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Frequency of Atrial Septal Aneurysm in Patients with Recent Stroke: Preliminary Results from a Multicenter Study

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Summary

Background: The role of atrial septal aneurysm (ASA) as a risk factor for cerebral ischemia of unknown etiology is controversial. Recent studies have found an association between ASA and focal ischemic events, while results from other studies suggest a low incidence of embolism in patients with ASA.

Hypothesis: The present study was designed to evaluate the frequency of ASA, a minor cardioembolic source, in patients with a recent stroke presenting with normal carotid arteries.

Methods: In all, 394 patients with cerebral ischemic stroke were referred to our institutions. Patients underwent transthracic and transesophageal echocardiography and carotid artery ultrasound examination. The study population included 215 patients without significant arterial disease. Frequency and morphologic characteristics of ASA were evaluated.

Results: Transthoracic examination showed ASA in 39 patients (18%), while transesophageal echocardiography showed ASA in 61 patients (28%). A patent foramen ovale was found in 47 patients (21.8%) and was associated with ASA in 40 patients (65.5%). We observed an increased thickness of the aneurysmatic wall (3.80 ± 1.7 mm) in all patients with ASA.

Conclusions: The present study confirms the relationship between ASA and stroke in patients with normal carotid arteries. The most common abnormality associated with ASA was patent foramen ovale. We suggest that patients who have a stroke in the absence of significant carotid disease undergo transesophageal echocardiography to identify possible underlying septal abnormalities.

Key words: atrial septal aneurysm, stroke, transesophageal echocardiography, carotid ultrasound

Introduction

Transesophageal echocardiography (TEE) has been accepted as a better method than transthoracic echocardiography (TTE) for the identification of potential cardiac causes of embolism.[1,2] In clinical practice, the most common use of TEE is for the evaluation of a suspected cardiac cause of stroke.[1] The absence of obvious cardiac causes of stroke, such as atrial fibrillation, acute myocardial infarction, and prosthetic valves, suggests the use of TEE to identify rare cardioembolic sources such as atrial septal aneurysm (ASA) or patent foramen ovale (PFO). In a multicenter study, Mugge *et al.* reevaluated the clinical significance of ASA in a large series of patients and concluded that ASA could be considered a risk factor for cardiogenic embolism in a significant subgroup of patients.[3] In the present prospective, multicenter study, adult patients with a recent stroke and with normal carotid artery and normal cerebral circulation underwent TEE in order to rule out possible cardioembolic sources. The aim of the study was to evaluate the prevalence and the morphologic characteristics of ASA, a minor cardioembolic cause of cerebral ischemia.

Methods

Patient Population

The study population included 215 of 394 patients (146 men and 69 women, mean age 63 ± 19 years, range 35–80 years) (Table I) referred to our three institutions with a clinical and instrumental diagnosis of cerebral ischemia. Inclusion criteria were (1) recent (< 7 days) ischemic stroke, (2) echocardiographic images of sufficient quality to allow evaluation of

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TABLE I Clinical characteristics of patients (n = 215)

Mean age (years)	63 ± 19
Male/female	146/69
Previous episodes of AF (%)	37 (17.2)
Heart disease (%)	30 (13.9)
Hypertension (%)	67 (31.1)
Echocardiographic LVEF (%)	61.1 ± 18
LA size (mm)	38 ± 0.9

Abbreviations: LVEF = left ventricular ejection fraction, LA = left atrium, AF = atrial fibrillation.

morphologic characteristics of ASA, and (3) normal carotid artery. Patients with cerebral hemorrhage events, chronic atrial fibrillation, acute myocardial infarction, cardiac valve prosthesis, and mitral stances were excluded from the study. The Ethical Committee of the University of Modena and Reggio Emilia approved the study protocol and informed consent was obtained from all participants.

Neurological Evaluation

A clinical diagnosis of transient ischemic attack or stroke, established by a trained neurologist, was used.[4,5] A computed tomographic (CT) scan was performed in all patients. Patients with evidence of mass or hemorrhage on head CT scan were excluded from the study. Stroke was defined as the sudden development of a permanent focal neurological deficit, after which a brain CT scan established a cerebrovascular accident as the cause; TIA was defined as an ischemic attack that resolved completely in 24 h.[6]

A cardioembolic source was suspected on clinical findings, brain imaging, and normal duplex carotid and vertebral ultrasound examination.

