Original articles

The association between atrial septal aneurysm and mitral valve prolapse in patients with recent stroke and normal carotid arteries

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Key words:
Aneurysm;
Atrial septal defect;
Mitral valve prolapse;
Stroke.

Background. **The association between mitral valve prolapse (MVP) and cryptogenic stroke is controversial. The Atrial Septal Aneurysm Multicenter Italian (ASA-MI) Study is a prospective multicenter study evaluating the prevalence of atrial septal aneurysm (ASA) in patients with a recent stroke and normal carotid arteries. The aim of the present research was to evaluate the frequency of ASA and its association with MVP in the stroke population and in the subgroup of young patients (< 55 years) included in the ASA-MI Study.**

Methods. **The study group included 245 of the 606 patients referred for transesophageal echocardiography (168 men and 77 women, mean age 65.7 ± 21 years). All patients were selected on the basis of a recent episode of unexplained cerebral ischemia and were included in the study if they had normal carotid arteries. The control population included 245 patients (mean age 64.7 ± 23 years) who underwent transesophageal echocardiographic evaluation during the same period for indications other than cerebral ischemia. The subgroup of young patients (< 55 years) included 90 patients (61 men and 29 women, mean age 49 ± 5 years).**

Results. **The prevalence of MVP was 18% (95% confidence interval 8 to 21%) in the stroke population and 15% (95% confidence interval 7 to 20%) in the control population ($\chi^2 = 2.1$, p = NS). The prevalence of MVP did not differ between young stroke patients (28.8%) and young controls (20%) ($\chi^2 = 0.835$, p = 0.3). MVP was not significantly associated with stroke. We found an association between ASA and MVP: there was a higher incidence of MVP in stroke patients with an ASA than in patients without stroke or an ASA (40.9 vs 25%, p < 0.05). There was also a higher frequency of MVP associated with ASA in the group of young patients than in all patients of the ASA-MI Study (28.8 vs 18%, $\chi^2 = 20.313$, p < 0.001).**

Conclusions. **We found an association between ASA and MVP in patients with recent stroke and this association bore a higher risk of cerebral events than in patients without these abnormalities.**

(Ital Heart J 2003; 4 (9): 602-606)

Received February 13, 2003; revision received July 7, 2003; accepted July 22, 2003.

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Background

Mitral valve prolapse (MVP) has been associated with cryptogenic ischemic stroke in young patients but the causal link has not yet been established[1-3]. Recently, a study by Gilon et al.[4] underlined the lack of any association between MVP and stroke. These different results depend on the diagnostic criteria for MVP and on patient selection. A recent paper from the Framingham Heart Study found similar incidences of atrial septal aneurysm (ASA) in the MVP and non-MVP subjects[5]. Hospital-based studies have reported an association between ASA and MVP in patients with previous stroke[6,7]. Previous reports described a higher prevalence of ASA in patients with MVP compared with the control population (9 vs 0.2 to 3%)[7,8]. The Atrial Septal Aneurysm Multicenter Italian (ASA-MI) Study is a prospective multicenter study evaluating the prevalence of ASA in patients with normal carotid arteries who had recently suffered from stroke[9]. The aim of the present research was to evaluate the frequency of ASA and its association with MVP in the stroke population and in the subgroup of young patients (< 55 years) included in the ASA-MI Study.

Methods

Study population. *ASA-MI Study.* The ASA-MI Study evaluated the prevalence of ASA and other cardioembolic sources in

patients with normal carotid arteries who had recently suffered from stroke. The study group included 245 patients referred for transesophageal echocardiography (168 men and 77 women, mean age of 65.7 ± 21 years, group A). All patients were selected on the basis of a recent episode of unexplained cerebral ischemia and were included in the study if they had normal carotid arteries. The exclusion criteria were significant carotid stenosis, chronic atrial fibrillation, mitral valve stenosis and prosthesis, and evidence of a mass or hemorrhage on a computed tomographic head scan. The control population included 245 patients (mean age 64.7 ± 23 years, group B) who underwent transesophageal echocardiography during the same period for indications other than cerebral ischemia[9].

Young patients. This subgroup of young patients aged < 55 years included 90 patients (61 men and 29 women, mean age 49 ± 5 years) (group AY).

This group was evaluated and compared with an age- and sex-matched control population (61 men and 29 women, mean age 48 ± 6 years) (group BY).

