

Transcatheter Closure of Congenital Defects

Transcatheter Closure of Perimembranous Ventricular Septal Defects Using the New Amplatzer Membranous VSD Occluder

Results of the U.S. Phase I Trial

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OBJECTIVES	This phase I study attempted to report the initial safety and efficacy results of transcatheter closure of perimembranous ventricular septal defects (PmVSDs) using the new Amplatzer Membranous VSD Occluder (AGA Medical Corp., Golden Valley, Minnesota) in the U.S.
BACKGROUND	The most common congenital heart disease is PmVSD. Surgical repair is widely accepted, but still carries a small but definite risk of morbidity and mortality.
METHODS	Between October 2003 and August 2004, a total of 35 patients with PmVSD underwent an attempt of transcatheter closure under transesophageal and/or intracardiac echocardiographic guidance. The median age was 7.7 years (range, 1.2 to 54.4 years) and median weight was 25 kg (range, 8.3 to 110 kg). The median Qp/Qs ratio was 1.8 (range, 1 to 4), and the median VSD size as assessed by echocardiography was 7 mm (range, 4 to 15 mm).
RESULTS	The attempt to place a device was successful in 32 patients (91%). The median device size used was 10 mm (range, 6 to 16 mm). The complete closure rates by echocardiography at 10 min (transesophageal/intracardiac), 24 h, 1 month, and 6 months (transthoracic) were 47% (15/32), 63% (20/32), 78% (25/32), and 96% (27/28), respectively. The median fluoroscopy time was 36 min (range, 14 to 191 min), and the median total procedure time was 121 min (range, 67 to 276 min). Three patients (8.6%) had serious adverse events of complete heart block, peri-hepatic bleeding, and rupture of tricuspid valve chordae tendineae. No other patient encountered serious adverse events during the follow-up.
CONCLUSIONS	Transcatheter closure of a PmVSD is technically feasible and seems safe enough in children over 8 kg in weight to warrant continuation of clinical trials to assess the long-term safety and efficacy. (J Am Coll Cardiol 2006;47:319–25) © 2006 by the American College of Cardiology Foundation

Ventricular septal defect (VSD) is the most common (approximately 20%) congenital heart disease (1). About 70% of these defects are perimembranous (PmVSD), involving the membranous septum and the adjacent area of muscular septum. Traditional treatment if necessary is surgical repair, which has been widely accepted with minimal mortality but still carries potential risks of complete heart block, chylothorax, phrenic nerve injury, early and late

arrhythmias, postpericardiotomy syndrome, wound infection, and neurologic sequelae of cardiopulmonary bypass (2–5). Moreover, the sternotomy scar may be a cosmetic concern for the patients and their parents.

Since 1987, the Rashkind and buttoned devices have been used to close PmVSDs, which were originally designed for patent ductus arteriosus and atrial septal defect, respectively (6–9). The major drawbacks of these devices were the large delivery sheaths (11-F) required, complex implantation techniques, inability to reposition and redeploy the device, interference with the aortic and tricuspid valves and significant residual shunts (25% to 60%) (6–10). The Amplatzer Membranous VSD Occluder (AGA Medical Corp., Golden Valley, Minnesota) is the only device that is specifically designed for PmVSDs (11). Its initial use in six patients in 2002 was associated with complete closure in all and absence of significant complications (12). After that, several centers reported similar encouraging results of initial complete closure rates of 90% to 92% (13–16). However, they were all reports with limited case numbers. The

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Abbreviations and Acronyms

AR	= aortic regurgitation
ICE	= intracardiac echocardiography
PmVSD	= perimembranous ventricular septal defect
TEE	= transesophageal echocardiography
TTE	= transthoracic echocardiography

purpose of this phase I study was to report the initial safety and efficacy results of transcatheter closure of PmVSD using the new Amplatzer Membranous VSD Occluder (AGA Medical Corp.) in the U.S.

METHODS

Study population. This study was conducted as a prospective, nonrandomized, phase I clinical trial involving seven cardiac centers in the U.S. The study was approved by the institutional review board of each participating center and by the U.S. Food and Drug Administration under a sponsor-initiated Investigational Device Exemption. All investigators were selected, qualified, and trained and a monitor was used to oversee the compliance with the study protocol.

