an impact on survival only and not on clinical outcome. 1,2,14 A large international trial is currently recruiting and randomizing patients with ICH into best medical versus surgical treatment. 3 The search for surrogate parameters that allow treatment stratification for spontaneous ICH continues.
tributing to secondary neuronal injury after ICH, but the results of different groups are inconsistent.6,15–18 Some investigators found autoradiographic evidence of perihematomal ischemic tissue in rats that returned to normal after evacuation of the hematoma6; others assessed perihemorrhagic perfusion with radiolabeled microspheres and could not reproduce these findings.19

Modern MRI protocols are the upcoming imaging standard for patients with hyperacute ischemic stroke.10 Only a few trials investigated the role of stroke MRI in patients with ICH20,21; however, their reports were restricted to diagnostic accuracy and MRI characteristics of hyperacute ICH. The diagnostic accuracy of stroke MRI for ICH has recently been established in a large multicenter trial.22 Two authors focused on the role of old microbleeds on stroke MRI for the subsequent hemorrhage risk after thrombolytic therapy23,24; others reported on perihemorrhagic findings of DWI and proton MR spectroscopic imaging in a study of human ICH patients. They found perihemorrhagic ADC changes suggesting ischemia in 1 of their patients.15 Another stroke MRI study of 12 ICH patients within 6 hours identified decreased ADC values in the perihematomatal region in 3 patients, all of whom subsequently showed clinical and radiological deterioration.9 They could not find any focal perihemorrhagic perfusion defects but found a diffuse hemispheric hypoperfusion in 5 of 6 patients who received PWI in addition to DWI sequences.

This is the first prospective trial that systemically investigated stroke MRI findings in a large set of hyperacute ICH patients. In brief, despite a mild perihemorrhagic MTT prolongation of 0.7 second on average, we detected no overall significant perihemorrhagic ADC or perfusion changes whether categorical or continuous tests or correlations were applied. ICH size, time to imaging, and clinical severity at baseline or outcome were not reflected by changes of rADC, either as increase (edema) or decrease (ischemia), either in single patients or in the whole cohort. Additionally, diffuse hemispheric and perihemorrhagic perfusion changes were not associated with clinical severity at baseline or outcome in the whole cohort. Single patients with a large MTT prolongation >2 seconds had a comparably worse outcome; however, this is not large compared with ischemic stroke patients, in whom a threshold of 4 to 6 seconds for functional impairment and >6 seconds for deep ischemia according to TTP maps was estimated.25 As others have discovered in clinical and experimental studies, we found a fair correlation of hematoma size with baseline clinical severity4 and a significant association and a significant negative correlation of ΔMTT with time from symptom onset.5,26 Interestingly, this was not associated with hematoma size, as other authors suggested.9 The presence of vasogenic edema, as shown by increased rADC values, was not associated with outcome, in contrast to other studies.27 However, the latter study argued that lack of edema is a sign of active bleeding, which again is associated with a worse clinical outcome. We doubt that rADC measurements of edema can provide a means to assess outcome prognosis in ICH patients.

The primary question is whether the changes in perfusion reflect true ischemia. Several facts do not support this concept. Old ICH in many instances leave only a small slitlike scar on CT scans, which is not consistent with major ischemic damage in the perihematomatal zone. Our findings show that while there are perihemorrhagic perfusion changes, there are no ischemic areas on rADC, there is no correlation of ΔMTT with rADC, and the imaging findings other than ICH size do not reflect the clinical course. Improvement of initially prolonged perfusion values reflects intact autoregulation in the surroundings of a hematoma.12 Since autoregulation is unimpaired, changes in blood pressure in different patients do not confound our data. One positron emission tomography (PET) study did not report any hypoxic changes within the first 2 days.28 The most convincing data and consequent hypothesis that support our findings that there is no perihemorrhagic penumbra are from a recent PET study.8 Cerebral blood flow, cerebral metabolic rate of oxygen (CMRO2), and oxygen extraction fraction were measured in 19 patients 5 to 22 hours after ICH onset. Periclot cerebral blood flow, CMRO2, and oxygen extraction fraction were determined in a 1-cm-wide area around the clot. Both periclot cerebral blood flow and CMRO2 were significantly reduced compared with contralateral values, but CMRO2 was reduced to a greater degree than cerebral blood flow, and thus oxygen extraction fraction was reduced rather than increased, as it would be in ischemia. The combination of preserved autoregulation, reduced perfusion due to a reduced metabolic demand, and lack of perihemorrhagic ischemia10,12 suggests that diaschisis, ie, reactive hypoperfusion rather than ischemia is the underlying cause of hemodynamic changes surrounding an ICH. Diaschisis may result in brain dysfunction from neuronal disconnectivity; the specific molecular and cellular changes that are associated with diaschisis are not known.29 Other explanations could involve direct effects of the ICH by mechanical disruption and toxic effects of blood constituents, matrix metalloproteinases, and cytokine-mediated apoptosis.18

There are some limitations to our study. We studied patients with hyperacute ICH within 6 hours after symptom onset only, and therefore we cannot account for findings in the subacute stage. PWI has not been established to assess quantified hemodynamic information and delivers semiquantitative data at best. Despite the substantial size of our study, there is the chance of a type II error, ie, rejection of the presence of a perihemorrhagic penumbra although it is there. The 4 patients with a relative MTT increase >2 seconds and a moderate or bad outcome may account for this. However, since our data are consistent with those of PET studies, we feel confident with regard to their accuracy. We did not study severely ill and comatose patients, and therefore ICH size in our study may be smaller than in the general patient population. However, coma and loss of vital functions are highly predictive of a fatal outcome in ICH. We did not correct our data for differences in blood pressure, which is not necessary when it is assumed that autoregulation is intact.12 In addition, we did not correct for presence of ventricular hemorrhage, which is an independent predictor of outcome. However, when these respective patients were omitted, our results did not change substantially. A 1-cm perihemorrhagic zone has been arbitrarily chosen in analogy to other studies.8 Addition-
ally, susceptibility artifacts may confound the interpretation of PWI and DWI, and furthermore, perihemorrhagic vasogenic edema may counteract an ischemic rADC decrease. Again, our prospective results in a large patient cohort fit well into the current and very recent PET literature and substantially strengthen the hypotheses created by small studies.

