Is Unexplained Early Neurological Deterioration After Intravenous Thrombolysis Associated With Thrombus Extension?

Pierre Seners, MD*; Robert Hurford, MSc*; Marie Tisserand, PhD; Guillaume Turc, PhD; Laurence Legrand, MD; Olivier Nagara, PhD; Jean-Louis Mas, MD; Catherine Oppenheim, PhD†; Jean-Claude Baron, ScD‡

**Background and Purpose**—Early neurological deterioration (END) after anterior circulation stroke is strongly associated with poor outcome. Apart from straightforward causes, such as intracerebral hemorrhage and malignant edema, the mechanism of END occurring after intravenous thrombolysis remains unclear in most instances. We tested the hypothesis that unexplained END is associated with thrombus extension.

**Methods**—From our database of consecutively thrombolysed patients, we identified anterior circulation stroke patients who had both admission and 24-hour T2*-magnetic resonance imaging, visible occlusion on admission magnetic resonance angiography and no recanalization on 24-hour magnetic resonance angiography. END was defined as ≥4 National Institutes of Health Stroke Scale–point deterioration on 24-hour clinical assessment and unexplained END as END without clear cause. The incidence of susceptibility vessel sign extension on T2* imaging, defined as any new occurrence or extension of susceptibility vessel sign from admission to 24-hour follow-up magnetic resonance, was compared between patients with unexplained END and those without END.

**Results**—Of 120 eligible patients for the present study, 22 experienced unexplained END. Susceptibility vessel sign extension was present in 41 (34%) patients and was significantly more frequent in the unexplained END than in the no-END group (59% versus 29%, respectively; adjusted odds ratio=3.96; 95% confidence interval, 1.25–12.53; \( P = 0.02 \)).

**Conclusions**—In this study, unexplained END occurring after thrombolysis was independently associated with susceptibility vessel sign extension, suggesting in situ thrombus extension or re-embolization. These findings strengthen the need to further investigate early post-thrombolysis administration of antithrombotics to reduce the risk of this ominous clinical event. (Stroke. 2017;48:348-352. DOI: 10.1161/STROKEAHA.116.015414.)

Key Words: angiography ■ cerebral infarction ■ magnetic resonance imaging ■ thrombolytic therapy

Early neurological deterioration (END) within the first 24 hours after intravenous thrombolysis (IVT) for acute ischemic stroke is relatively common, occurring in ≈14% of cases, as well as ominous as it consistently predicts poor outcome.1,2 Although END may have straightforward causes, such as symptomatic intracerebral hemorrhage, malignant edema, and early recurrent stroke, no clear mechanism is found in ≈2/3 of END cases, to be referred to as unexplained END below.1–3 We previously reported that unexplained END is associated with higher blood glucose, no previous use of antiplatelets, larger diffusion-perfusion mismatch, persistent proximal occlusion, and diffusion-weighted imaging lesion growth beyond the initial ischemic penumbra.4 This led us to suggest that unexplained END is linked to secondary hemodynamic compromise in the context of persistent occlusion, with potential mechanisms including in situ thrombus extension and new embolic events in the same arterial territory.4,14

In this proof-of-concept, mechanistic study, we used the susceptibility vessel sign (SVS), a specific marker of thrombus on T2*-MR,5 to test the hypothesis that post-thrombolysis unexplained END, compared with non-END controls, is associated with extension of the original thrombus.

**Methods**

**Patients**

Given our underlying hypothesis that thrombus extension underlies unexplained END, only patients with both arterial occlusion on admission and persistent occlusion on 24 hours imaging, in whom

---

Received September 12, 2016; final revision received November 29, 2016; accepted December 2, 2016.