The inclusion criteria of patients included: 1) PmVSD as shown by echocardiography, and 2) symptoms of heart failure or evidence of left atrial and or left ventricular enlargement for body surface area. Exclusion criteria included: 1) body weight <8 kg, 2) subaortic rim as shown by echocardiography in the long-axis view <2 mm, 3) left ventricle to right atrial shunting, 4) right to left shunting through the defect, 5) PmVSD with an aneurysm and multiple shunts that could not be successfully closed with one device, 6) sepsis, 7) complex heart lesions such as tetralogy of Fallot, 8) contraindication to antiplatelet therapy, 9) patients unable to be followed up for the duration of the trial, and 10) inability to obtain informed consent.

Between October 2003 and August 2004, a total of 35 patients (23 male, 12 female) underwent an attempt at transcatheter device closure (Table 1). Among them were 3

Table 1. Data for 35 Patients Who Underwent the Attempt of Transcatheter Closure of Perimembranous VSD

	Median	Range
Age (yrs)	7.7	1.2-54.4
Weight (kg)	25	8.3-110
Echocardiography		
Subaortic rim (mm)	3	2-12
VSD size (mm) in TEE (n = 30) or ICE (n = 5)	7	4-15
Catheterization		
VSD size (mm) in LVG	7.7	4-11.7
Qp/Qs	1.8	1-4
PA systolic pressure (mm Hg)	32	15-70
PA mean pressure (mm Hg)	19	9-47

ICE = intracardiac echocardiography; LVG = left ventriculography; PA = pulmonary artery; Qp/Qs = pulmonary to systemic flow ratio; TEE = transesophageal echocardiography; VSD = ventricular septal defect.

(9%) patients with postoperative residual VSDs, 16 (46%) patients had aneurysm formations around the VSDs, and 11 patients had associated other congenital heart diseases, including patent foramen ovale in 4, pulmonary valvular stenosis/dysplasia in 3, bicuspid aortic valve in 2, small muscular VSDs in 1, patent ductus arteriosus in 1, mild Ebstein anomaly of the tricuspid valve in 1, and dextrocardia with situs inversus in 1. Trivial and mild aortic regurgitation with no aortic valve prolapse before the procedure was noted in nine (25.7%) patients. Six patients had congestive heart failure, three had recurrent respiratory infections, three had failure to thrive, two had pulmonary hypertension, one had cyanosis attributable to her underlying cardiac anatomy of corrected transposition and right-to-left shunt at the atrial level, and one had palpitations.

Data collection. Data were collected prospectively at the time of the procedure at each participating center by the responsible investigator and submitted to a central database at the Clinical Research Division of AGA Medical Corp. Data collected included demographic details (date of procedure, age, gender, height, weight), symptoms/signs (congestive heart failure, failure to thrive, recurrent respiratory tract infections, sepsis, heart murmur), electrocardiography (left atrial enlargement, left ventricular hypertrophy, rhythm abnormality), chest X-ray (cardiomegaly, increased pulmonary vascularity), echocardiography (VSD size, left atrial end-systolic dimension, left ventricular end-diastolic dimension, associated anomalies), and procedure details (anesthesia method, echocardiographic guidance, access route, sheath size, heparin, fluoroscopy time, procedure time). For any adverse event occurring during the clinical trial, the investigator reported the information regarding the circumstances, treatment, and outcome to the sponsor. A Data Safety Monitoring Board determined whether the adverse events were serious adverse events, adverse events or observations, device or procedure related, and anticipated or unanticipated. A serious adverse event was defined as an event that resulted in death or long-term sequelae (effects or treatment lasting longer than six months). Potentially life-threatening events were also included in this group. Serious adverse events included but were not limited to death during or after the procedure because of complications of the procedure, cerebral or pulmonary embolism, bacterial endocarditis, device embolization that required surgical removal, persistent cardiac arrhythmia that required long-term medical treatment (>6 months) or pacemaker placement, ongoing hemolysis that required more than one blood transfusion, other ongoing therapy or device removal, thrombosis that required thrombolytic therapy, any event that required acute resuscitation, and any persistent (>30 days) increase in valvar regurgitation of two grades or more, or new or worsened valvar regurgitation that required drug treatment. Events that required surgical repair (i.e., arterial pseudoaneurysm) or significantly prolonged hospitalization (i.e., wound infection) were also considered in this category. An adverse event was defined as those events that required