Echocardiography

All patients underwent complete TTE and TEE studies 1 to 7 days after the cerebral ischemic event. A commercial Hewlett Packard (Agilent Technologies, Andover, Mass., USA) system with 2.5 and 3.5 MHz probes and a 5 MHz multiplane frequency probe with color Doppler and spectral pulsed Doppler was used. Standard views from the gastric and lower esophageal windows were obtained in every patient. All patients who underwent TEE were given diazepam and pharyngeal xylocaine.

Cardiac abnormalities and potential cardiac source were evaluated as follows: thrombi in the left atrium or appendage, spontaneous echo contrast, and complicating aortic plaque.[7] Atrial septal aneurysm was defined as a bulge of > 15 mm beyond the plane of the atrial septum as measured by TEE. Atrial septal aneurysm was classified according to Hanley's diagnostic criteria as modified by Pearson.[8,9] The type of aneurysm was determined according to morphology and bulging: Type 1A: constant protrusion toward the right atrium; Type 1B: protrusion predominantly to the right with movement toward the left atrium in systole; Type 1C: protrusion toward the left atrium with Valsalva; Type 2C: fixed protrusion toward the left atrium.

The following parameters were also evaluated: length of the ASA, maximal protrusion of the ASA beyond the plane of the atrial septum, direction of the maximal protrusion, oscillation of the ASA during normal respiratory cycle, and thickening of the ASA. Patent foramen ovale (PFO) was diagnosed using a rapid hand injection of 5 cc solution of emagel through an antecubital vein. Injection was repeated for each patient during Valsalva release, and the contrast was considered positive if it showed a paradoxical shunt across the interatrial septum.[7]

Carotid and vertebral ultrasound studies were performed with a linear 7.5 MHz probe. Patients were excluded if they presented a vessel stenosis > 15% in the carotid or vertebrobasilar systems.

Statistical Analysis

Continuous variables are presented as means ± standard deviation. Echocardiographic variables were screened by the log-rank test to identify those associated with stroke. A multivariate linear model was used to test the association between stroke and atrial septal aneurysm and other variables. A p value of < 0.05 was considered significant.

Results

Of the study population of 215 patients, 112 had TIA and 103 had stroke. A head CT scan confirmed the clinical diagnosis. All patients underwent Doppler carotid study that excluded carotid artery stenosis.

Transthoracic examination was performed in all patients and showed ASA in 39 patients (18%), while TEE showed ASA in 61 patients (28%). A PFO was detected in 47 patients (21.8%) and was associated with ASA in 40 patients (65.5%). Mitral valve prolapse was observed in 53 patients (24.6%) and was associated with ASA in 8 patients (15%) (Table II). A

TABLE II Prevalence of potential cardioembolic sources in the transesophageal echocardiography study

	No. of patients (%)
Without cardiac source	30 (13.9)
Thrombus in LA or AU	23 (10.7)
Spontaneous echo contrast	40 (18.6)
Aortic debris	43 (20)
Vegetations	3 (1.4)
Mitral valve disease	27 (12.5)
Mitral valve prolapse	53 (24.6)
Mitral annulus calcification	20 (9.3)
Atrial septal aneurysm	61 (28)
Patent foramen ovale	47 (21.8)

Abbreviations: LA = left atrium, AU = appendage.

TABLE III Characteristics of atrial septal aneurysms as determined by transesophageal echocardiography (n = 61)

Length of ASA, mm	25.3 ± 7.4
Extent of protrusion, mm	13.9 ± 2.1
Oscillation present, n	30
Type IA, n (%)	9 (14.7)
Type IB, n (%)	37 (60.6)
Type IC, n (%)	11 (18)
Type II, n (%)	4 (6.5)
Thickness, mm	3.80 ± 1.7
Association with PFO, n (%)	40 (65.5)
Association with mitral valve prolapse, n (%)	17 (27.8)

Abbreviations: ASA = atrial septal aneurysms, PFO = patent foramen ovale.

multivariate linear model showed that the combined variables ASA and PFO were significantly associated with the risk of stroke ($F = 225$; $p < 0.001$).

The most frequent type of ASA was type IB followed by type IC. Atrial septal aneurysm characteristics including length, maximal extent of protrusion, predominant side of bulging, and incidence of spontaneous oscillation are shown in Table III. An increased thickness of the aneurysmatic wall (3.80 ± 1.7 mm) was observed in all patients with ASA. Left atrial thrombi, spontaneous echocontrast, and mitral annulus calcifications were identified as another potential source of embolism (Table II).