From the Departments of Neurology (P.S., G.T., J.-L.M., J.-C.B.) and Radiology (L.L., O.N., C.O.), Hôpital Sainte-Anne, Paris, France; Université Paris Descartes, Sorbonne Paris Cité, INSERM UMR S894, DHU Neurovase, France (P.S., G.T., L.L., O.N., J.-L.M., C.O., J.-C.B.); Department of Clinical Neurosciences, University of Cambridge, United Kingdom (R.H.); and Service de Radiologie, Hôpital Foch, Suresnes, France (M.T.).

*Dr Seners and R. Hurford contributed equally.

†Drs Oppenheim and Baron are joint senior authors.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.orglookup/suppl/doi:10.1161/STROKEAHA.116.015414/-/DC1.

Correspondence to Jean-Claude Baron, ScD, INSERM UMR S894, 2ter rue d’Alésia, 75014 Paris, France. E-mail jean-claude.baron@inserm.fr

© 2016 American Heart Association, Inc.

**Stroke** is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.116.015414
SVS would be expected to be present, were included in the present study. From our prospective database of consecutive acute stroke patients treated only with IVT <4.5 hours between January 2001 and December 2015, we therefore identified patients with (1) middle cerebral artery stroke, (2) magnetic resonance imaging (MRI) obtained on admission and at the 24-hour follow-up, (3) visible occlusion on admission magnetic resonance angiography (MRA), and (4) persistent occlusion (arterial occlusive lesion score: 0–1) on 24-hour MRA. Patients with clear-cause END and those with severe artifacts on either T2* scan were excluded a priori. After this screening procedure, only patients with SVS on either the admission or the follow-up T2* scan were included for the statistical analysis because only in this situation can the hypothesis of SVS extension be tested (see below).

In accordance with French legislation, this study did not need approval by an Ethics Committee because it implied only retrospective analysis of anonymized data collected prospectively as a part of routine clinical care.

Unexplained END
As described in detail elsewhere,2 END was defined as a ≥4-point increase in National Institutes of Health Stroke Scale score between admission and 24 hours and unexplained END as END without evident cause, including symptomatic intracerebral hemorrhage, malignant edema, early recurrent stroke, or other medical complications.

Imaging
MRI is systematically implemented as first-line pretreatment work-up in candidates for thrombolysis in our center. The admission protocol, performed on a 1.5-T scanner (GE Healthcare), includes fluid-attenuated inversion recovery, diffusion-weighted imaging, T2*-weighted gradient echo imaging, and intracranial MRA. Computed tomography and computed tomographic angiography are performed only when MRI is contraindicated. The acquisition parameters of the 2-dimensional T2*-weighted gradient echo sequence were as follows: repetition time/echo time 460/13 ms, flip angle 25°, 24×18 cm² field of view, 256×224 matrix, 1 excitation, 24 slices, 6-mm contiguous slice thickness. A follow-up imaging (MRI, or computed tomography if contraindicated) is systematically performed ≥24 hours after treatment and includes the same set of sequences as the admission MRI. In case of >1 follow-up MRI, the MRI performed closest in time with END occurrence was used for the present analysis.

As to the best of our knowledge, no previous study has assessed SVS extension to date, a visual-analysis-based method was devised for the purpose of the present study. Two stroke physicians (P.S. and R.H., in consensus) and 1 experienced neuroradiologist (M.T.) independently compared spatially coregistered admission and 24-hour follow-up T2* scans. Another experienced neuroradiologist (C.O.) adjudicated any discrepancies. Observers had access to diffusion-weighted imaging and MRA, but were blinded to the clinical data. They were asked to search for SVS, that is, a hypointense signal on T2* within a vascular cistern, exceeding the size of the homologous contralateral arterial diameter; this search was performed for 4 predefined arterial segments, namely the supraclinoid internal carotid artery, proximal part of middle cerebral artery (M1), insular middle cerebral artery segment (M2), and more distal middle cerebral artery segment (>M2). Each eligible patient was then classified as SVS extension or no-extension in the above 4 arterial segments. Figures 1 and 2 show the 5 main SVS evolution patterns. The following patterns were classified as SVS extension: (1) extension or new occurrence of SVS in any segment, without any regression (Figure 1A); (2) stable length of the SVS within M1 but displacement of the SVS within the M1 segment (Figure 1B), which might occlude previously unaffected M1 perforators and lead to END; and (3) regression of proximal SVS associated with extension/new SVS occurrence in a more distal arterial segment (Figure 1C), which might occlude perforators or collaterals.7 The no-SVS extension group included (1) unchanged SVS length and location (Figure 2A); and (2) SVS regression without any new SVS occurrence or extension (Figure 2B).