Neurologic evaluation. Trained neurologists established a clinical diagnosis of a cerebral ischemic event in the stroke patients. Cerebral ischemia was classified on the basis of previously published criteria[10] as:
- stroke: the sudden development of a permanent focal neurological deficit after which a brain computed tomographic scan establishes a cerebrovascular accident as the cause;
- reversible ischemic attack, with complete or almost complete recovery without the need for therapeutic rehabilitation;
- transient ischemic attack, which resolves completely within 24 hours;
- reversible ischemic neurological deficit, in which full clinical recovery occurs within 7 days.

All patients had a computed tomographic scan. A cardioembolic source was suspected on the basis of clinical findings, brain imaging and of a normal duplex carotid ultrasound examination.

Transthoracic and transesophageal echocardiography. All transthoracic and transesophageal studies were performed during the same period of time and within 24 hours of each other in each patient. In patients of group A the examinations were performed 1 to 7 days after the cerebral ischemic event. A commercial Hewlett Packard system with 2.5 and 3.5 MHz probes and a 5 MHz biplane or multiplane frequency probe with color Doppler and spectral pulsed Doppler was used. Standard views from the gastric and lower esophageal windows were obtained for every patient. All patients who underwent transesophageal echocardiography were given diazepam and pharyngeal xylocaine[11].

ASA was defined as a bulging > 15 mm beyond the plane of the atrial septum as measured at transesophageal echocardiography. ASA was classified according to Hanley's diagnostic criteria, modified by Pearson et al.[12]. The type of aneurysm was determined according to its morphology and bulging. The following parameters were also evaluated: the length of the aneurysm, the maximal protrusion beyond the plane of the atrial septum, the direction of the maximal protrusion, the presence of an oscillation during a normal respiratory cycle, and thickening of the ASA. Patent foramen ovale was defined when an interatrial right-to-left shunt was detected. For contrast imaging, a saline solution was agitated and injected through an antecubital vein both with the patients at rest and during provocative maneuvers (Valsalva maneuver and coughing). Multiple injections of agitated saline were performed. The appearance of > 3 microbubbles in the left atrium was considered as diagnostic of a right-to-left shunt.

MVP was evaluated at two-dimensional transthoracic echocardiography. The displacement of the anterior and posterior leaflets was measured in the parasternal and apical long-axis views. Since the lateral scallop of the posterior leaflet is very difficult to measure from these views we also evaluated the displacement of this leaflet in the apical 4-chamber view. The thickness of the mitral leaflets during diastasis was measured from the leading to the trailing edge of the thickest area of the mid portion of the leaflets. Prolapse was diagnosed if the displacement was > 2 mm but the maximal thickness was < 5 mm[4,13].

Unileaflet prolapse was diagnosed when prolapse or flail of one leaflet was apparent. Bileaflet prolapse was diagnosed when prolapse or flail of both leaflets was observed. The combination of MVP with a color Doppler flow jet of mitral regurgitation was also evaluated.

Carotid ultrasonography was performed using a 7.5 MHz linear array probe. Transverse and longitudinal images were obtained with two-dimensional, color and pulsed Doppler imaging. The categories of carotid disease were based on published criteria: normal (< 1% stenosis), mild stenosis (< 49%), moderate stenosis (50-79%), and severe stenosis (80-99%)[14]. Patients were excluded from the study if they presented a more than mild stenosis.

All measurements were obtained off-line using standard echocardiographic measurement software and techniques.

Statistical analysis. Continuous variables are presented as means ± SD. Differences between groups in the prevalence of transesophageal echocardiographic findings were tested using χ^2 analysis and, for small numbers, using the Fisher's exact test. Comparison of continuous variables was performed using the unpaired Student's t-test. Echocardiographic variables were screened using the log-rank test to identify those associated with stroke. The variables with significant independent predictive values were identified. The odds ra-

tio was defined as the relative likelihood of developing ischemic events. In the stepwise logistic regression analyses we used a model with MVP and ASA as independent variables and stroke as a dependent variable. To assess the role of MVP and ASA independently of or in association with each other, we used a model with isolated MVP, isolated ASA and both abnormalities as independent variables and stroke as dependent variable.

The Ethics Committee of our University approved the study protocol and informed consent was obtained from all participants.

Results

The clinical characteristics of the patients are shown in table I. The mean age, sex and frequency of stroke risk factors did not significantly differ between the two groups of patients. At the time of echocardiographic examination, all patients were in sinus rhythm and none had an intracardiac thrombus.

Seventy-five percent of the patients of group A had unileaflet prolapse and 25% had bileaflet prolapse. In the group of young patients with stroke, 34.6% had bileaflet prolapse. The echocardiographic data are shown in table II.

The prevalence of MVP was 18% (95% confidence interval 8 to 21%) in the stroke population and 15% (95% confidence interval 7 to 20%) in the control population (χ^2 =2.1, p = NS). The prevalence of MVP did not differ between young stroke patients (28.8%) and young controls (20%) (χ^2 = 0.835, p = 0.3). MVP was not significantly associated with stroke (Fig. 1).

