Incidence of Thrombus Formation on the CardioSEAL and the Amplatzer Interatrial Closure Devices

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Transcatheter closure for atrial septal defect (ASD) and patent foramen ovale (PFO) is a promising alternative to surgical closure or anticoagulant therapy. A potential complication is thrombus formation on the device after implantation. From February 2001 to June 2003, 66 patients with atrial communication were treated successfully with the Amplatzer device (16 septal and 20 PFO occluders) or the CardioSEAL device (30). Patients were discharged on antiplatelet medication (aspirin and clopidogrel) and/or anticoagulation. Fifty patients (76%) had transesophageal echocardiography (TEE) 1 month after device implantation (28 ± 10 days). No patient experienced a thromboembolic episode during follow-up. TEE revealed that thrombus formation occurred more frequently on the CardioSEAL device (5 of 23 patients; 22%) than on the Amplatzer device (0 of 27 patients; 0%) (p = 0.02). Although thrombus disappeared or markedly diminished after additional anticoagulation therapy in 3 patients, 1 patient had surgical explantation of the device due to progressive increase in the size of thrombus with hypermobility despite intensive anticoagulation therapy. There was no variable associated with the presence of thrombus formation on the occluder other than the use of the CardioSEAL device. One month after insertion, the CardioSEAL device is more likely to have thrombus present than the Amplatzer device. ©2004 by Excerpta Medica, Inc.

METHODS

Patient population: From February 2001 to June 2003, 66 consecutive adult patients underwent transcatheter closure of an interatrial communication using the CardioSEAL or the Amplatzer device. Indications for PFO closure included: (1) the presence of a large left to right shunt (Qp/Qs ratio >1.5) and an enlarged right-sided cardiac chamber detected by echocardiography, with or without symptoms, or (2) a history of ≥1 cryptogenic stroke or transient ischemic attack.

Before treatment, the benefits and risks associated with transcatheter closure compared with other treatment options (anticoagulation or surgical closure) were explained. Patients were permitted to receive a PFO closure device only after consenting to the institutional review board protocol for use of these devices under the Humanitarian Device Exemption guideline.

Device descriptions: The Amplatzer occluder device is a self-expandable, double-disk device with a connecting waist made from a Nitinol wire mesh (0.004 to 0.0075 in). Dacron patches are sewn within each disk and the connecting waist, which serve to occlude blood flow through the device. The Amplatzer septal occluder device is available in sizes measured by the diameter of the connecting waist, ranging from 4 to 40 mm. The Amplatzer PFO occluder device comes in only 2 sizes, 25 and 35 mm, which describe the diameter of the larger right atrial disk. The CardioSEAL device is also a self-expanding device, which consists of 2 square “umbrellas” made by Dacron cloth that are attached to each other in the center. Each umbrella is supported by 4 nitinol spring arms radiating from the center of the device. The CardioSEAL device sizes, measured by the length of the diagonal of an umbrella, are 17, 23, 28, 33, and 40 mm.

Patients with ASD were treated with the Amplatzer septal occluder. When treating patients with a PFO, either the Amplatzer PFO occluder or the Cardio-
The PFO occluder was approved available until November 2002 when the Amplatzer institution in February 2001 and was the only device. The CardioSEAL device became available at the discretion of the operator. The CardioSEAL device was chosen instead of the Amplatzer.

**Procedure:** Patients were usually given aspirin (81 to 325 mg/day) and clopidogrel (75 mg/day) a few days before the procedure. When a patient had been taking warfarin, warfarin was discontinued 4 days before the procedure. The initial 5 consecutive patients had the procedure performed under general anesthesia with endotracheal intubation due to concerns about aspiration during prolonged TEE performance in the supine position. However, the procedures subsequent to August 2001 were performed without general anesthesia. TEE was used to guide the procedure to achieve an activated clotting time of >250 seconds. Two patients had a history of suspected heparin-induced thrombocytopenia; therefore, argatroban was used for anticoagulation during the procedure instead of heparin.

**Follow-up evaluation:** Patients were usually discharged on aspirin (325 mg/day) and clopidogrel (75 mg/day). Amoxicillin was prescribed before dental work to prevent bacterial endocarditis. Warfarin use, in addition to antiplatelet therapy, was determined by the patient’s concomitant disease, such as a hypercoagulation disorder, deep venous thrombosis, or pulmonary embolism. Patients were followed clinically and TEE was performed at 1 month after implantation.

**Definitions of echocardiographic findings:** The presence of a residual shunt at follow-up TEE examination was determined by color flow Doppler for left to right shunt and by agitated saline contrast injection into an antecubital vein for the presence of right to left shunt.

These residual shunts were categorized as follows: (1) color flow Doppler, none: no color disturbances through the defect; small: color Doppler jet <2 mm through the defect; moderate to large: >2 mm through the defect; and (2) contrast injection, none: no microbubbles in the left atrium after injection of agitated saline; small: presence of 3 to 9 microbubbles in the left atrium; moderate: 10 to 30 microbubbles in the left atrium; and large: >30 microbubbles in the left atrium.

