

Atrial Septal Defect Occlusion with the Buttoned Device (a Multi-Institutional U.S. Trial)

Thomas R. Lloyd, MD, P. Syamasundar Rao, MBBS, Robert H. Beekman III, MD,
Alan M. Mendelsohn, MD, and E. B. Sideris, MD

A clinical trial was conducted of the buttoned device for transcatheter closure of ostium secundum atrial septal defect. Occlusion was attempted in 57 patients aged 1 to 62 years (median 5). The procedure was abandoned in 7 patients after 1 or more unsuccessful attempts, and devices were released in 50 patients. Urgent surgical retrieval was necessary in 4 patients because of unstable device position: 3 devices "unbuttoned," with migration of the counteroccluder to the pulmonary artery or inferior vena cava, and 1 intact device embolized to the main pulmonary artery. All patients remained stable and underwent successful operation. Successful device implantation was therefore achieved in 46 patients, with immediate reduction in Qp/Qs from 1.8 ± 0.6 to 1.1 ± 0.2 (mean \pm SD, $p < 0.0001$). At most recent follow-up (1 to 20 months), 45 of 46 patients (98%) have no shunt or a trivial residual shunt. The prevalence of residual shunts declined from 65% at 1 month to 19% at 12 months after the occlusion procedure ($p < 0.0001$). Complications included unbuttoning of a fourth device, transient tricuspid regurgitation in 2 patients, and transient mitral regurgitation in 2 patients. An episode of asymptomatic atrial flutter was noted in a 46-year-old patient which may have been related to device implantation, but which has not recurred. There have been no cases of endocarditis or thromboembolism in 350 patient-months of follow-up. The buttoned device provided effective closure of the atrial septal defect in 45 of 57 patients (79%) in whom implantation was attempted and in 45 of 46 patients (98%) in whom device implantation was successfully accomplished. Unbuttoning remains the ma-

ajor complication of the procedure; increased operator experience and design modifications to the device may reduce the frequency of this problem in the future.

(Am J Cardiol 1994;73:286-291)

Trascatheter closure of secundum atrial septal defect (ASD) has been attempted with a number of devices over the last 3 decades.¹⁻⁵ The buttoned device for occlusion of intracardiac defects is the latest of these devices to be developed and to undergo clinical trials.⁵⁻⁹ We report the results of the multi-institutional U.S. trial of the buttoned device for transcatheter ASD closure.

METHODS

The trial was conducted in 3 centers (University of Arizona, University of Michigan, and University of Wisconsin), and Institutional Review Board approval was obtained at each center. Informed consent was obtained from patients or their legal representatives, and assent obtained from minors when appropriate. The trial was supervised by the U.S. Food and Drug Administration and sponsored by Custom Medical Devices (Amarillo, Texas), which supplied the devices.

Patient selection: Patients were eligible for inclusion in this study if they had ostium secundum ASD thought to warrant surgical closure. The indications for closure fell into 2 categories: (1) Most patients had significant left to right shunts through their ASD, i.e., a ratio of pulmonary to systemic blood flow (Qp/Qs) ≥ 1.5 at cardiac catheterization and/or other clinical and noninvasive evidence of significant shunt (e.g., diastolic flow rumble in the tricuspid area, echocardiographic right ventricular volume overload, Qp/Qs ≥ 2 by nuclear shunt study). (2) Some patients had a history of presumed paradoxical arterial embolism through a small ASD or patent foramen ovale (no other source identified). Patients were excluded from the study if they had other cardiac defects requiring surgery, if they had predominantly right to left atrial shunting, if the balloon occlusion diameter of their defects was >25 mm, if the size of the left atrium or the rim of atrial septum was considered inadequate to position or support the device, or if the iliofemoral veins or inferior vena cava were obstructed or interrupted.

Buttoned device: The buttoned device has been described previously.⁵⁻⁹ The second-generation device,⁸ which has a radiopaque marker at the button and in which stronger suture material is used for the button

From the Steele Memorial Children's Research Center, University Heart Center, and Department of Pediatrics (Cardiology), University of Arizona, Tucson, Arizona; the Division of Pediatric Cardiology, Department of Pediatrics, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, Michigan; the Department of Pediatrics, Division of Pediatric Cardiology, University of Wisconsin Children's Hospital and University of Wisconsin Medical School, Madison, Wisconsin; and Pediatric Cardiology and Custom Medical Devices, Amarillo, Texas. This study was supported in part by Grants MO1 RR 00042 and RR 03186 from the National Institutes of Health, Bethesda, Maryland. Dr. Mendelsohn was supported by National Research Service Award Grant HL08709-01 from the National Institutes of Health, Bethesda, Maryland. Manuscript received May 14, 1993; revised manuscript received and accepted August 4, 1993.