Statistical Analysis
Interobserver agreement for categorization as SVS extension/no-extension was studied on the entire cohort using Cohen Kappa statistics and their 95% confidence intervals (CIs). Continuous variables were compared with Student t test or a Mann-Whitney U test, and categorical variables were compared using χ² or Fisher exact test, as appropriate. We compared pretreatment characteristics in univariable analyses between unexplained END and no-END patients. To adjust for potential confounders, we performed a multivariable binary logistic regression analysis with stepwise variable selection. Accordingly, at each step of this process, variables automatically entered the regression analysis at P<0.30 and were retained as long as they remained associated at P<0.05. Statistical analyses were performed using SPSS 16.0 (SPSS Inc) and SAS 9.4 (SAS Institute, Inc). Two-tailed P<0.05 was considered statistically significant.

Results
After exclusion of clear-cause ENDs (n=11: symptomatic intracerebral hemorrhage n=5; malignant edema n=6) and patients without SVS on both the admission and the follow-up T2* scans (n=12), a total of 120 patients met the study’s entry criteria (see Figure 3). Mean age was 69±15 years, median National Institutes of Health Stroke Scale was 16 (interquartile range, 12–20), and proximal occlusion (internal carotid artery or M1) was present in 83% of patients. Unexplained END occurred in 22 patients.

SVS was present on admission MRI in 98% of the patients included in the present study. In the remaining 2% (3 patients), there was no SVS on admission MRI but a new SVS appeared on follow-up MRI (these patients were included in the new occurrence SVS category; see Methods).

Figure 1. Illustration of the 3 patterns of susceptibility vessel sign (SVS) extension between coregistered admission and 24-hour follow-up T2* magnetic resonance (MR) scans. A, M1 SVS on admission MR, still present at follow-up MR with new SVS in terminal internal carotid artery and SVS extension in distal M1; B, long proximal M1 SVS on admission, with stable length but distal displacement within the M1 segment at follow-up; C, extensive SVS affecting whole M1 and proximal M2 on admission, with partial regression of its proximal portion and M2 extension. See Methods for operational definition of terms. M1 indicates proximal part of the middle cerebral artery (MCA); and M2, insular MCA segment.
In 11 (9%) patients, the SVS present on admission MRI disappeared on follow-up MRI, despite persistent occlusion on MRA. On admission MRI, an SVS involved the internal carotid artery, M1, M2, and >M2 arterial segments in 12%, 73%, 47%, and 10% of the eligible patients, respectively (>1 segment affected in 36%). Forty-one (34%) patients were classified as SVS extension and 79 (66%) as no-SVS extension (Cohen Kappa for interobserver agreement: 0.71; 95% CI, 0.59–0.84).

The admission and follow-up characteristics of the unexplained END and no-END groups are shown in the Table. SVS extension was significantly more frequent in unexplained END than in no-END patients (59% versus 29%; odds ratio, 3.61; 95% CI, 1.39–9.40; \( P < 0.01 \); Table).

The characteristics of the SVS extension and no-extension groups are shown in Table I in the online-only Data Supplement.

In multivariable analysis, SVS extension (adjusted OR=3.96; 95% CI, 1.25–12.53; \( P=0.02 \)), age (adjusted OR; per 10-year increase=1.62; 95% CI, 1.03–2.57; \( P=0.04 \)), and admission National Institutes of Health Stroke Scale score (adjusted OR; per 1-point increase=0.80; 95% CI, 0.72–0.89; \( P<0.01 \)) were significantly associated with unexplained END.

