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Susceptibility Vessel Sign and Cardioembolic Etiology in the THRACE Trial

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THRACE investigators

Abstract

Purpose The susceptibility vessel sign (SVS) has been described on gradient echo (GRE) magnetic resonance imaging (MRI) in acute ischemic stroke patients by large vessel occlusion. The presence of SVS (SVS+) was associated with treatment outcome and stroke etiology with conflicting results. Based on multicenter data from the THRombectomie des Artères CÉrebrales (THRACE) study, we aimed to determine if the association between SVS and cardioembolic etiology (CE) was independent of GRE sequence parameters.

Material and Methods Patients with a pretreatment brain GRE sequence were identified. Logistic regression tested the association between SVS+, CE, time from onset to imaging and GRE sequence parameters (e.g. echo time, voxel size, field strength). We calculated the sensitivity, specificity, positive and negative predictive values (PPV and NPV) for the SVS to predict a stroke from a CE.

Results An SVS+ was observed in 237 out of 287 (83%) patients. In the univariate analysis, there was a significant association between SVS+ and a CE with an odds ratio (OR) and 95% confidence interval (95% CI) of 2.10 (1.02–4.29), respectively ($p = 0.04$) but not with GRE sequence parameters. In multivariate analysis, there was an independent relationship between SVS+ and CE (OR [95% CI]: 2.14 [1.02–4.45], $p = 0.04$). Sensitivity and specificity of SVS+ to predict CE were 0.89 and 0.21, respectively. The PPV and NPV of SVS+ were 0.44 and 0.78, respectively.

Conclusion The presence of SVS is associated to CE, independent of GRE sequence parameters. While the specificity and the PPV of the sign were low, CE seems less likely in the absence of an SVS.

Keywords Thrombus · Magnetic resonance imaging · Ischemia

Olivier Naggara and Catherine Oppenheim have equally contributed to this work.

Contributorship Statement Romain Bourcier had the original idea and co-wrote the manuscript. Catherine Oppenheim and Olivier Naggara co-wrote the manuscript. Marine Beaumont, Sebastien Soize, Laurence Legrand, Serge Bracard, Hubert Desal, Imad Derraz made a critical interpretation of the data and a critical review of the manuscript. Beatrice Delasalle made the statistical interpretation of the data and revised the article.

Data Sharing Data are available upon request from the corresponding author.

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Background

Unravelling the etiology in acute ischemic stroke (AIS) is important because it could potentially affect secondary stroke prevention strategies. In many AIS patients, however, risk factors for both large artery atherosclerotic and cardioembolic etiologies (CE) are present. Furthermore, for up to 30% of strokes, the exact etiology remains uncertain [1]. Due to the technique of endovascular retrieval, thrombus composition could potentially provide an important clue regarding stroke etiology; however, no clear association between thrombus composition and the etiology was found in the literature [2–9]. Further understanding of the association between imaging characteristics of a thrombus and the etiology could be useful to help determine stroke etiology. The susceptibility vessel sign (SVS) on gradient echo (GRE) imaging is defined as a hypointense signal exceeding the diameter of the contralateral artery at the site of

the thrombus [10]. The SVS is seen in 50–85% of cases of AIS, particularly in cases of a red blood cell-dominant thrombus, whereas a lack of SVS is indicative for a fibrin-dominant thrombus [11–17]. The SVS has been related to the stroke etiology with variable degrees of reliability [2, 12–14, 17–19]. Only small retrospective monocentric studies have found an association between the presence of SVS and CE in AIS [15, 20, 21].

With more than 300 hundred patients included with magnetic resonance imaging (MRI) performed at the acute phase of stroke, the multicenter THRombectomie des Artères CErebrales (THRACE) study [22] offers a unique opportunity to determine if there is an association between SVS and CE independent of GRE sequence parameters.