Address for reprints: Thomas R. Lloyd, MD, Pediatric Cardiology, University of Michigan Medical Center, F1310 Maternal-Child Health Center, Box 0204 Ann Arbor, Michigan 48109-0204.

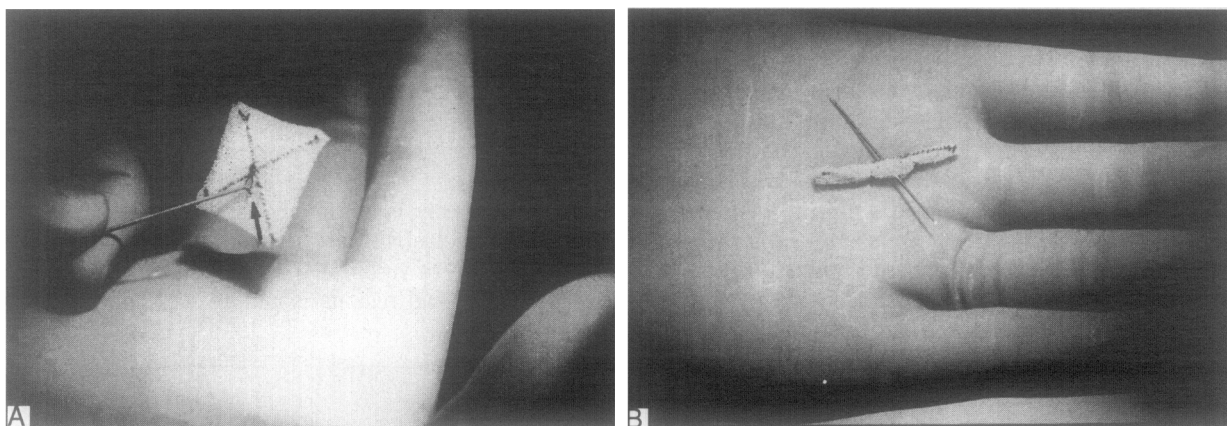


FIGURE 1. Components of the buttoned device. *A*, the occluder, attached to its delivery wire. The x-shaped wire skeleton (0.018-inch, floppy for 2 mm at each end) can be seen through the polyurethane foam. Arrow indicates the button at the end of its short suture loop, which is also the point of attachment to the delivery wire. Note the eccentricity of the button from the axis of the delivery wire. *B*, the counteroccluder, with a needle passed through the rubber piece which serves as the buttonhole. The rubber piece is secured to the wire skeleton of the counteroccluder and covered with polyurethane foam, and the needle serves to guide the delivery wire through the rubber piece.

loop and the delivery wire loop, was used in this study. The buttoned device is composed of 2 parts: the occluder, which is placed along the left atrial side of the septum, and the counteroccluder, which is placed along the right side (Figure 1). The delivery system consists of a long 8 or 9Fr sheath, a pushing catheter (an 8Fr pigtail cut short and used to push the device components through the sheath) and the delivery wire. The delivery wire (Figure 1) is a long loop of nylon suture, interlocked into the button loop and passed through the hollow shell of a Teflon®-coated guide wire. The nominal size of each device is the length of the counteroccluder and the diagonal length of the occluder. Device sizes of 25, 30, 35, 40, 45 and 50 mm were used in this study.

Occlusion procedure: Devices were selected to be at least twice the stretched diameter of the ASD and preferably ≥ 20 mm larger as well. An 8Fr long sheath (9Fr for 50 mm and some 45 mm devices) was positioned across the ASD, and the occluder was folded and advanced with the pushing catheter through the sheath into the left atrium. The occluder assumes its square shape when free in the left atrium, and is withdrawn to the left side of the atrial septum. The delivery wire is then passed through the latex "buttonhole" of the counteroccluder (Figure 1), and the counteroccluder is advanced through the sheath into the right atrium. Upon exiting the delivery sheath, the counteroccluder assumes a position roughly perpendicular to the sheath, and then the sheath is advanced with controlled traction on the delivery wire to position the counteroccluder along the right side of the atrial septum. Further traction on the delivery wire and advancement of the sheath causes the "button" to pass through the buttonhole, securing the counteroccluder to the occluder (Figure 2). The device is released from the delivery wire by opening the proximal end of the delivery wire nylon loop, pulling the guide wire shell off the nylon loop, and pulling gently on 1 limb of the nylon loop until the other end passes out of the button loop and delivery sheath.