Table II. Echocardiographic features of mitral valve prolapse.

	Group A (n=44)	Group B (n=37)
Unileaflet mitral valve prolapse	33 (75%)	27 (73%)
Bileaflet mitral valve prolapse	11 (25%)	10 (27%)
Mild mitral regurgitation	8 (18%)	7 (19%)
Moderate mitral regurgitation	4 (9%)	6 (16%)
Anterior leaflet thickness (mm)	5.02 ± 0.2	4.6 ± 0.1
Posterior leaflet thickness (mm)	5.7 ± 0.1	4.9 ± 0.2
Anterior leaflet length (mm)	27 ± 0.5	28 ± 0.4
Posterior leaflet length (mm)	19 ± 0.2	20 ± 0.3
Mitral annular diameter (mm)	37 ± 0.5	35 ± 0.6
Mitral annular calcification	10 (22%)	11 (29%)

Table I. Clinical characteristics of patients.

Variable	Group A (n=245)	Group B (n=245)	Group AY (n=90)	Group BY (n=90)
Age (years)	65.7 ± 21	64.7 ± 23	49 ± 5	48 ± 6
Sex (M/F)	168/77	168/77	61/29	61/29
Systemic hypertension (%)	31.8	27.8	15.5	17.7
Heart disease (%)	14.2	11.9	3	4
Previous episodes of atrial fibrillation (%)	17.1	14.3	20	16
Left atrial antero-posterior diameter (mm)	38 ± 0.9	39 ± 0.8	37 ± 1.2	36 ± 1.5
Left ventricular ejection fraction (%)	61.1 ± 18	60 ± 19	58 ± 11	59 ± 10
Patent foramen ovale	56 (22.8%)	24 (9.8%)	55.5 (50%)	27.7 (25%)

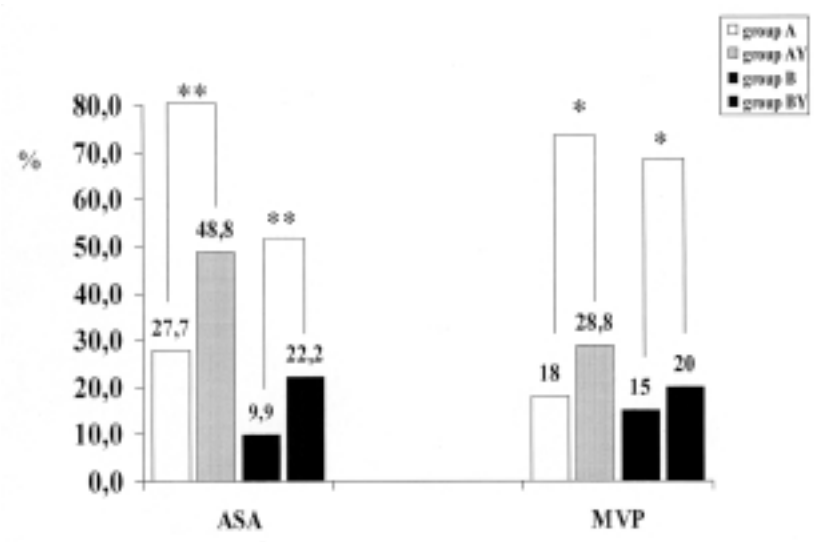

Figure 1. *Prevalence of atrial septal aneurysm (ASA) and mitral valve prolapse (MVP). Comparison within groups.*

However, we found an association between ASA and MVP: there was a higher incidence of MVP in stroke patients with an ASA than in patients without stroke and an ASA (40.9 vs 25%, $p < 0.05$). There was also a higher frequency of MVP associated with ASA in the group of young patients than in all patients of the ASA-MI Study (28.8 vs 18%, $\chi^2 = 20.313$, $p < 0.001$).

The morphological features of patients with MVP and ASA were compared with those of patients with isolated ASA. The ASA involved the entire septum in 75% of patients with ASA plus MVP compared with 25% of patients with isolated ASA ($p < 0.01$). In patients with ASA plus MVP the aneurysm bulged predominantly toward the right atrium in 26 patients and toward the left atrium in 23 patients. A similar distribution was reported in control patients with isolated ASA. There was no significant association with age, sex, cigarette smoking, and stroke risk factors.

The prevalence of patent forame ovale was 56% (95% confidence interval 43 to 62%) in patients with MVP and ASA and 22% in patients with ASA but without MVP (95% confidence interval 17 to 35%) ($\chi^2 = 3.857$, $p < 0.05$).