The diagnostic criteria for atrial septal aneurysm were a base width of >15 mm and septal excursion of >10 mm into the right or left atrium or bilateral excursions of >10 mm.

The presence of thrombus on the device during follow-up was defined as a new hypoechogenic nonplanar, partially mobile structure.

**Statistical analysis:** Continuous variables were analyzed using t tests and dichotomous variables were analyzed using chi-square tests or Fisher’s exact tests. Continuous variables are expressed as mean ± SD and dichotomous variables are expressed as a frequency percentage. A p value of <0.05 was considered statistically significant.

**RESULTS**

**Patient population:** Sixty-six consecutive adult patients underwent transcatheter closure therapy of interatrial communications. The closure devices were successfully deployed in all 66 patients. Baseline demographics of the patients are shown in Table 1. Forty-four of the 66 patients (67%) were women; mean age was 47 ± 14 years (range 17 to 77). Most of the patients (n = 48) had a PFO alone (73%). There were morphologic variations of the ASD, including 5 fenestrated septums. An atrial septal aneurysm was found in 21 patients (32%). There were 5 patients who had concomitant heart disease (2 with dilated cardiomyopathy, 2 with Ebstein’s anomaly, and 1 with transposition of the great arteries). Five patients were

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**TABLE 1 Baseline Demographics [n = 66]**

| Age (yrs) | 47 ± 14 |
| Women | 44 (67%) |
| Baseline disease | PFO alone 48 (73%), ASD alone 9 (14%), PFO and ASD 4 (6%), Fenestrated septum and PFO 5 (8%), Atrial septal aneurysm 21 (32%), Concomitant heart disease 2 (3%), Dilated cardiomyopathy 2 (3%), Transposition of great arteries 1 (2%), Coagulation disorder 5 (8%), Indication Large left to right shunt 13 (20%), Paradoxic embolization 48 (73%), Hypoxemia 5 (8%) |

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**TABLE 2 Antithrombotic Medication After the Procedure**

| | Amplatzer (n = 36) | CardioSEAL (n = 30) |
|---|---|---|
| Aspirin and clopidogrel | 28 | 22 |
| Aspirin alone | 1 | 0 |
| Warfarin alone | 5 | 1 |
| Aspirin and warfarin | 0 | 2 |
| Clopidogrel and warfarin | 1 | 0 |
| Aspirin, clopidogrel, and warfarin | 1 | 5 |

No statistical difference between the 2 groups.

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**TABLE 3 Transesophageal Echocardiographic Findings at One Month**

| | Amplatzer | CardioSEAL (n = 23) |
|---|---|---|
| Septal Occluder | PFO Occluder | Total (n = 27) |
| Residual shunt (small*) | 6 (43%) | 3 (23%) | 9 (33%) | 5 (22%) | 0.36 |
| Thrombus formation | 0 | 0 | 0 | 5 (22%) | 0.02 |
| Device deformation | 0 | 0 | 0 | 2 (9%) | 0.21 |

*Small: color Doppler jet <2 mm through the defect or the presence of 3 to 9 microbubbles in the left atrium by contrast injection.
found to have a hypercoagulable state consisting of anticardiolipin antibodies (1), factor VIII elevation (1), prothrombin 20210A variant (1), protein C deficiency (1), and protein S deficiency (1). The indication for closure consisted of ischemic cerebral events due to presumed paradoxic embolization in 48 patients (73%), large left to right shunt in 13 patients with ASDs (20%), and arterial hypoxemia due to right to left shunt in 5 patients (4 chronic arterial hypoxemia and 1 platypnea orthodeoxia) (8%).

Procedural results: The devices were successfully deployed in all patients. The CardioSEAL device was used in 30 patients (45%), the Amplatzer septal occluder device in 16 patients (24%), and the Amplatzer PFO occluder device in 20 patients (30%). Two patients had 2 CardioSEAL devices implanted during the same procedure. One of these 2 patients presented with a large atrial septal aneurysm and a long PFO and the other patient had a fenestrated septum with 3 separate shunts. All procedures were performed with TEE guidance, except 1 in which the patient was not able to tolerate the TEE probe. Intracardiac echocardiographic imaging was used instead of TEE.9 A transseptal puncture technique was used in 11 patients (17%)10 because the PFO was long or there was a large atrial septal aneurysm.

Follow-up TEE results: Patients were treated with several antithrombotic regimens after implantation, but there was no difference in treatment between patients who received the CardioSEAL or the Amplatzer device (Table 2).

