Significant Association of Atrial Vulnerability With Atrial Septal Abnormalities in Young Patients With Ischemic Stroke of Unknown Cause

Karine Berthet, MD; Thomas Lavergne, MD; Ariel Cohen, MD, PhD; Louis Guize, MD; Marie-Germaine Bousser, MD; Jean-Yves Le Heuzey, MD; Pierre Amarenco, MD

Background and Purpose—Atrial septal abnormalities have been associated with cryptogenic ischemic stroke in young patients, but the causal link has not yet been established. Paradoxical embolism is considered the most likely mechanism but is rarely proven. It can be hypothesized that, in those patients, paroxysmal atrial arrhythmias, potentially favored by the anatomic abnormalities, can be another cause of thrombus formation and subsequent embolism to the brain. In this study we assessed the relationship between atrial vulnerability, reflecting arrhythmogenic properties of the atria, and atrial septal abnormalities in young patients with cryptogenic ischemic stroke.

Methods—We enrolled 62 consecutive patients aged <55 years who had ischemic stroke of unknown cause and transesophageal echocardiography to assess atrial septal aneurysm (ASA) or patent foramen ovale (PFO) (ie, atrial septal abnormalities). These patients underwent electrophysiological study to measure atrial refractoriness and conduction time defining a vulnerability index (ie, latent atrial vulnerability) and to assess the inducibility of sustained (lasting >60 seconds) atrial fibrillation with the use of programmed atrial stimulation. Actual atrial vulnerability was defined by the presence of both latent vulnerability and inducibility of sustained atrial fibrillation lasting >60 seconds.

Results—We found atrial vulnerability in 58% of patients with atrial septal abnormalities and in 25% of patients without (odds ratio 4.1 [95% CI, 1.3 to 12.7; P <0.02]). The difference between patients with and without PFO or between patients with both PFO and ASA and those without were also significant. Patients with inducible sustained atrial fibrillation had more frequent past history of palpitations and syncope than patients without (P <0.02).

Conclusions—Atrial vulnerability is associated with atrial septal abnormalities in patients with cryptogenic stroke. This result raises the question of the potential role of transient atrial arrhythmias in thrombus formation in the presence of PFO or ASA. (Stroke. 2000;31:398-403.)

Key Words: heart septal defects, atrial ■ stroke, ischemic ■ young adults

Atrial septal abnormalities, ie, patent foramen ovale (PFO) or atrial septal aneurysm (ASA), are frequent findings in young patients with brain infarction of unknown cause.1–7 These abnormalities have been independently associated with ischemic stroke in case-control studies, particularly when PFO and ASA coexist.8–11 However, the causal relationship between PFO, ASA, and ischemic stroke is not established.12 Whether mural thrombus is formed locally within the atrial septum or deep venous thrombosis serves as a donor source of transcardiac cerebral emboli is still debated.12–14 Another possibility could be thrombus formation due to atrial arrhythmias, such as paroxysmal atrial fibrillation or atrial flutter.15 In the presence of ASA or ASA plus PFO, these arrhythmias have been reported in 20% to 42% of cases.15–18 Atrial fibrillation may be transient and hence very difficult to detect with standard ECG or even ambulatory Holter recording, particularly in young stroke patients in whom arrhythmias may be rare and asymptomatic. Electrophysiological predictors of atrial fibrillation are thus needed. Some authors have introduced the concept of atrial vulnerability based on the study of effective refractory periods and atrial conduction time (latent vulnerability) and inducible sustained atrial fibrillation determined during electrophysiological studies.19–21 Atrial vulnerability indeed explores the electrophysiological substrates underlying paroxysmal atrial fibrillation, which is related to multiple micro-reentrant circuits.22 Although its predictive value is still under evaluation, atrial vulnerability has been reported to be frequent in patients with stroke of unknown cause23 and more frequent in patients with cryptogenic stroke than in controls without

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ischemic stroke. We thus hypothesized that atrial vulnerability may be more frequently observed in young patients with stroke of unknown cause and with atrial septal abnormalities than in patients without septal abnormality.

Subjects and Methods
All patients aged <55 years admitted to the Neurology Department at Saint-Antoine Hospital, Paris, France, with brain infarction or transient ischemic attack were screened during a 24-month period. We enrolled consecutive patients with ischemic stroke of unknown cause. Cryptogenic ischemic stroke was defined according to criteria that we have previously described elsewhere. This diagnosis was based on an extensive workup that included, for all patients, transesophageal echocardiography, 12-lead ECG, neck ultrasound examination, transcranial Doppler, either x-ray or MR angiography, and search for hypercoagulable state. Patients qualified as having brain infarct of unknown cause were subsequently considered for inclusion in the study.