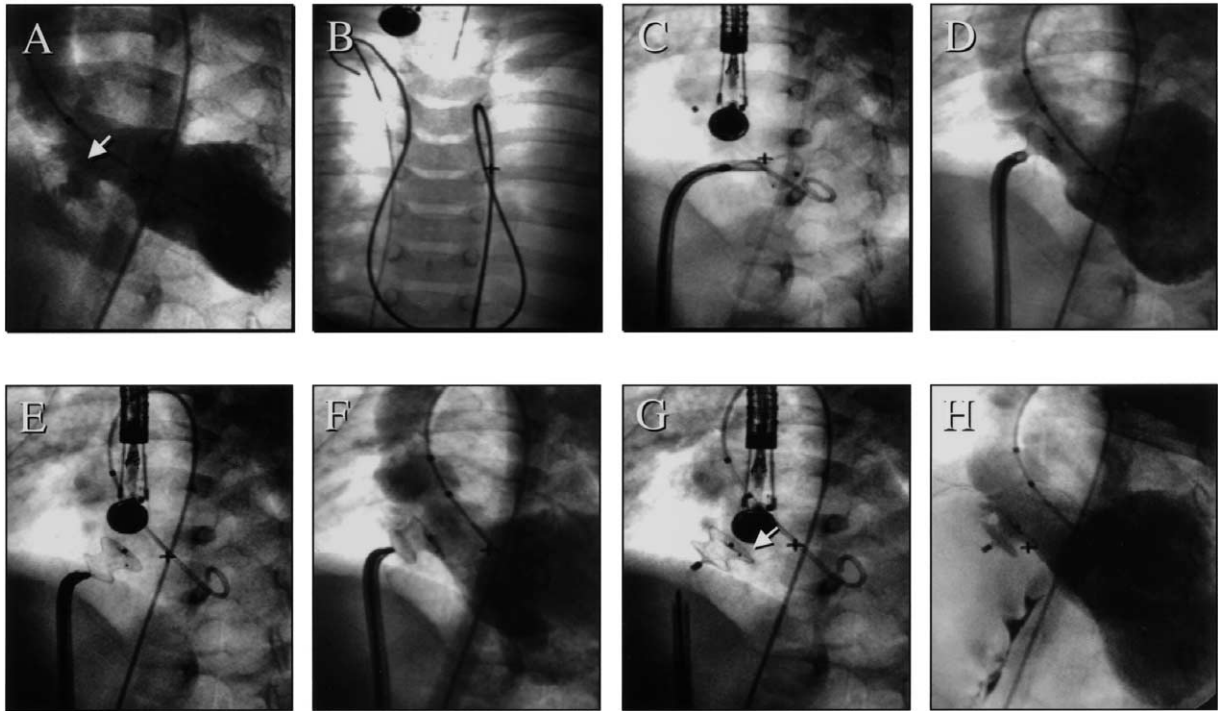


Figure 1. (A) Left ventriculography in the left anterior oblique view showing a 9-mm perimembranous ventricular septal defect (arrow) in a 22-month-old boy. (B) Cine image showing the arteriovenous loop. (C) Left ventricular disk has been deployed. (D) Left ventriculography showing good position of left ventricular disk. (E) Cine image immediately after the right ventricular disk has been deployed. (F) Left ventriculography showing good device position before its release. (G) Cine image after the device has been released. The platinum marker is pointed to the apex (arrow), indicating good device position. (H) Final left ventriculography indicating good device position and no residual shunt.

medical intervention but that were not life threatening, did not have long-term (>6 months) sequelae, and did not require long-term (>6 month) therapy. These events included but were not limited to loss of peripheral pulse (transient or required only heparin therapy); cardiac arrhythmia that required cardioversion or medication; blood transfusion because of blood loss; persistent (>30 days) new or increased valvar regurgitation; hematoma of the groin; valvar, device, or intracardiac thrombus without embolization and not treated with thrombolytic medication; and device embolization with transcatheter removal.