Occlusion protocol: All patients underwent diagnostic cardiac catheterization to confirm the diagnosis of os-

tium secundum ASD or patent foramen ovale, to exclude other defects requiring surgery, to measure Qp/Qs by oximetry, and to measure the stretched diameter of the defect by balloon occlusion.^{10,11} When practical, a second right-sided heart catheter was positioned in the pulmonary artery before occlusion in order to measure Qp/Qs after occlusion without disturbing the occlusion device. Patients received antibiotic prophylaxis beginning with an intravenous dose during the catheterization

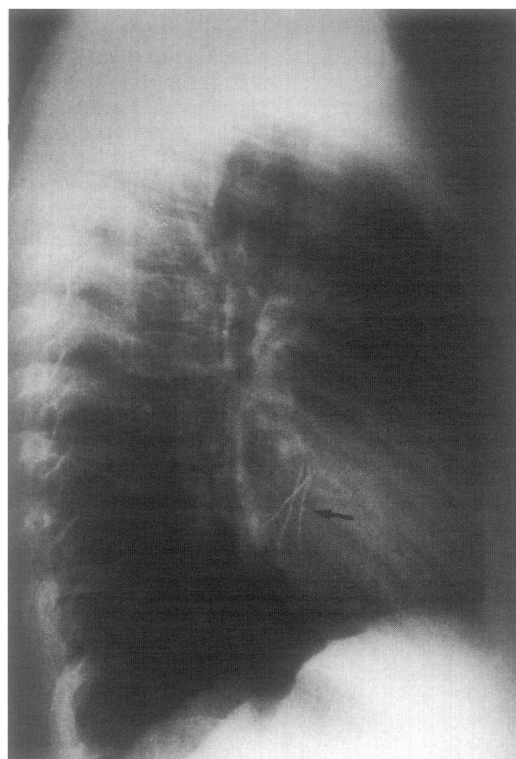


FIGURE 2. Lateral chest roentgenogram after successful implantation of the buttoned device. Arrow indicates the radioopaque button marker, and the wire skeleton of the counteroccluder is positioned between the button marker and the wire skeleton of the occluder.

procedure and continuing with oral doses for 24 to 48 hours thereafter. Heparin (50 to 100 U/kg) was given before occlusion, and patients were also treated with aspirin, 5 to 10 mg/kg/day, beginning the day after occlusion and continuing for 1 to 6 months. Follow-up studies (clinical examination, chest roentgenogram and echocardiogram) were obtained within 24 hours of occlusion, within 1 month of occlusion, and at 6 and 12 months after occlusion. Standard antibiotic prophylaxis against endocarditis was recommended for 6 months after occlusion. Use of conscious sedation versus general anesthesia, echo guidance during the procedure, and

duration of hospitalization, if any, were left to the discretion of each investigator.

Statistical analysis: Continuous, normally distributed variables are presented as mean \pm SD. Variables with substantially skewed distribution are presented as median and range. Comparisons between groups were performed by analysis of variance, and comparisons before and after occlusion were performed by repeated-measures analysis of variance. The relation between duration of follow-up and residual shunting was analyzed using