All patients were interviewed with a structured questionnaire regarding main risk factors, history of palpitations and syncope, and history of peripheral or cerebral ischemic events. All patients had a neurological examination and MRI of the brain. We noted the size, location, and number of focal ischemic lesions of the brain. Cerebral angiogram was normal in all patients except for 6 intracranial location, and number of focal ischemic lesions of the brain. Patients qualified as having brain infarct of unknown cause were subsequently considered for inclusion in the study.

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Transesophageal Echocardiography Studies
A senior echocardiographer (A.C.) performed transesophageal echo- cardiography with contrast injection in all patients following a standard protocol. In none of these patients was a definite cardiac source of embolism identified. In all patients we were able to determine the presence or absence of atrial septal abnormalities, ie, PFO or ASA. Criteria for right to left shunting were detected after intravenous administration of contrast material. The contrast material was prepared by use of 2 syringes mounted on a 3-way stopcock to mix saline or gelatin with air, and 10 mL of this mixture was injected in bolus into an antecubital vein. Three to 6 contrast injections were systematically performed in each patient, in the resting state and during provocative maneuvers (Valsalva maneuver and cough test), to transiently reverse the interatrial pressure gradient. Although most patients received slight sedation with oral midazolam (5 mg), all were able when ordered to cough vigorously and to perform a Valsalva maneuver. The echocardiographic diagnosis of PFO was based on the appearance of >5 microcavitations, either spontaneously or after provocative maneuvers, into the left atrium within 3 cardiac cycles of the total opacification of the right atrium. All diagnoses of PFO were further confirmed by transcardiac catheterization. In 1 patient no PFO was diagnosed on transesophageal echocardiography, but a transcardiac passage of the catheter occurred. This patient was finally diagnosed as having a PFO.

ASA was diagnosed when the atrial septum appeared abnormally redundant and mobile and exhibited an excursion into the left or the right atrium or both of ≥10 mm. The distance between the plane of the atrial septum and the point of maximal aneurysmal bulging was measured from the stopped-frame image. In case of phasic excursion, we considered the sum of outpouching in both atria.

ECG Studies
All patients had 12-lead ECG at admission, before and after cardiac pacing.

Electrophysiological Studies
All patients agreed to undergo an electrophysiological study to assess both latent and patent atrial vulnerability. The study was performed with patients on effective anticoagulation and in a nonsedated state. Two quadripolar electrode catheters (10-mm interelectrode distance) (USCI, Bard) were advanced via transfemoral vein catheterization in the heart. One quadripolar electrode catheter was placed in the high right atrium. The other was positioned first in the atrioventricular junction to record the basal right atrium and His bundle electrogram, then this catheter was placed either in the left atrium, in case of presence of PFO, or in the coronary sinus to record and pace the left atrium. Pacing was performed by the distal electrode pair and recording of atrial electrogram by the proximal electrode pair.

Surface ECG leads (I, II, III, V1, V6) and bipolar intracardiac electrograms filtered at 30 to 500 Hz were recorded with a polygraph (Midas 2500, Biomedical System) at paper speed of 25 and 100 mm/s. Pacing stimuli were provided by a stimulator (Explorer 2000, VPA MEDICAL) at twice the diastolic threshold and 2 ms in duration.

The study included measurement of basic conduction intervals, including AH, H, and HV intervals, determination of Wenckebach’s point of the atrioventricular node, and assessment of latent atrial vulnerability and inducibility of sustained atrial fibrillation.

Latent Atrial Vulnerability
Latent atrial vulnerability assessment included determination of the effective (ERP) and functional (FRP) right and left atrial refractory periods and measurement of duration of atrial electrogram at 3 different pacing rates: 100, 120, and 150 bpm. Refractory period was determined by means of an extrastimulus (S2) delivered with a 10-ms decremental coupling interval after 8 consecutive beats (S1S8) at a constant pacing interval. The ERP was defined as the longest attainable S1-S2 interval that did not produce atrial electrogram A2. The FRP was defined as the shortest atrial activation interval A1-A2 (ie, delay between atrial electrogram following S1 [A1] and atrial electrogram following S2 [A2]) (Figure 1). Duration of atrial electrogram (A1-A2 duration) was measured as the width of the bipolar A2 electrogram elicited by S1 extrastimulus at the FRP value.