All other adverse events were considered observations. The accuracy of the submitted data was verified for each participating institution using source documents (catheter reports, case notes, medical records) that were analyzed by monitors from the sponsor during control visits to these institutions.

Measured outcome parameters. Procedure success was defined by device release in the appropriate position without embolization. The residual shunt was classified as trivial (width of the color jet as assessed by color Doppler echocardiography as it exited the septum of <1 mm), small (width of 1 to 2 mm), moderate (width of 3 to 4 mm) or large (width \geq 4 mm), in a way similar to the protocol reported by Boutin et al. (17) for shunt assessment after device closure of atrial septal defects. Experienced echocardiographers at the echocardiography core laboratory (based

at the sponsor's headquarters) verified the pre-closure, closure, and post-closure echocardiograms.

The device. The Amplatzer Membranous VSD Occluder (AGA Medical Corp.) is a self-expandable double-disk device made of a nitinol wire mesh. The details of the device description were previously reported (12).

Closure protocol. The protocol used has been described in detail in previous reports (11,12). Briefly, access was obtained in the femoral artery (4- to 5-F sheath) and the femoral vein (7- to 9-F sheath). Heparin was given to keep an activated clotting time of >250 s. Routine right and left heart catheterizations were performed to assess the degree of shunting and to evaluate pulmonary vascular resistance. Left ventriculography in the long axial oblique view (60° left anterior oblique/20° cranial) defined the location and size of the VSD. The appropriate device size was chosen to be at least 1 to 2 mm larger than the VSD size as measured by color Doppler echocardiography or ventriculography. Transesophageal echocardiography (TEE) and/or intracardiac echocardiography (ICE) were used to guide and monitor the procedure. Figures 1 and 2 show the various steps of closure by cine fluoroscopy and echocardiography, respectively. The follow-up protocol included physical examination and electrocardiogram and echocardiography at 10 min (TEE/ICE), pre-discharge, one month, and six months (transthoracic echocardiography [TTE]) after the procedure. Chest X-ray was required before discharge and 24 h