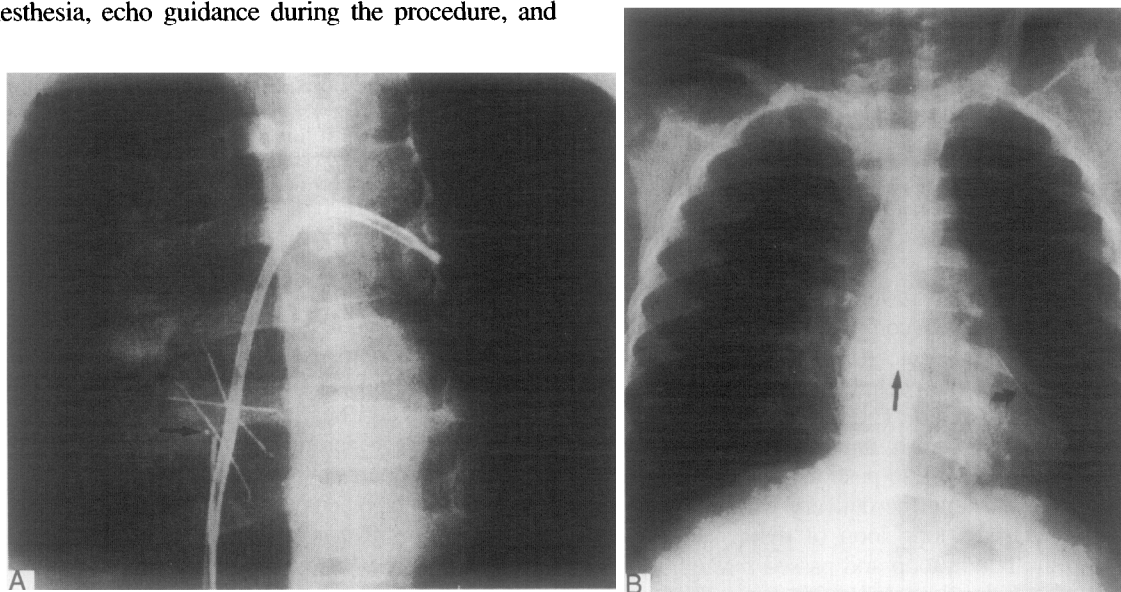


FIGURE 3. *A*, cineangiographic frame recorded in a cranially angulated left anterior oblique projection. *Arrow* indicates the button marker, which has been passed through the counteroccluder and lies on the right atrial side of the counteroccluder skeleton. The device remains attached to the delivery wire, and this position was stable after release during 20 minutes of observation in the catheterization laboratory. *B*, frontal chest roentgenogram of the same patient, obtained 4 hours later. The button marker (*straight arrow*) remains attached to the occluder, which remains against the atrial septum. The counteroccluder (*curved arrow*) has become unbuttoned from the occluder and has migrated to a lower lobe branch of the left pulmonary artery. The occluder was retrieved at the time of surgical atrial septal defect closure, and the counteroccluder was retrieved later by catheter snare.

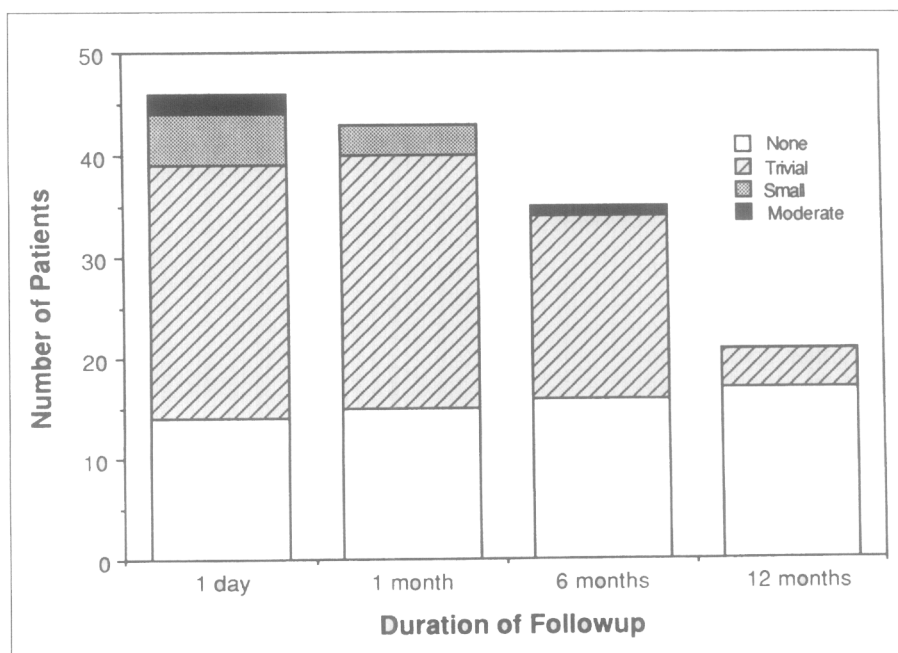


FIGURE 4. Residual shunts by clinical examination and Doppler echocardiography after implantation of the buttoned device. *Open bars* represent the number of patients with no shunt; *hatched bars* are the number of patients with trivial residual shunts; *stippled bars* are the number of patients with small residual shunts; *solid bars* are the number of patients with moderate residual shunts (see text for definitions). The prevalence of residual shunts, which are of potential clinical significance (small or moderate), decreased from 15% immediately after implantation to 0% at 12 months, whereas the prevalence of complete closure increased from 30 to 81%. Reduction in prevalence and size of residual shunts during follow-up was statistically significant ($p < 0.0001$, Spearman's rank correlation test).