Latent vulnerability index was defined as the ratio between ERP and A2 duration (ERP/A2) at a pacing rate of 100 bpm. This index was chosen because its predictive value for spontaneous and inducible atrial fibrillation was found to be better than that of the use of effective refractory periods or A2 duration alone.

Inducibility of Sustained Atrial Arrhythmia
Inducibility of atrial arrhythmia was assessed by programmed atrial stimulation with up to 3 extrastimuli (S3, S4, S5) during sinus rhythm and after 8 paced beats at a rate of 100 (600 ms), 120 (500 ms), and 150 (400 ms) bpm. First, 1 extrastimulus S1 was introduced late in diastole, and the coupling interval was shortened by steps of 10 ms until the ERP of the atrium was reached. Then, after the coupling of the first extrastimulus was increased by 20 ms, S2 was introduced, and the coupling interval was again shortened until no atrial depolarization was observed. The same procedure was used with S3.

Definition of Atrial Vulnerability
Latent vulnerability was defined by latent vulnerability index <2.5 (4.6 ± 1.7 in control group). Inducibility of atrial arrhythmia was defined as induction of sustained atrial arrhythmia lasting >60 seconds. Atrial arrhythmias included atrial fibrillation (82%), flutter (10%), or atrial tachycardia (8%). Atrial vulnerability was defined by the presence of both latent vulnerability and inducible atrial arrhythmia.

In 4 patients, sustained atrial fibrillation was mechanically induced by the introduction of the lead catheter into the right atrium. These arrhythmias lasted >30 minutes, and no cardioversion was performed. Since no electrophysiological parameters have been recorded and atrial fibrillation was not induced by programmed atrial stimulation, we excluded these 4 patients from the analysis, thereby including 62 patients in the series.

Statistical Analysis
Results are expressed as mean±SD. We used 2-tailed t tests and ANOVA for comparisons of means and χ² tests for comparisons of proportions.
Figure 1. A, Determination of the right atrial (RA) ERP. Top to bottom: surface ECG lead (II) followed by 8 consecutive intracardiac recordings of the same RA bipolar electrogram corresponding to the sequence used for the determination of the right atrial ERP. Pacing protocol consisted of 8 consecutive stimuli (S1) at a basic rate of 100 bpm (600 ms) followed by an extrastimulus (S2) with a 10-ms decremental coupling interval. S1-S2 value is reported in the left panel. RA ERP (230 ms) was defined as the longest attainable S1-S2 interval that does not produce atrial response. Paper speed= 100 mm/s. B, Example of RA electrogram fragmentation observed during ERP determination. Compared with the RA electrogram A1 duration during pacing at a rate of 100 bpm (600 ms), duration of the RA electrogram A2 induced by the extrastimulus S2 is lengthened and fragmented (160 versus 70 ms). This lengthening reflects an increase in local atrial conduction time, which is 1 parameter of atrial vulnerability. Top to bottom: surface ECG leads (II, V1, V6), left atrial (LA) electrogram recorded through a PFO, and RA electrogram. Paper speed=25 mm/s. C, Induction of a sustained episode of atrial fibrillation (AF) during the RA programmed stimulation protocol. AF was induced by 2 extrastimuli (S2, S3) delivered at a coupling interval of 220 and 200 ms, respectively, after 8 consecutive pacing beats (S1) at a basic rate of 120 bpm (500 ms). Top to bottom: 3 surface leads ECG (II, V1, V6), intracardiac LA electrogram recorded in the coronary sinus, and RA electrogram. Paper speed=25 mm/s.
Septal Abnormalities Cause According to Presence or Absence of Atrial Vulnerability in 62 Patients With Brain Infarction of Unknown Cause

TABLE 1. Baseline Characteristics in 62 Patients With Brain Infarction of Unknown Cause According to Presence or Absence of Atrial Septal Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>PFO and/or ASA (n=38)</th>
<th>No PFO and ASA (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>37.76±11</td>
<td>41.79±8</td>
<td>NS</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>20/18</td>
<td>13/11</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (5%)</td>
<td>4 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>18 (47%)</td>
<td>14 (58%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>3 (8%)</td>
<td>5 (21%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (2.6%)</td>
<td>1 (4.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>8 (44%)</td>
<td>4 (36%)</td>
<td>NS</td>
</tr>
<tr>
<td>Brain infarct</td>
<td>33 (87%)</td>
<td>21 (88%)</td>
<td>NS</td>
</tr>
<tr>
<td>TIA</td>
<td>5 (13%)</td>
<td>3 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>History of palpitation/syncope</td>
<td>19 (50%)</td>
<td>9 (38%)</td>
<td>NS</td>
</tr>
<tr>
<td>History of brain infarct/TIA</td>
<td>13 (34%)</td>
<td>14 (58%)</td>
<td>NS</td>
</tr>
<tr>
<td>Size of left atrium, mm</td>
<td>33.12±5</td>
<td>33.28±7</td>
<td>NS</td>
</tr>
<tr>
<td>PAP (mean)</td>
<td>26.8±5</td>
<td>25.2±5</td>
<td>NS</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack; PAP, pulmonary arterial pressure.