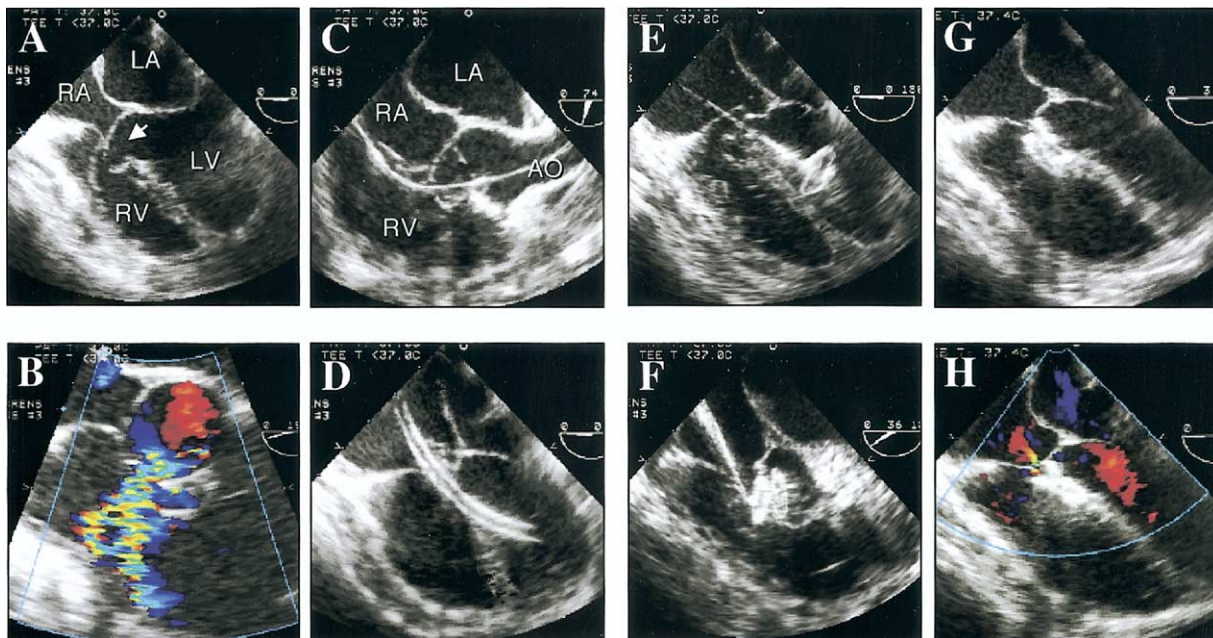


Figure 2. Transesophageal echocardiographic images of the same patient as in Figure 1. (A) Four-chamber view showing the perimembranous ventricular septal defect (VSD) with aneurysm formation (arrow). (B) Short-axis view with color Doppler at the subaortic level showing the shunt. (C) The wire of the arteriovenous loop passing from the aorta through the VSD to the right atrium (RA). (D) Four-chamber view showing the delivery sheath in the left ventricular apex. (E) The left ventricular disk is deployed. (F) Short-axis view showing good device position before its release. (G) Final image in the four-chamber view indicates good device position. (H) Color Doppler mapping showing no residual shunt with a trivial tricuspid regurgitation. LA = left atrium; LV = left ventricle; RV = right ventricle.

after the procedure. Patients were routinely maintained on aspirin 3 to 5 mg/kg daily or equivalent antiplatelet therapy for six months. Patients were instructed to receive infective endocarditis prophylaxis when needed until complete closure was documented at the six-month follow-up visit.

Statistical analysis. Medians and ranges were calculated for individual parameters, and the differences between the baseline and follow-up Z scores of left atrial and left ventricular dimensions were assessed by paired *t* test. Changes in categorical variables were compared using a paired sign test. A *p* value of <0.05 was considered statistically significantly. No corrections were made for multiple comparisons.

RESULTS

Procedural data. General anesthesia was used in 31 (89%) patients and conscious sedation in 4 (11%). The right femoral vein was mainly used for the venous access, and in two patients, both veins were cannulated. The transhepatic access was used in one patient because of thrombosis of both femoral veins. The right femoral artery was mainly used for the procedure; however, in eight patients both arteries were cannulated. Transesophageal echocardiography was used to guide the procedure in 32 (91%) and/or ICE in 5 (14%) patients. Device placement was successful in 32 patients (91%). Three patients failed the attempt, and their devices were retrieved because of significant device-related aortic regurgitation in two and inability to achieve a good device position in one. The median VSD size was 7 mm (range, 4

to 15 mm), and the median device size used was 10 mm (range, 6 to 16 mm). The median fluoroscopy time was 36 min (range, 14 to 191 min), and the median total procedure time was 121 min (range, 67 to 276 min). A VSD with aneurysm formation was noted in 45.7% (16 of 35) of our patients. Two of them had multiple fenestrations.

Follow-up data. Table 2 summarizes the data before and after device insertion, including presence of heart murmur, electrocardiogram, chest radiograph, and echocardiographic assessment of shunt status, size of the left atrium and ventricle, and presence or absence of valvar regurgitation. The complete closure rate increased from 20 of 32 at 24 h after the procedure to 27 of 28 at six-month follow-up. Furthermore, as noted in Table 2, aortic regurgitation (AR) was present in 9 of 35 (25.7%) patients before closure (6 with trivial and 3 with mild AR). At discharge, 17 of 32 (53.1%) patients had AR (11 with trivial and 6 with mild AR). At one-month follow-up, 15 of 32 (46.9%) patients had AR (10 with trivial and 5 with mild AR), and at six-month follow-up, 11 of 28 (39.3%) patients had AR (7 with trivial and 4 with mild AR). Because of the small sample size in each category of AR, we were unable to predict who would develop or have an increase in the severity of AR. Data for the tricuspid and mitral valves are shown in Table 2.