Spearman's rank correlation test. Statistical significance was assigned to analyses with $p < 0.05$.

RESULTS

Study population: Occlusion was attempted in a total of 57 patients, 6 of whom have been reported on previously.⁹ The indication for closure was significant left to right shunt in 48 patients and presumed paradoxical embolism in 9 patients. Multiple ASDs were present in 6 patients and atrial septal aneurysm in 3. Additional diagnoses included Down's syndrome and Marfan's syndrome in 1 patient each, branch pulmonary artery stenosis in 2 patients, congenital complete heart block in 1 patient and essential hypertension in 1 patient. The patients ranged in age from 1 to 62 years (median 5). Patients with systemic embolism were older (median age 43 years, range 16 to 55) than those with significant left to right shunts (median 4 years, range 1 to 62, $p < 0.0001$). Patient weight followed a similar pattern (patients with shunt 10 to 88 kg, median 17; patients with embolism 64 to 105 kg, median 75, $p < 0.0001$). Stretched ASD diameter and Qp/Qs were larger in enrolled patients because of left to right shunt than in those with systemic embolism (mean \pm SD 15 ± 4 vs 10 ± 3 mm, $p = 0.01$; 2.0 ± 0.5 vs 1.1 ± 0.2 , $p < 0.0001$, respectively). Echocardiographic guidance was utilized in 45 patients (32 transthoracic and 13 transesophageal). General anesthesia was used in 16 procedures, including all involving transesophageal echocardiography. Median fluoroscopy time was 22.9 minutes (12.6 to 80 minutes, $n = 34$), and total procedure time was typically 2 to 3 hours. Duration of hospitalization for ASD occlusion ranged from 0 to 3 days (13 outpatient procedures).

Percutaneous device removal: Percutaneous device removal before release from the delivery wire was accomplished in 14 patients (19 devices). Device removal was attempted when the occluder was inadvertently pulled through the ASD before buttoning or when the position of the fully buttoned device was unsatisfactory. Delivery of another (generally larger) device was achieved in 8 of these patients, and the procedure was abandoned after device removal in the other 6 patients. Stretched ASD diameter in these 6 patients averaged 21 mm, and after difficulty was encountered in device placement, it was considered that ASD size had been underestimated or that the rim of supporting septal tissue was inadequate. Percutaneous device removal was attempted unsuccessfully in 1 patient: A patient enrolled because of systemic embolism was noted to have increased interatrial shunting by transesophageal echocardiography with the device in place, despite what appeared to be excellent placement of the device. Removal was therefore attempted, but the occluder was entrapped by the large flap of the septum primum and could not be pulled through the defect. Retrieval of this device was accomplished surgically, with concomitant repair of the ASD. Devices were therefore released in 50 of 57 patients enrolled in the trial.

Retrieval of released devices: Devices released from the delivery system were surgically retrieved in 4 patients. In the first patient, the counteroccluder separated from the occluder (i.e., it "unbuttoned") within min-

utes after release. The occluder remained in position, but the counteroccluder migrated to the junction of the right atrium and inferior vena cava. Unbuttoning was discovered on routine chest roentgenograms obtained < 24 hours after device implantation in 2 patients. In both cases, the occluders had remained in position, but the counteroccluders had embolized to distal pulmonary arteries (Figure 3). In the fourth patient, the entire buttoned device embolized to the main pulmonary artery immediately upon release. All patients remained clinically stable, and surgical ASD repair and device retrieval was performed without incident.