Results

During 40 months (February 1994 to June 1997), we found 62 patients aged ≤55 years with ischemic stroke of unknown cause who met the inclusion criteria. All 62 patients had transesophageal echocardiography, with special attention to atrial septal abnormalities. We found 38 patients (61%) with PFO, ASA, or both and 24 patients (39%) without PFO and ASA. Baseline characteristics of these 2 groups according to the presence or absence of atrial septal abnormalities are shown in Table 1. Among the 62 patients, 41 (66%) had a sustained induced atrial fibrillation lasting >60 seconds. Inducible atrial fibrillation lasted 1 to 5 minutes in 22 patients and 5 minutes to 24 hours in 19 patients. They more frequently had a history of palpitation than patients without inducible atrial fibrillation (56% versus 25%; P<0.02). Baseline characteristics were otherwise similar (data not shown). Twenty-two patients reported abnormal chest sensations during the induced atrial fibrillation (58% versus 13%; P<0.003). Among them, 14 patients a posteriori recognized a previous chest sensation that they experienced before and that was therefore reproduced by the induced atrial fibrillation. Some of them did not identify this sensation before as actual palpitation. We found significantly more inducible sustained atrial fibrillation in patients with PFO or in patients with atrial

septal abnormality than in patients without any of these abnormalities (P<0.05 for both), but 50% of patients without atrial septal abnormalities had inducible sustained atrial arrhythmia (Table 2). ERP/A2 ratio <2.5 (ie, latent atrial vulnerability) was significantly more frequent in patients with atrial septal abnormalities than in patients without (Table 2).

Atrial vulnerability (including both sustained inducible atrial fibrillation lasting >60 seconds and latent atrial vulnerability) was present in 58% of patients with atrial septal abnormalities compared with 25% of patients without (odds ratio=4.1 [95% CI, 1.3 to 12.7; P<0.02]) (Table 3). The difference between patients with and without PFO was also significant, and for patients with and without ASA alone the difference approached statistical significance (Table 3). Finally, the presence of both PFO and ASA (20 patients) was also strongly associated with atrial vulnerability compared with patients without PFO and ASA (odds ratio=4.5 [95% CI, 1.2 to 16.3; P<0.02]).

Electrophysiological parameters of right and left atria for groups with and without atrial septal abnormalities are shown in Figure 2. These findings tend to show that in the presence of atrial septal abnormalities, effective refractory periods were shorter and A2 durations were prolonged without reach-

TABLE 2. Inducible Atrial Fibrillation and Latent Atrial Vulnerability in 62 Patients With Brain Infarction of Unknown Cause According to Presence or Absence of Atrial Septal Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>PFO and/or ASA (n=38)</th>
<th>No PFO and ASA (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducible atrial fibrillation</td>
<td>29 (76%)</td>
<td>12 (50%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Latent atrial vulnerability (ie, ERP/A2 &lt;2.5)</td>
<td>25 (66%)</td>
<td>9 (38%)</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

A2 indicates duration of atrial electrogram.

Figure 2. Electrophysiological parameters of latent atrial vulnerability. Shown are ERP at 100, 120, and 150 bpm and A2 auriculo gram duration. AS+ indicates atrial septal abnormalities; R, right atrium; L, left atrium.
ing statistical significance. ERPs at a pacing rate of 100 bpm were significantly shorter in the presence of ASA than in patients without ASA (199 ± 5 versus 213 ± 4 ms; P = 0.004).