Complications. Serious adverse events were encountered in three (8.6%) patients. In one patient (a two-year-old girl; weight, 9.1 kg; with a 6-mm PmVSD with left-sided chamber enlargement requiring anti-congestive medica-

Table 2. Data Before and After Implantation of the Amplatzer Membranous VSD Occluder

	Before Implantation	After Implantation			
		10 min	24 h	1 month	6 months
Murmur	100% (35/35)		53%* (17/32)	53%* (17/32)	35.7%* (10/28)
ECG					
LVH	38.2% (13/34)		34.4% (11/32)	25.0% (8/32)	25.9% (7/27)
LAE	11.8% (4/34)		0 (0/31)	0 (0/32)	0 (0/27)
CXR					
Cardiomegaly	54.3% (19/35)		40.6% (13/32)	24%* (6/25)	16.7% (2/12)
Echocardiography		n = 32	n = 32	n = 32	n = 28†
Complete closure		15	20	25	27
Trivial shunt		7	4	2	1
Small shunt		9	6	4	0
Moderate shunt		1	1	0	0
Large shunt		0	1	1	0
LAESD (mean ± SD, Z score)	3.4 ± 2.1 (n = 32)		2.7 ± 1.7 (n = 32)	2.5 ± 1.7* (n = 30)	2.2 ± 2.0* (n = 27)
LVEDD (mean ± SD, Z score)	1.8 ± 1.7 (n = 32)		1.3 ± 1.9 (n = 31)	0.7 ± 1.5* (n = 30)	0.6 ± 1.8* (n = 25)
AR	25.7% (9/35)	37.5% (12/32)	53.1% (17/32)	46.9% (15/32)	39.3% (11/28)
TR	74.3% (26/35)	81.3% (26/32)	78.1% (25/32)	65.6% (21/32)	69.2% (18/26)
MR	34.3% (12/35)	28.1% (9/32)	31.3% (10/32)	12.5%* (4/32)	18.5% (5/27)

*p < 0.05 compared with the pre-device closure data. †The remaining four patients who did not make the follow-up at 6 months had complete closure at the 30-day follow-up. AR = aortic regurgitation; CXR = chest X-ray; ECG = electrocardiography; LAESD = left atrial end-systolic dimension; LAE = left atrial enlargement; LVEDD = left ventricular end-diastolic dimension; LVH = left ventricular hypertrophy; MR = mitral regurgitation; TR = tricuspid regurgitation.

tions; increased vascular markings on chest radiograph) there developed a complete heart block with intermittent second-degree atrioventricular block approximately 2 h after an 8-mm device was implanted without any difficulty. The complete heart block persisted with few symptoms despite treatment with a course of corticosteroids. A permanent pacemaker was implanted three months after the closure. One patient who underwent the attempt using the trans-hepatic approach experienced peri-hepatic bleeding requiring blood transfusion. Finally, transcatheter device retrieval failed in a three-year-old boy; weight, 8 kg; with a 7.5-mm PmVSD with left ventricular and left atrial enlargement. The procedure was performed in routine fashion, and a 10-mm device was implanted. Before device release, TEE did not show any AR; however, after device release, ascending aortography showed moderate to severe aortic insufficiency. Device removal was attempted using a biopsy forceps. The device was pulled into the right ventricle; however, it was entangled in the tricuspid valve apparatus and the retrieval was abandoned because of increased tricuspid insufficiency. The child was sent to the operating room for device retrieval and VSD closure. At operation, the right atrium was opened and the device was seen protruding through the anterior leaflet of the tricuspid valve. The device was removed, the tricuspid valve apparatus was repaired, and the VSD was closed. The child has done very well without any complication, including absence of aortic or tricuspid regurgitation. Adverse events developed in 15 patients, including 2 patients in whom hemolysis developed and improved without transfusion, 2 patients with femoral hematoma, and one patient each with right bundle branch block, fever, transient hypotension, transient bradycardia, transient ventricular tachycardia, left bundle branch block,

emesis, migraine, trivial AR, mild-moderate tricuspid regurgitation, and bleeding.