Material and Methods

THRACE Study Design

The THRACE study was a randomized controlled trial carried out in 26 centers in France. The study design and protocol were previously detailed [22]. Patients with AIS were eligible for inclusion if they were aged 18–80 years, had a US National Institutes of Health Stroke Scale (NIHSS) score of 10–25, had an occlusion of the intracranial internal carotid artery (ICA) or the M1 segment of the middle cerebral artery (MCA) on MR angiography, could be administered intravenous thrombolysis within 4 h of symptom onset and if thrombectomy could be initiated within 5 h of symptom onset. Patients who had cervical ICA occlusion and subocclusive stenosis were excluded. Patients were randomized (1:1) as soon as possible to receive either intravenous thrombolysis and mechanical thrombectomy (IVTMT group) or intravenous thrombolysis alone (IVT group). Randomization was done at the coordination center by a computer analyst who was masked to the investigation centers and to the patients. Before randomization, written informed consent was obtained from all patients or their legal representatives. The study protocol was approved by the Comité de Protection des Personnes III Nord Est Ethics Committee and the research boards of the participating centers.

Clinical and Biological Data

Clinical and biological data included age, gender, smoking rate, history of high blood pressure, diabetes mellitus, hypercholesterolemia, coronary artery disease, previous stroke, mean glycemia level at inclusion, topography of occlusion (M1 or ICA) and time from onset to imaging. At day seven or at discharge, a vascular neurologist recorded the suspected etiology of cerebral infarction with

the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [23].

Work-up for Cardioembolic Stroke

In the THRACE trial the recommended general work-up according to the European Stroke Organisation (ESO) guidelines [24], included physiological parameters and routine blood tests, a 12-lead electrocardiography (ECG) and continuous ECG. In addition, a 24-h Holter ECG monitoring was performed when arrhythmia was suspected and no other causes of stroke were found. The echocardiography was recommended when ECG abnormalities or evidence of cardiac disease from the patient history were reported or when no other identifiable causes of stroke were found.

Imaging Data

This study included patients screened with MRI GRE sequence in the THRACE trial and analysis of the SVS available. Patients with severe motion artefacts on GRE sequences were excluded when the presence or absence of SVS could not be reliably determined and patients who were screened with susceptibility-weighted imaging instead of a GRE sequence were also excluded because susceptibility-weighted imaging was scarcely used in THRACE patients. The MRI acquisition parameters of the sequence were left to the discretion of the recruitment centers according to their routine practice without any standardization. Hence, MRI and GRE sequence parameters recorded included slice thickness, interslice gap, flip angle, echo time, field strength and voxel acquisition size. An imaging core laboratory centrally analyzed MRI images and SVS was defined as a hypointense signal on GRE within a vascular cistern exceeding the size of the homologous contralateral arterial diameter [10]. The core laboratory reading team consisted of 4 neuroradiologists with >5 years of experience in stroke imaging. For the purpose of this ancillary study, a fifth reader with <2 years of experience in stroke imaging, performed an independent reading session and, 1 month apart, a second reading session to test intrareader agreement.

Statistical Analysis

Continuous data are presented as mean (\pm standard deviation) or median (interquartile range, IQR) based on the distribution. Categorical variables are presented as counts (proportions). The Mann-Whitney U-test and the t-test were performed to test for statistical differences in continuous parameters between two groups. The χ^2 -test or Fisher's exact test (based on expected frequency) was used to com-

pare categorical variables between groups. Intrareader and interreader agreement for determination of SVS were assessed using kappa statistics. A multivariable mixed logistic regression model was used to examine the association between SVS and CE adjusted for potential confounders, selected a priori technical parameters (echo time, 3T and voxel size) and time from onset to imaging or those that differed with a p value < 0.20 in the SVS subgroups univariate analysis ($p < 0.20$). To account for a potential variability across centers, this was considered as a random effect in the mixed logistic regression model. Odds ratio (OR) and the 95% confidence intervals (CI) were derived from the logistic model as effect size. Finally, the diagnostic values and the 95% CI for the SVS, e.g. sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy rate were calculated to predict a stroke from a CE. A p -value < 0.05 was considered statistically significant. All p -values are two-sided. Data were analyzed with the SAS packages (SAS Institute, version 9.4, Cary, NC, USA).

Results

The flow chart for inclusion is presented in Fig. 1. Of the 412 patients included in the THRACE trial, 301 were included in THRACE based on pretreatment brain MRI, 14 patients were excluded from the analysis (poor imaging quality, $n=9$; no GRE sequence, $n=5$) and 287 patients were included with a 1.5T ($n=176$, 61.3%) or a 3T field strength MR unit ($n=111$, 38.7%). An SVS was observed in 237 out of 287 patients (83%). Data for the TOAST evaluation were lacking in 26 patients who were excluded from the regression analysis. Intrareader and interreader agreement for determination of SVS were 0.94 and 0.83, respectively.