Discussion

Atrial fibrillation is the most common of all sustained cardiac arrhythmias. Experimental studies and human surgical mapping studies have shown that this arrhythmia is perpetuated by coexistence of several reentrant wavelets propagating in abnormal atrial tissue substrate. 19,25–27 This perpetuation requires a critical mass of tissue with particular electrophysiological properties allowing multiple micro-reentrant circuits. 19 In experimental models, Allessie et al 19 showed that these reentrant circuits were closely linked to a short wavelength of the atrial tissue, which is defined as the product of atrial effective refractory period by intra-atrial conduction velocity. In humans, the propensity to sustain atrial fibrillation can be expressed through the concept of atrial vulnerability, which can be assessed by programmed atrial stimulation (inducibility of sustained atrial arrhythmia) and by measurement of refractory period and conduction velocity approximated by intra-atrial conduction time. 22 These observations constituted the basis for studying latent atrial vulnerability in patients with paroxysmal atrial fibrillation, then inducibility of sustained atrial fibrillation and latent atrial vulnerability in patients with brain infarction of unknown cause. 22–24 In patients with cryptographic brain infarction, several studies found inducible atrial fibrillation in 54% to 61%, but these studies had no controls. 23,28,29 In our study the percentage of inducible sustained atrial arrhythmia (66% of 62 patients) was very comparable. Quatre et al 24 have shown that atrial fibrillation was inducible in 85% of patients with documented paroxysmal atrial fibrillation and in 85% of patients with brain infarction compared with 20% of controls. In this study they showed that latent vulnerability in patients with stroke was equivalent to that observed in a group of patients with documented paroxysmal atrial fibrillation. 22,24 This is the only case-control study in the literature. Since inducibility of sustained atrial fibrillation may be obtained in patients without abnormal electrophysiological substrate (ie, normal ERP or intra-atrial conduction time), Attuel et al 22 defined a criterion for actual atrial vulnerability combining the presence of both inducibility of atrial arrhythmia and abnormal electrophysiological substrate (latent atrial vulnerability). We used this criterion because it is more specific and restrictive than using only inducible atrial arrhythmia. We found atrial vulnerability less frequently (45% of cases) than inducible sustained atrial fibrillation lasting >60 seconds (66% of cases).

The aim of our study was to look for atrial vulnerability in a population of patients with cryptogenic stroke according to the presence or absence of atrial septal abnormalities. We found a significant association between atrial vulnerability and the presence of PFO, ASA, or both. Up to 58% of patients with atrial septal abnormalities had atrial vulnerability compared with 25% of patients without atrial septal abnormalities. These findings raise some important points of discussion about mechanisms and etiologic implications.

In animal models, mechanical atrial stretching induces cellular action potential modifications of atrium, with shortening of atrial ERPs and increased inducibility of atrial fibrillation. 30 These electrophysiological changes may be relevant to clinical atrial arrhythmias. 31 We hypothesized that atrial septal abnormalities favor local stretching of atrial septum, which could increase atrial vulnerability due to modifications of electrophysiological substrate. 30,31 Indeed, in 39 newborn children with atrial arrhythmias, ASA was found in 64% of cases compared with 26% in 66 fetuses without arrhythmia. 32 This is in agreement with the empirical observation of Hanley et al 33 that very mobile ASAs in adults were associated with atrial fibrillation. As for PFO, we can only speculate that PFO could also create hemodynamic stretching of atrial septum, particularly in cases of the Valsalva maneuver.

Our results suggest that transient atrial arrhythmias may occur in the presence of PFO or ASA and that the higher embolic risk may be due to a greater potential for paroxysmal atrial fibrillation. In our study we found that patients with inducible sustained atrial fibrillation had more frequent history of palpitations and syncope than patients without atrial vulnerability. Although this retrospective information should be viewed with caution, this result reinforces the suspicion of spontaneous arrhythmia in these patients. Interestingly, during the procedure several patients had abnormal chest sensations concomitantly with the induced atrial fibrillation that they a posteriori recognized as a sensation they previously experienced.

Although the technique of atrial pacing we used was standard, it induced atrial arrhythmia in 20% of control patients in the study of Quatre et al 24 and in 25% of our patients without atrial septal abnormalities. Further studies are thus needed to determine the risk of spontaneous atrial fibrillation in patients with atrial vulnerability.

Thus, atrial arrhythmia may play a role in causing thrombus formation and brain emboli in the presence of atrial septal abnormalities. Besides transcardiac paradoxical emboli and thrombus formation within atrial septum, atrial arrhythmia is another hypothesis for explaining the causal link between PFO or ASA and brain infarction of unknown cause. Further prospective studies are needed to assess both positive and negative predictive values of atrial vulnerability for spontaneous atrial fibrillation and for predicting clinical embolic events and hence to elaborate therapeutic strategies.

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References


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