DISCUSSION

The Amplatzer Membranous VSD Occluder (AGA Medical Corp.) is the only device specifically designed for closure of PmVSDs. It has the following advantages. First, it is an asymmetric device with a short aortic end of the left ventricular disk, thereby avoiding potential impingement on the aortic valve. A special pusher catheter that has a metal capsule at its end facilitates orientation of the device in the correct position. Second, the operator has full control and can recapture and redeploy the device before release should the device be deployed in the wrong position or location. Third, the high closure rates achieved with this device are attributable to the mechanism of closure (stenting the defect with the waist). This is one of the reasons that it can achieve a better complete closure rate than other devices (90% to 100% vs. 25% to 60%) (6-16). Fourth, the device requires a small delivery sheath (7- to 9-F) for deployment; this makes it easily applicable to smaller children. Fifth, it is round in shape without the corners or spokes that have potential risks of immediate or delayed injury of valves or tissues.

Because the membranous septum is very thin, the operator may not feel any resistance during device pullback from the left ventricle to the septum. As a result, the device might be misplaced in the right ventricle. Therefore, echocardiography (TEE or ICE) and angiography are crucial to identify correct device deployment. In addition, echocardiography can recognize immediate possible adverse events of AR caused by impingement of the device on the valve leaflets and mitral or tricuspid regurgitation caused by the interference with the chordae tendineae.

Our results showed that presence of an aneurysm did not prevent device closure. If the aneurysm was large and the opening was solitary, the device could be accommodated within the aneurysmal sac, away from the aortic valve, thereby preventing AR (9). In most situations, the device was placed in the usual septal position (Figs. 1 and 2).

This series reports the largest cohort of patients with PmVSDs who underwent transcatheter closure using the new Amplatzer Membranous VSD Occluder (AGA Medical Corp.). The successful procedure rate was 91%. The complete closure rate was excellent, 96% at six months after the procedure, with the remaining 4% (one patient) having only trivial residual shunt.

The left atrial and ventricular sizes decreased after the procedure. Both left atrial and ventricular dimensions achieved a significant decrease in the Z score at 30 days and six months (Table 2). This indicates that the device was effective in abolishing the left-to-right shunt that resulted in a decrease in the left heart chambers. Mitral and tricuspid regurgitation improved in some patients after the procedure. The proportion of mitral regurgitation decreased from 34.3% before device implantation to 12.5% at one-month follow-up. This again indicated that patients benefited from elimination of the shunt.

No mortality, stroke, or neurologic deficit was noted in our series. This compares favorably to the current surgical results for isolated PmVSDs (4,5).

Hobbins et al. (18) reported that complete right bundle branch block occurred in 79% and 33% of patients after surgical repair of VSD through the right atrium or right ventricle approach, respectively. Yeager et al. (3) reported that 75.3% of patients had persistent postoperative conduction abnormality including complete heart block (2.3%), complete right bundle branch block (64%), and bifascicular block (9%). However, patients who were in that study (3) were younger than one year of age; therefore, direct comparison with our series of patients, who were older, should be viewed with caution. The current study found that bundle branch block occurred in only 6% of patients (2 of 32) who underwent device closure. Permanent complete heart block requiring a pacemaker developed in one patient.

The development of AR is an important concern for device closure of PmVSDs. In the 32 patients undergoing device closure, new trivial AR without clinical or hemodynamic significance within 24 h developed in 5 patients (15.6%), and new mild AR within 24 h developed in 3 patients (9%), for a total of 17 of 32 (53%) patients with AR (Table 2). This might be related to the configuration change of the subaortic septum or repeated crossing of the aortic valve by catheters and guidewires. At six-month follow-up, 11 of 28 (39%) patients had AR. This indicates that some of the aortic regurgitation was transient.

Study limitations. The patients in our study were larger and older than those in whom surgical closure of a VSD is considered. The application of the Amplatzer Membranous VSD Occluder (AGA Medical Corp.) in small infants may

carry a higher risk and remains to be determined. Our follow-up period was only six months. The preliminary results and possible delayed adverse effects, including heart block, need to be confirmed by a larger trial and by long-term follow-up.

Conclusions. Transcatheter closure of PmVSDs using the Amplatzer Membranous VSD Occluder (AGA Medical Corp.) is technically feasible and seems safe enough in larger children to warrant continuation of clinical trials to assess the long-term safety and efficacy of this device.

ADDENDUM

Since the acceptance of this paper, one more patient developed complete heart block 16 months after device closure requiring pacemaker implantation.

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