In conclusion, we present the first prospective trial and largest trial to date of stroke MRI for perihematomal ischemic lesions in hyperacute ICH patients. Despite the presence of a mild diffuse as well as focal perihemorrhagic hyperperfusion in some patients, this was neither predictive of outcome nor associated with definite ischemia according to the perilesional rADC in the whole cohort. Consistent with PET studies, hyperperfusion is a consequence of reduced metabolic demand, ie, diaschisis rather than a sign of ischemia. Stroke MRI with DWI and PWI does not provide additional prognostic information that could be utilized to facilitate decision making in hyperacute ICH on the basis of hemodynamic changes. The term ischemic penumbra, which is frequently used in the context of patients with hyperacute ischemic stroke, should not be applied to ICH patients because, at least at <6 hours after onset, they do not have salvageable ischemic tissue at risk. Further research regarding changes that take place in the close proximity of ICH should focus on metabolic, toxic, apoptotic, and microvascular aspects as well as on the subacute stage.

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References

Is There a Perihematomal Ischemic Penumbra? More Questions and an Overlooked Clue

“It is, of course, a trifle, but there is nothing so important as trifles.”
—Sherlock Holmes, as told by Arthur Conan Doyle

Compared with ischemic stroke, relatively little is known about the events leading to permanent parenchymal damage due to a primary intracerebral hematoma (ICH). It has been hypothesized that one aspect of the final pathology may be an ischemic penumbra surrounding the hematoma due in part to pressure exerted by the mass on surrounding vasculature. This hypothesis has been difficult to study in human ICH. If such a penumbra exists, then it may be most likely found in the sickest patients—those too unstable to tolerate study or those quickly referred to surgical intervention before the possibility of a penumbra can be investigated. Thus the dilemma of finding a penumbral signature in the first 6 hours is that one must examine a subgroup of ICH patients that may be less likely to demonstrate it. If a penumbra exists, could one detect it using MRI in the average hyperacute ICH patient available to study?

Would a perihemorrhagic ischemic penumbra have the same imaging features as the penumbra about an ischemic stroke? Are the cellular and molecular mechanisms that cause cerebral injury in perihemorrhagic ischemia the same as in a purely ischemic stroke? The biology of perihematomal ischemia may be quite different than that of pure ischemic stroke, as the brain is exposed to blood cells and molecules from which it is normally protected. Required features of a penumbra in ischemic stroke include evidence of reduced blood flow with adverse tissue or clinical consequences. Based on prior work in ischemic stroke, the present study defined a relative prolongation of MTT of 2 seconds or more or ADC reduction by 10% or more as evidence of perihematomal ischemic injury. No follow-up imaging was performed to assess the tissue outcome of perihematomal disturbances, but an association of these physiological changes in the 1-cm broad swath of tissue surrounding the hematoma with clinical outcome was considered evidence of penumbra. The imaging issues and complexities are even more challenging for ICH than for ischemic stroke. The perihematomal measurement of diffusion may be a mixture of reduced ADC due to ischemia, canceled out by the effects of hemorrhage-related extracellular edema, which would elevate the ADC and mask the signature of an ischemic ADC. Hemoglobin leakage into the region of interest may confound accurate quantification of ADC and MTT due to its paramagnetic properties on deoxygenation.

Overall, a statistically significant but subthreshold delay (0.7 seconds) in perihematomal MTT was observed in the 32 patients studied in this report. No overall difference in ADC and no significant association of MTT or ADC with clinical outcome were demonstrated. Is there, nonetheless, a clue of a penumbra within this sample?

If there is a proportion of patients with a perihematomal penumbra, then whole group statistics in this relatively small sample may have obscured the effect, which would have emerged as significant if a sufficient sample had been studied. The very hypothesis and quest for an imaging marker to discriminate patients presume that there will be 2 subgroups, 1 with the marker who will deteriorate and would be the target of therapies, and the other without the marker who would have a good recovery without specific intervention.

Examining the individual patient data presented, there was evidence of perihematomal ischemia, as defined by the criteria used in this study, on PWI in 4 patients, all of whom had poor outcome (modified Rankin score of >2), and evidence of perihematomal decrease in ADC in 7 patients, 5 of whom had poor outcome. In total, 9 of the 32 patients had evidence of perihematomal ischemic disturbance on PWI and/or DWI, 7 (78%) of whom had poor outcome, whereas 11 (49%) of 23 patients without that evidence had poor outcome. Four of the 8 (50%) patients with the worst outcome (modified Rankin score of 5 or 6, dead or total nursing care required) had perumbral signatures but only 5 of 24 (21%) with a better outcome score had that signature. A similar proportion, 3 of 12 patients, had perihematomal ADC declines and clinical deterioration in a previous report. A sample several times larger than in the present study might have proven these associations to be statistically significant.

The data in the present study are important for several reasons. The results argue against the average ICH having a perihematomal ischemic penumbra as defined by MRI criteria applicable to ischemic stroke. But rather than refute the notion of a perihematomal penumbra, this study actually provides further data suggesting the possibility of a subset of patients with clinically important perihematomal ischemic changes. If the goal is to search for evidence of a penumbra in ICH, then we are back to where we started: an unanswered question, but now with a clue of an affected subgroup. The game’s afoot!

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