**Discussion**

In this large and prospectively collected cohort of IVT-treated stroke patients with persistent occlusion, unexplained END occurred in 18%, that is, higher than in unselected IVT populations but consistent with previously reported rates in non-recanalizers.\(^1,2\) Our 34% rate of SVS extension in persistent occlusion is also consistent with 2 previous small scale studies,\(^8,9\) which however did not report the clinical course (ie, occurrence of END or not).

Consistent with our hypothesis, the multivariable logistic regression model revealed an independent association between unexplained END and SVS extension. Only age and admission National Institutes of Health Stroke Scale were otherwise retained in the model. Forcing the inclusion of admission glycaemia and previous use of antiplatelets\(^2\) into the multivariable model did not affect the results (data not shown).

Our observation is consistent with a pre-IVT era study of 15 patients in whom conventional angiography was obtained both before and after neurological deterioration occurring during the first days poststroke and which reported various angiographic changes, such as thrombus extension and re-embolization.\(^7\) However, the association between these changes and neurological deterioration could only be inferred from this study as a control group (ie, nondeteriorating patients) was not included for comparison.

Although we found a significant association between unexplained END and SVS extension in our cohort, this association was not systematic at the individual patient level (Table). This might reflect other potential mechanisms underlying...
unexplained END, such as blood pressure drops or hyper-/hypoglycemia worsening neuronal status in hypoperfused tissue. Furthermore, because the sensitivity of T2* to detect thrombi is not perfect, thrombus extension might have been missed in some patients.

Conversely, SVS extension was present in a fraction of no-END patients. Two main possibilities may account for this observation. First, we categorized the SVS evolution subtype regression of proximal SVS associated with extension/new SVS occurrence in a more distal segment as SVS extension because of the reasonable assumption that new occlusion of collaterals may cause unexplained END. However, post hoc inspection of our data suggests this subtype was in fact largely unassociated with unexplained END (Table I in the online-only Data Supplement). In a post hoc analysis reclassifying this subgroup into the no-SVS extension group, the association between unexplained END and SVS extension became as expected stronger (55% versus 17%; OR=5.72; 95% CI, 2.12–15.37; P<0.001). A second, and entirely different, possibility to explain the occurrence of SVS extension in no-END patients is that thrombus extension may lead to infarction of clinically noneloquent tissue.

The exact underlying process, or processes, that lead to thrombus extension in the first 24 hours after thrombolysis remain speculative. First, in situ extension of the original thrombus may be caused by (1) pathological thrombosis pathways, such as increased coagulation activity and resistance to fibrinolysis, or (2) activation of the physiological coagulation cascade because of blood stasis adjacent to the original thrombus (eg, because of poor collateral flow or inefficient vascular architecture). Second, proximal thrombus extension could be explained by re-embolization in the same territory from a proximal embolic source.

