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Left Atrial Dysfunction in Patients With Patent Foramen Ovale and Atrial Septal Aneurysm

An Alternative Concurrent Mechanism for Arterial Embolism?

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Objectives We postulate that, in patients with large patent foramen ovales (PFO) and atrial septal aneurysms (ASA), left atrial (LA) dysfunction simulating "atrial fibrillation (AF)-like" pathophysiology might represent an alternate mechanism in the promotion of arterial embolism.

Background Despite prior reports concerning paradoxical embolism through a PFO, the magnitude of this phenomenon as a risk factor for stroke remains undefined, because deep venous thrombosis is infrequently detected in such patients.

Methods To test our hypothesis, we prospectively enrolled 98 consecutive patients with previous stroke (mean age 37 ± 12.5 years, 58 women) referred to our center for catheter-based PFO closure. Baseline values of LA passive and active emptying, LA conduit function, LA ejection fraction, and spontaneous echocontrast (SEC) in the LA and LA appendage were compared with those of 50 AF patients as well as a sex/age/cardiac risk-matched population of 70 healthy control subjects.

Results Pre-closure PFO subjects demonstrated significantly greater reservoir function as well as passive and active emptying, with significantly reduced conduit function and LA ejection fraction, when compared with AF and control patients. Furthermore, in PFO patients, 66.3% (65 of 98) had moderate-to-severe ASA and basal shunt; SEC was observed in 52% of PFO plus ASA patients before closure. Multivariate stepwise logistic regression revealed moderate-to-severe ASA (odds ratio: 9.4, 95% confidence interval: 7.0 to 23.2, $p < 0.001$) as the most powerful predictor of LA dysfunction. After closure, all LA parameters normalized to the levels of control subjects: no SEC, device-related thrombosis, or aortic erosion were observed on follow-up echocardiography.

Conclusions This study suggests that moderate-to-severe ASA might be associated with LA dysfunction in patients with PFO. The resultant similarities to the pathophysiology of AF might represent an additional contributing mechanism for arterial embolism in such patients. (J Am Coll Cardiol Intv 2009;2:655–62) © 2009 by the American College of Cardiology Foundation

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Despite numerous reports regarding the association of arterial embolism with patent foramen ovale (PFO) (1–3), the causality of paradoxical embolism remains speculative in many cases. The true impact of this phenomenon as a risk factor for stroke in such patients with PFO is unknown, because deep vein thrombosis is frequently not identified in these individuals (4). The diagnostic accuracy for detection of small thrombi might, however, be limited by standard available techniques. Because patients with presumed paradoxical embolism frequently share functional features with

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those with atrial fibrillation (AF), such as impairment of the left atrial (LA) function, we postulate that an "AF-like" physiology might contribute to LA thrombosis and subsequent arterial embolism. Thus, we assessed the presence of classical LA anatomic and functional predictors of AF and stroke such as LA dysfunction, LA spontaneous echocontrast (SEC) or thrombosis, and reduced left atrial appendage (LAA) velocity amongst control subjects and AF and PFO patients before and after percutaneous closure.

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
ICE = intracardiac echocardiographic
LA = left atrium/atrial
LAA = left atrial appendage
OR = odds ratio
PFO = patent foramen ovale
SEC = spontaneous echocontrast
TCD = transcranial Doppler
TEE = transesophageal echocardiography
TTE = transthoracic echocardiography

Methods

We prospectively enrolled 98 consecutive patients (mean age 37 ± 12.5 years, 58 women) with previous stroke who had been referred to our center for catheter-based closure of interatrial shunts according to standard indications (5) over a 36-month period (Table 1). Written informed consent was obtained from all patients enrolled in the study.

Echocardiographic protocols and definitions. Transthoracic (TTE) and transesophageal echocardiography (TEE) was conducted with a GE Vivid 7 (General Electric Corp., Norfolk, Virginia) 1 month before the procedure and repeated 1 month after closure: LA volumes and function as well as shunt degree as assessed by contrast injection and Valsalva maneuver under local anesthesia were recorded (6).

The LA passive and active emptying, LA conduit function, and LA ejection fraction were evaluated by TTE before and 1 month after PFO closure. Assessed parameters included: LA volumes as determined at the mitral valve opening (maximal, Vmax), at the onset of atrial systole (P-wave of the electrocardiogram, Vp), and at mitral valve closure (minimal, Vmin) from the apical 2- and 4-chamber views by means of the biplane area-length method via software within the system. The following formula was used to calculate LA volume (7,8): volume = 8 × 4 × Ach (A2ch/3Π) × common length (where A4ch and A4ch = LA area in 4- and 2-chamber views, respectively). The LA functional parameters were calculated as described in Table 2. The LA ejection fraction served as a measure of LA systolic performance; and acceleration and deceleration times of systolic phase of pulmonary venous flow corresponded to LA relaxation and compliance, respectively.

The LAA peak flow velocity as well as SEC or thrombosis in LA and LAA were also evaluated among the 3 groups, because low LAA peak flow velocity and SEC have been associated with risk of stroke (9,10). The pre- and post-operative echocardiographic findings were blindly evaluated by 2 blinded physicians.

Intracardiac echocardiography protocol. Patients who fulfilled the criteria for PFO closure underwent intraprocedural intracardiac echocardiographic (ICE) assessment with the mechanical 9-F 9-MHz UltraICE catheter (EP Technologies, Boston Scientific Corporation, San Jose, California). The ICE study was conducted as previously described (11,12), by performing a manual pull-back from the superior vena cava to the inferior vena cava through 5 sectional planes. The ICE monitoring of the implantation procedure was conducted in the 4-chamber plane. Special attention was posed in visualizing potential smoke-like phenomenon in the LA before closure with standard gray-scale set-up, although the eventual thrombogenic process might be of a minor entity than in patients with AF or rheumatic disease and thus probably difficult to visualize by TEE.

Closure protocol. Combined antibiotic therapy (gentamicin 80 mg plus ampicillin 1 g or Vancomicin 1 g if allergy had been recorded on anamnesis) was administered intravenously 1 h before the procedure. The right femoral vein was catheterized through an 8-F sheath and used for pre-closure right heart catheterization; the sheath was subsequently replaced with a 10- or 12-F long sheath for device implantation. The left femoral vein was catheterized with an 8-F sheath and replaced with a precurved 9-F long sheath for ICE study.

Intraoperative closure criteria and device selection. On the basis of ICE study and the presence/absence of moderate-to-large ASA and long tunnel-like PFO (tunnel length ≥12 mm), the operators selected either the Amplatzer Occluder family (PFO Occluder, Cribriform Occluder, AGA Medical Corporation, Golden Valley, Minnesota) or the Premere Closure System (St. Jude Medical Inc. GLMT, St. Paul, Minnesota), as previously described (13). The Amplatzer family, a well-known device composed of 2 parallel nitinol wire-mesh disks was selected in cases of ASA, because its more rigid design offered superior interatrial septal stabilization, as previously suggested (14). The PFO Occluder was