Overall, the mean (SD) slice thickness (mm), interslice gap (mm), echo time (ms) and voxel size were 4.96 (0.42), 0.55 (0.51), 19.47 (6.50) and 4 (1.02), respectively. In the univariate analysis (Table 1), there was a significant association between the presence of SVS and a CE (OR [95% CI]: 2.10 [1.02–4.29], $p=0.037$) but not with time from onset to imaging, echo time, 3T field strength and voxel size. In multivariate mixed logistic regression analysis including time from onset to imaging, echo time, 3T field strength and voxel size as fixed effects and center as a random effect, the relationship between SVS and CE was significant with a similar estimate as obtained in univariate analysis (OR [95% CI]: 2.14 [1.02–4.45], $p=0.041$). In comparison to a no information rate of 58.8%, the sensitivity and the specificity of the SVS to predict a stroke from a CE origin was 0.89 (95% CI, 0.83–0.95) and 0.21 (95% CI, 0.14–0.27), respectively, while PPV and NPV were 0.44 (95% CI, 0.37–0.51) and 0.73 (0.59–0.86), re-

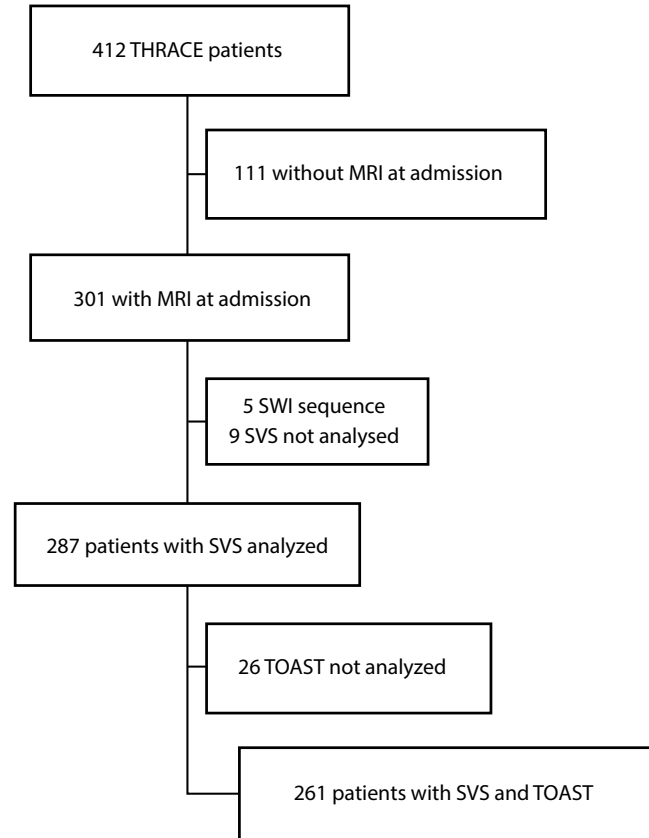


Fig. 1 Flow chart for inclusion of subjects in the study. *MRI* magnetic resonance imaging, *SVS* susceptibility vessel sign, *SWI* susceptibility-weighted imaging, *THRACE* THRombectomie des Artères CErebrales study, *TOAST* Trial of Org 10172 in Acute Stroke Treatment

spectively. Overall the diagnostic accuracy was 0.49 (95% CI, 0.42–0.55).

Discussion

In this study SVS was associated with CE after adjustment for GRE sequence parameters and time from onset to imaging. Furthermore, in the absence of SVS cardioembolism was unlikely. Randomized control trials that have demonstrated superiority of bridging therapy over best medical care included patients based on the presence of a large vessel occlusion, without any information on thrombus characteristics [25]. Studies on human thrombi retrieved from AIS patients have revealed varying compositions [3, 6, 8, 9]. Published articles failed to find a reliable and reproducible association between the thrombus histology and stroke etiology [2]. There is an inherent bias in assessing the histological characteristics of retrieved thrombi in vivo in relation to the stroke etiology: IVT is administered before histological analysis and only the thrombi retrieved are available for analysis, which might bias the analysis [26, 27]. Hence,