In the total population of the ASA-MI Study, stepwise logistic regression analysis with MVP and ASA as the independent variables and stroke as the dependent variable showed that ASA was significantly associated with stroke (odds ratio 14.72, 95% confidence interval 2.1-87). MVP was not significantly associated with stroke. The analysis with ASA and MVP independently of or in association with each other as the independent variables and stroke as the dependent variable identified MVP in association with ASA as the best predictor of stroke (odds ratio 2.6, 95% confidence interval 1.9-4.0, $p < 0.01$). Isolated MVP was not selected as a significant predictor of stroke.

Discussion

Community studies analyzed the natural history and the prevalence of MVP in the general population and found heterogeneous data[15,16]. The present paper evaluated the clinical impact of the association between ASA and MVP in a selected population of patients with a recent cryptogenic stroke[9]. We observed an association between ASA and MVP in patients with stroke and patients with both anomalies had a higher risk of stroke compared to patients without this association.

The role of MVP as a risk factor for stroke is controversial. Several studies reported an association between MVP and stroke[2,3,17,18]. Many reports underlined the high prevalence of MVP in young patients with unexplained cerebral ischemia; conversely another study by Gilon et al.[4] concluded that the prevalence of MVP in young patients is low and is not associated with cerebral events. Skepticism on the role of MVP in the development of stroke is the consequence of the low frequency of cerebral ischemia in patients with this disease. The prevalence of MVP in young patients with stroke varies widely in different reports and ranges between 2 to 40%[2,18]. Devereux et al.[19] reported that MVP occurs infrequently in the community with a prevalence of 1 to 2% among adults.

In the present study isolated MVP was not associated with stroke and the frequency of MVP was similar in patients with a recent cerebral ischemic event and control patients. The subgroup of young patients with stroke showed a higher frequency of MVP as compared with older patients. These features could depend on patient selection. Patients with carotid artery stenosis were excluded from the study and this led to a selection bias that involved older patients more than younger ones. We also found that the association between ASA and MVP was more frequent in patients with a recent stroke compared to controls. This investigation has a strong limitation in the selection criteria of the study population. The incidence of the association between ASA and MVP cannot be generalized to other patient populations. Additional long-term investigations are needed to explore the risk of stroke in patients with MVP.

The mechanism of stroke in patients with MVP and ASA is unknown. It has been suggested that ASA, isolated or in association with other cardiac abnormalities, may cause arterial embolism[20,21]. Different mechanisms could be involved in the development of stroke in patients with ASA. The ASA itself is a direct source of thrombi due to the presence of thrombotic material attached to the atrial septum[21]. An increased thickness of the ASA was found in patients with bileaflet MVP; thrombi could be attached to the left side of the interatrial septum suggesting a direct mechanism for cerebral ischemia. Another mechanism of stroke is paradoxical embolism through an interatrial communication; i.e. a patent foramen ovale. MVP and supraventricular arrhythmias have been found to be associated with ASA[21]. The pathophysiology could be an increased atrial vulnerability[22]. Atrial septal abnormalities favor local stretching of the atrial septum and induce electrophysiological changes that increase atrial vulnerability[23]. These results support the hypothesis that transient supraventricular arrhythmias may be at the origin of embolic events in patients with atrial septal abnormalities and MVP[22].

Clinical implications. The risk of stroke associated with isolated MVP is very low and does not suggest prophylactic treatment for primary prevention. Patients with a previous cerebral event need prophylactic treatment independently of the presence of MVP. If there are no causes of stroke other than MVP, an accurate evaluation of the coagulation status could be useful[24]. The results of our study suggest that the association between ASA and MVP in young patients carried a high risk of stroke. Few data are available on the therapeutic

approach to patients with MVP and ASA. The STEP study evaluates the role of aspirin compared to warfarin in patients with cerebral ischemia[25]. The treatment was nonrandomized, but was defined after transesophageal echocardiography. This may have influenced the decision-making. The study showed that warfarin offers better secondary prevention than aspirin and the effects are more evident in the presence of aortic plaque and left ventricular enlargement[25]. Anticoagulant therapy may be indicated in patients with stroke which is unexplained by carotid disease. In young patients the association between ASA and patent foramen ovale carried an increased risk of stroke. These patients are likely to be treated with anticoagulant therapy.

Appendix

ASA-MI Study Investigators

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- Department of Cardiology, Modena: Emma Tarabini Castellani, MD; Silvia Bonatti, MD; Mauro Zennaro, MD
- Department of Neuroradiology, Modena: Paolo Carpeggiani, MD

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