The only possible cardioembolic sources in patients aged < 45 years were the presence of ASA (13 cases) and mitral valve prolapse (17 cases; in four patients it was associated with ASA).

Discussion

The present study evaluated the prevalence of ASA in a population with stroke and normal carotid arteries undergoing TEE to evaluate potential underlying cardioembolic source. One conclusion of the study is that underlying cardioembolic causes are common in patients with a recent stroke. Atrial septal aneurysm was more frequent in patients with a previous stroke and was an independent predictor of embolic events. Another conclusion is that ASA was the only potential cardioembolic source in patients aged < 45 years.

An aneurysm of the interatrial septum is rare in the adult population. The clinical impact of this cardiac anomaly is unclear, but several papers suggest a potential causative role in cerebral ischemia.[10, 11] The incidence of ASA in the normal population varies in different studies because of different diagnostic criteria, methodologies used, and the age of the patient population. Autoptic studies have reported an incidence of 1% in the normal population over a 4-year period; these data are in contrast with the data of several clinical studies in living patients.[12–14] The estimated incidence of ASA varies from 3 to 10% in TEE studies.[13, 14] In the present study, the frequency of ASA was 28% in a patient population evaluated shortly after an embolic event. Other investigators have observed that a number of patients with ASA presented with cerebral ischemic events that were otherwise unexplained.[14, 15] Nighoghossian *et al.* found ASA in 34.5% of 79 patients who had an unexplained stroke.[15] A recent study from the Mayo Clinic found a prevalence of 7.7% of ASA in patients with a cerebral embolic event.[14] In the present study, the most frequent type of ASA was type 1B, which occurred in 59% of the patients; these data are consistent with the literature.[9] Hanley *et al.* suggested that an aneurysm of the interatrial septum protrudes toward the atrium, where the pressure is lower. With a type 2 aneurysm, higher pressure should exist on the right, and there should be a pathologic condition of the right heart.[8]

The Thickness of the Aneurysm

Schneider *et al.*[13] reported that a thickness of > 5 mm was associated with a statistically significantly higher embolic risk; in contrast, Pearson *et al.*[2] found that thickness was greater in the group of patients without stroke. Mugge *et al.* evaluated 195 patients with ASA and found the aneurysm to be of normal thickness; nevertheless, they did not exclude the possibility that microthrombi were attached to the ASA.[3] In the current study, we found an increased thickness of the atrial aneurysm wall. Since it was done in patients with a recent embolism, it is possible that thrombotic material is present on the aneurysm in this early phase of events.

Association with Patent Foramen Ovale and Mitral Valve Abnormalities

An association between ASA and PFO has been documented by many authors.[16–19] Cabanes *et al.* found a strong association in a selected group of young patients, of whom 72% had both cardiac abnormalities.[17] They concluded that each of the two cardiac disorders contributes significantly to the risk of stroke and that their association has a synergistic effect. The exact mechanism of stroke in patients with ASA is unknown but, on the basis of the frequent association between ASA and PFO, paradoxical embolism has been suggested to be a cause of cerebral ischemia.[17, 18] We observed a PFO in 47 patients (21.8%), and PFO was associated with ASA in 40 patients (65.5%). The induction of a paradoxical shunt using the Valsalva maneuvers during TEE must be underlined, as it occurred in three of our patients who had cerebral embolization during spontaneous Valsalva.

Clinical Impact and Management

The diagnosis of ASA by TEE in a patient with a previous ischemic attack may alter patient management. Patients with ASA have a recurrent event rate of 14 to 20% at 3 years.[3, 20] Preliminary data from Spes *et al.* suggest that patients with ASA have a lower recurrent stroke rate when treated with warfarin rather than with antiplatelet agents.[20] The association with PFO strongly increases the risk of a recurrent episode.[21]

Preliminary studies suggest that the rate of recurrence can be reduced by mechanical closure of the PFO.[22] No data are available on the impact of surgical intervention on ASA, even though this technique has been suggested for young patients who have no other indication for stroke.

Conclusion

Atrial septal aneurysm is an important cardioembolic source of cerebral ischemia in patients with normal carotid arteries. The association with PFO could explain the possibility of paradoxical embolization without clinical evidence of pulmonary embolization. We observed an increase in the thickness of the aneurysmal membrane, which supports the theory that a stratified thrombus is associated with increased embolic risk. The increased risk suggests the use of anticoagulant or antiplatelet therapy in patients with ASA and PFO. In addition, in young patients subject to TIA relapse, surgical intervention should be considered.

Appendix 1

Investigators

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