Table 1 Univariate and multivariate analysis for the presence of SVS

<i>Univariate analysis</i>	<i>OR</i>	<i>95% CI</i>	<i>p-value</i>
Time from onset to imaging in minutes	1.10	0.68–1.81	0.67
Cardioembolic stroke	2.10	1.02–4.29	0.04
Echo time	1.21	0.72–2.01	0.46
3T	0.94	0.50–1.74	0.83
Voxel size in micrometer	1.06	0.78–1.44	0.70
<i>Multivariate analysis^a</i>			
Time from onset to imaging in minutes	1.12	0.66–1.88	0.68
Cardioembolic stroke	2.14	1.02–4.45	0.04
Echo time in seconds	1.02	0.95–1.10	0.57
3T	1.04	0.44–2.41	0.93
Voxel size in micrometer	0.92	0.66–1.28	0.62

^aMultivariate mixed logistic regression model including center as random effect

Figures given in bold type are statistically significant
OR odds ratio, *CI* confidence interval,

the GRE imaging characteristics of thrombi could therefore provide a relevant short-cut towards the stroke etiology without histological examination. A previous, smaller and monocentric study has already found a positive association between the GRE SVS on a 1.5T MR unit and a CE [15]. This study provides the largest prospective study with a systematic evaluation of the SVS related to the stroke etiology and exhaustive GRE sequence parameters could also be precisely recorded in order to analyze the weighting in the relationship between SVS visibility and CE. Several GRE parameters theoretically modify the detection of SVS on GRE sequence. The SVS is due to the presence of a paramagnetic blood clot which induces local magnetic field heterogeneities, proportional to the static magnetic field (B_0). The protons submitted to these field distortions precess at frequencies different from the Larmor frequency, resulting in signal shift and/or signal loss, especially with a GRE sequence which does not correct for spin dephasing. The so-called susceptibility artifact is proportional to the dephasing time of the spins (echo time) and to the frequency spectrum

Table 2 Baseline characteristics and gradient echo sequence parameters of SVS+ and SVS– patients

		SVS– (<i>n</i> = 50)	SVS+ (<i>n</i> = 237)	<i>p</i> -value
Age (years)	(mean, SD)	62 (14)	63 (14)	0.40
Female sex	(<i>n</i> , %)	26 (52)	112 (47)	0.54
Smoking	(<i>n</i> , %)	19 (44)	89 (41)	0.74
Hypertension	(<i>n</i> , %)	30 (60)	119 (51)	0.24
Diabetes mellitus	(<i>n</i> , %)	6 (12)	23 (10)	0.65
Hypercholesterolemia	(<i>n</i> , %)	22 (55)	113 (53)	0.82
Coronary artery disease	(<i>n</i> , %)	8 (17)	34 (15)	0.67
History of stroke	(<i>n</i> , %)	3 (6)	15 (7)	0.61
Glycemia (gram/liter)	(mean, SD)	1.21 (0.35)	1.24 (0.43)	0.64
M1 versus ICA occlusion	(<i>n</i> , %)	42 (84)	197 (83)	0.90
Time from onset to MRI (minutes)	(median, IQR)	113 (61)	113 (48)	0.41
TOAST classification	Large artery atherosclerosis (<i>n</i> , %)	9 (20)	31 (14)	0.14
	Cardioembolic stroke (<i>n</i> , %)	12 (27)	96 (44)	–
	Other determined cause of stroke (<i>n</i> , %)	5 (11)	11 (5)	–
	Undetermined cause of stroke (<i>n</i> , %)	18 (41)	79 (36)	–
Cardioembolic stroke vs. others	(<i>n</i> , %)	12 (27)	96 (44)	0.04
Manufacturer	GE ^a medical system (<i>n</i> , %)	25 (50)	102 (43)	0.62
	Philips Healthcare ^b (<i>n</i> , %)	14 (32)	85 (36)	–
	Siemens ^c (<i>n</i> , %)	9 (18)	50 (21)	–
Slice thickness (millimeter)	(mean, SD)	4.94 (0.47)	4.98 (0.44)	0.53
Inter slice gap (millimeter)	(mean, SD)	0.53 (0.47)	0.55 (0.52)	0.95
Flip angle (°)	(mean, SD)	21.1 (10)	20.05 (5)	0.83
Echo time (millisecond)	(mean, SD)	18.64 (8.56)	19.35 (5.92)	0.13
3T	(<i>n</i> , %)	30 (60)	146 (62)	0.83
Voxel size (micrometer)	(mean, SD)	3.99 (1.12)	4.05 (0.97)	0.24