### Table. Characteristics of the Population and Univariate Relationships With Unexplained END*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whole Sample (n=120)</th>
<th>Unexplained END (n=22)</th>
<th>No-END (n=98)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>69.4±15.3</td>
<td>75.7±11.4</td>
<td>68.0±15.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Male sex</td>
<td>56 (47)</td>
<td>8 (36)</td>
<td>48 (49)</td>
<td>0.28</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (17)</td>
<td>4 (18)</td>
<td>16 (16)</td>
<td>0.76</td>
</tr>
<tr>
<td>Current smoking</td>
<td>19 (16)</td>
<td>2 (10)</td>
<td>17 (17)</td>
<td>0.52</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>33 (28)</td>
<td>7 (32)</td>
<td>26 (27)</td>
<td>0.64</td>
</tr>
<tr>
<td>Antiplalets</td>
<td>37 (31)</td>
<td>6 (27)</td>
<td>31 (32)</td>
<td>0.69</td>
</tr>
<tr>
<td>Statins</td>
<td>36 (30)</td>
<td>6 (27)</td>
<td>30 (31)</td>
<td>0.76</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>68 (57)</td>
<td>12 (55)</td>
<td>56 (57)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Pretreatment characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score</td>
<td>16 (12–20)</td>
<td>10 (6–13)</td>
<td>17 (13–21)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Glycemia, mmol/L</td>
<td>6.9 (6.0–8.5)</td>
<td>7.5 (6.2–8.3)</td>
<td>6.8 (5.9–8.5)</td>
<td>0.44</td>
</tr>
<tr>
<td>Onset-to-treatment time, min</td>
<td>155 (130–195)</td>
<td>167 (135–199)</td>
<td>152 (125–195)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Admission MRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset-to-admission MRI time, min</td>
<td>123 (91–166)</td>
<td>135 (88–171)</td>
<td>120 (91–164)</td>
<td>0.60</td>
</tr>
<tr>
<td>Proximal occlusion on MRA†</td>
<td>100 (83)</td>
<td>19 (86)</td>
<td>81 (82)</td>
<td>1.0</td>
</tr>
<tr>
<td>SVS in ICA</td>
<td>14 (12)</td>
<td>3 (14)</td>
<td>11 (11)</td>
<td>0.72</td>
</tr>
<tr>
<td>SVS in M1</td>
<td>88 (73)</td>
<td>16 (73)</td>
<td>72 (74)</td>
<td>0.94</td>
</tr>
<tr>
<td>SVS in M2</td>
<td>56 (47)</td>
<td>6 (27)</td>
<td>50 (51)</td>
<td>0.04</td>
</tr>
<tr>
<td>SVS in &gt;M2</td>
<td>12 (10)</td>
<td>2 (9)</td>
<td>10 (10)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Follow-up MRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVS extension‡</td>
<td>41 (34)</td>
<td>13 (59)</td>
<td>28 (29)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

END indicates early neurological deterioration; ICA, internal carotid artery; M1, proximal part of the middle cerebral artery (MCA); M2, insular MCA segment; >M2, more distal MCA segment; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NIHSS, National Institute of Health Stroke Scale; and SVS, susceptibility vessel sign.

Categorical variables are expressed as n (%), whereas continuous variables are expressed as mean±standard deviation or median (interquartile range).

†ICA or M1 occlusion.

‡See Methods for operational definitions.
This study has limitations. As already mentioned, the sensitivity of T2* to detect acute intracranial thrombi is not perfect. This likely explains why 12 patients with arterial occlusion on admission MRA did not have SVS. Furthermore, SVS extension or regression might reflect structural or metabolic changes within the thrombus over time rather than true thrombus evolution, which may explain why 10 patients had complete regression of SVS on follow-up MRI, despite persistent occlusion on MRA. Although some MR sequences, such as susceptibility-weighted imaging, are more sensitive than T2* for thrombus detection, they are more time-consuming and particularly their use in the hyperacute stroke setting is questionable. Lastly, the purposely devised assessment of SVS extension relied on qualitative, although expert-based, visual image analysis.

To conclude, this study showed an independent association between unexplained END and SVS extension, supporting the hypothesis that in situ thrombus extension or re-embolization from a proximal embolic source may underlie unexplained END, at least in a fraction of cases. These findings strengthen the hypothesis that in situ thrombus extension or re-embolization might underlie unexplained END. Moreover, preventing thrombus extension by early administration of antithrombotics might reduce the risk of this ominous event. However, ultraearly administration of antithrombotics after IVT may involve a higher risk of symptomatic intracerebral hemorrhage in unselected populations, calling for caution regarding this approach, which will have to be tested in selected populations at high risk of unexplained END.

Sources of Funding
Dr Seners is funded by les Journées de Neurologie de Langue Française.

Disclosures
None.

References