Fifty of 66 patients (76%) were evaluated by TEE at 28 ± 10 days (range 7 to 47) after implantation. Follow-up TEE was not scheduled in the initial 4 patients. Six patients were not able to have follow-up TEE because of their unstable health conditions. One patient died because of severe underlying disease (pulmonary embolism, myocardial infarction, and multiple embolic cerebral infarctions) before the follow-up TEE. The other 4 patients have not undergone follow-up TEE examination yet. Table 3 outlines the TEE findings at 1 month after implantation between the CardioSEAL and the Amplatzer devices. The incidence of a small residual shunt did not differ between the CardioSEAL and the Amplatzer devices (22% vs 33%, p = 0.36). All residual shunts were small (color Doppler jet <2 mm through the defect or the presence of 3 to 9 microbubbles in the left atrium by contrast injection).

The Amplatzer device had no deformation, such as...
a cobra-like structure. However, there were 2 CardioSEAL devices with abnormal positions of the arms. On these devices, 1 of the 4 spring arms was in an abnormal position, perpendicular to the plane of the cloth sheet. One of these occurred on the left atrial side and 1 in the right atrium. Dislodgement or erosion was not observed with either device.

**Incidence of thrombus:** Thrombus formation was detected on the device in 5 of 50 patients (10%). However, all of the patients with thrombus received the CardioSEAL device. No patient who received the Amplatz device had thrombus on the device (5 of 23 patients, 22% vs 0 of 27 patients, 0%, p = 0.02) (Table 3). The size of thrombus ranged from 5 to 8 mm at the first follow-up TEE examination. Thrombus was attached on the left atrial side in 4 patients and on the right atrial side in 1 patient. The thrombus was mobile in 3 patients. In 3 of 5 patients with thrombus formation on the device, the thrombus resolved after anticoagulation therapy with warfarin. One patient did not have a repeat TEE examination. In 1 patient, the CardioSEAL device was surgically removed because of continuous growth of thrombus on the device. No patient developed a thromboembolic episode during the 2.5-year follow-up period, including those patients with thrombus formation on the device.

**Predictors for thrombus formation on the device:** An analysis of risk factors for thrombus formation on the device is shown in Table 4. Use of the CardioSEAL device was the only variable associated with the presence of thrombus formation on the device (p = 0.02).

**DISCUSSION**

Although results from recent reports are encouraging, there remain several possible complications related to transcatheter closure of interatrial communications. These include air embolism, device embolization, atrial perforation, device malposition, residual shunt, device arm fracture, arrhythmia, infection, and thrombus formation on the device. Although most of these complications are caused by technical problems and may be solved by refinements of the device and implantation technique, thrombus formation on the device is still a major concern because it may result in embolic events and recurrent neurologic deficits.

A summary of previous reports describing thrombus formation on these devices is listed in Table 5. The incidence of thrombus in these studies varied between 3% and 27%. Our results were comparable in terms of the incidence of thrombus formation on the device, the tendency for thrombus to resolve subsequently, and the observation that no thrombus has been reported on the Amplatz device. Although the shape and structure of these devices are different, there is no obvious reason why there should be a difference in thrombus or scar formation. The Amplatz device consists of Nitinol metal with smooth rounded disks. The polyester fabric of the Amplatz is sewn inside the meshed disks; in the CardioSEAL device, the fabric is directly exposed to blood (Figure 3). The structure and composition could affect the process of endothelialization on the 2 devices. Endothelialization and scar tissue formation on the implanted device is necessary to obtain complete closure of the atrial communication and is believed to be necessary to prevent thrombus formation. Although animal studies show sufficient cell proliferation covering the device 4 weeks after implantation, in human hearts the detailed time course of endothelialization is not known. Another potential reason might be...
different antithrombotic regimens after implantation or unknown underlying hypercoagulation disorders, including aspirin resistance.22 Warfarin is known to have a procoagulant effect during initiation,23 and there is 1 report that has suggested that anticoagulation with warfarin after implantation has a tendency toward a higher rate of thrombus on the device compared with antiplatelet therapy.19 However, in our study, all 5 patients who experienced thrombus formation did not have warfarin initially after implantation.

Previous reports document that most recurrent neurologic events after percutaneous closure of PFO occurred within the first year after device implantation.12,24–26 This has been ascribed to incomplete closure of the PFO. Several reports indicate a close association between the recurrence of embolic events and a residual shunt.25,27 It has also been reported that there is a gradual reduction of the residual shunt after implantation associated with the healing process.28,29 However, there are patients without a residual shunt who have recurrent neurologic symptoms.30 It is possible in these cases that thrombus formed on the left side of the device, producing embolic events before the device surface was completely endothelialized. These TEE observations may be visualizing a part of the natural healing process, in which thrombus evolves into a fibrous scar. The finding of hypoechochogenic structures on the device does not necessarily imply that embolization is imminent; these may resolve with time, with or without anticoagulation therapy. However, the mobile polypoid structure seen in Figure 1 may carry a higher risk of embolization. The primary distinction of this report is that none of these hypoechochogenic structures suggestive of thrombus was seen on the Amplatzer devices.
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