ICA Intracranial carotid artery, *MRI* Magnetic Resonance Imaging, *TOAST* Trial of ORG 10172 in Acute Stroke Treatment, *SVS* Susceptibility Vessel Sign, *SD* Standard Deviation, *IQR* Inter Quartiles Range

^a GE Medical Systems, Chicago, IL, USA

^b Philips Medical Systems, Best, The Netherlands

^c Siemens Healthineers, Erlangen, Germany

within a voxel. In theory, the main GRE sequence parameters prone to modify the SVS should be B0, TE and the voxel size [28, 29]; therefore, the multivariate analysis was adjusted based on these parameters. Besides the association between SVS and CE independent of GRE sequence parameters, the sensitivity of the SVS to identify a CE stroke was found to be 0.89 and the negative predictive value was 0.78. The small number of false negative patients (i.e. no SVS but CE) suggest that CE is unlikely in patients without SVS. The few false negative patients might be explained by the limited paramagnetic effect, i.e. blooming effect in smaller thrombi, which might be more difficult to identify [10]. Furthermore, interreader agreement was high (0.94) but not perfect and some false negative cases may have been the consequence of imperfect rating. In addition, small-sized red thrombi might have been missed because of the GRE interslice gap; however, the mean slice thickness and the interslice gaps of MRI acquisition were similar in the SVS- and the SVS+ patients (Table 2). These results contradict previous results [30–33], which suggested that CE was related to fibrin-rich thrombi. Indeed, the SVS reflects higher red blood cell content, which seems to be less prevalent in cardioembolic stroke.

On the other hand, the specificity (21%) and the positive predictive value (44%) of the SVS to identify CE were low in this study: 121 SVS+ patients were classified as having a stroke etiology other than cardioembolism and among them, 31 of the 40 large artery atherosclerosis had an SVS+. This may be attributable to the process of clot formation; however, SVS alone cannot differentiate the initial thrombus from the secondary components promoted by the blood stasis proximal and distal to the occlusion site, which may also increase the content of red blood cells in SVS [34].

The authors acknowledge limitations in the study. First, detailed information on the quality of work-up was lacking and therefore a bias in analysis regarding the difference in work-up quality across centers cannot be excluded; however, all THRACE centers followed the general work-up according to the ESO guidelines [24]. Second, in this study the no information rate has a better accuracy value as compared to considering the SVS+ vs. SVS- (58.8% estimated vs. 49.0% using SVS). Hence, the overall performance is worse than simple guessing and the overall weak performance of the SVS in predicting stroke etiology has to be mentioned. Third, the International Normalized Ratio (INR), platelet count and previous use of antiplatelets were not recorded and these factors may have an influence on SVS detectability [35, 36]. Fourth, the SVS was only analyzed as a binary variable (presence/absence; [10]), whereas others distinguished different subtypes of SVS (namely “two-layer SVS”) on 3T MRI, or quantitative estimation based on susceptibility-weighted imaging to assess the overestimation ratio. In line with these findings, the two latter stud-

ies demonstrated an association with CE [21, 37]. Fifth, because SWI was seldom performed in THRACE patients (5/301 in the THRACE trial), we chose to exclude them from the current study, despite its inherent better sensitivity than GRE in detecting the SVS, particularly for distal or fragmented thrombi [38–40]. Last, band width, which may also influence SVS visibility had not been recorded.

Conclusion

After adjustment for GRE sequence parameters, an independent association was found between CE and SVS. In the absence of SVS, CE was unlikely. These results from the largest series to date could guide the stroke etiological work-up and interpretation of the visualization of this radio marker in the context of AIS.

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Compliance with ethical guidelines

Conflict of interest R. Bourcier, I. Derraz, B. Delasalle, M. Beaumont, S. Soize, L. Legrand, H. Desal, S. Bracard, O. Naggara and C. Oppenheim declare that they have no competing interests.

Ethical standards Written informed consent was obtained from all patients or their legal representatives. The study protocol was approved by the Comité de Protection des Personnes III Nord Est Ethics Committee and the research boards of the participating centers.

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