Successful implantations: Devices were therefore successfully implanted in 46 of 57 patients attempted (81%). The age (median 4 years, range 1 to 62), weight (median 18 kg, range 10 to 105), stretched ASD size (14 ± 4 mm) and Qp/Qs before occlusion (1.8 ± 0.6) of the implanted group were similar to the study population as a whole. Qp/Qs was measured immediately after occlusion in 44 patients, and decreased significantly to 1.1 ± 0.2 ($p < 0.0001$). Of the 38 patients with significant left to right shunts in whom devices were successfully implanted, 31 had no shunt or only a trivial residual shunt (Qp/Qs ≤ 1.2) immediately after implantation, and 7 had small (Qp/Qs 1.3 to 1.4, $n = 5$) or moderate (Qp/Qs 1.5–2.0, $n = 2$) residual shunts. No large (Qp/Qs > 2.0) shunts were observed after occlusion.

Residual shunts in follow-up: Duration of follow-up was 12 to 20 months in 21 patients, 6 to 11 months

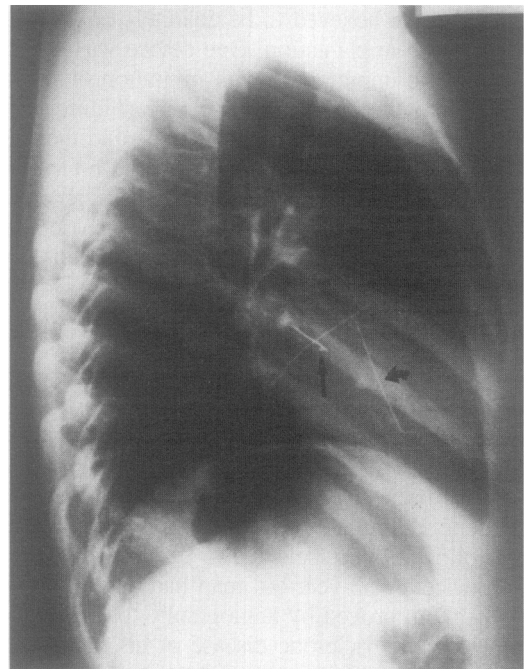


FIGURE 5. Lateral chest roentgenogram obtained 1 month after implantation of a buttoned device. The opaque button marker (straight arrow) remains attached to the occluder, which is positioned against the atrial septal defect. The counteroccluder (curved arrow) has become unbuttoned from the occluder and its distal end has passed through the tricuspid valve. This patient has been followed for 20 months, with no change in radiographic position of either device component, and no residual shunt by Doppler echocardiography.

in 15 patients, and 1 to 5 months in 10 patients. Residual shunts were classified by clinical and echocardiographic criteria as follows: moderate shunts were those with a diastolic flow rumble in the tricuspid area, a widely split second heart sound, or evidence of right ventricular volume overload on echocardiography; small shunts were those without these findings, but with 1 to 2 mm defects visible by echocardiography and confirmed by color flow and pulsed Doppler; trivial shunts were those evidenced only by Doppler (i.e., small color flow flares along the atrial septum, with or without pulsed Doppler confirmation) without a visible defect in the atrial septum. Figure 4 shows the distribution of residual shunts at follow-up. The prevalence of small or moderate residual shunts was 15% immediately after the occlusion procedure, and declined to 7% at 1 month, 3% at 6 months and 0% at 12 months. Of the 7 patients with small or moderate residual shunts immediately after occlusion, 1 had no shunt, 5 had trivial shunts, and only 1 still had a moderate residual shunt at 6-month follow-up. By 12 months, most trivial shunts have also resolved, with 81% of patients having no shunt. The decrease in prevalence and severity of residual shunting during follow-up was statistically significant by Spearman's rank correlation test ($\rho = -0.329$, $Z = -3.97$, $p < 0.0001$). Cardiac catheterization has been performed in 11 patients with trivial residual shunts by color flow Doppler at 6 to 12 months after occlusion: 9 had no shunt by oximetry and angiography, and 2 had trivial shunts confirmed.

Complications: The following complications observed during follow-up (≥ 2 weeks after the occlusion procedure) were believed to be definitely or possibly related to device implantation: One device was noted at 1 month to have unbuttoned, with migration of the counteroccluder to the tricuspid valve ring (Figure 5). This position has been stable for 20 months, and the ASD is completely occluded. The patient has had no symptoms of arrhythmia, and Holter recordings have shown only sinus rhythm. Mild tricuspid regurgitation noted in this and in 1 other patient resolved within 6 months. Trivial mitral regurgitation was found by color flow Doppler in 2 patients in whom an arm of the occluder was positioned in the mitral funnel. The regurgitation has resolved in 1 patient, and is inaudible in the other. Asymptomatic atrial flutter was noted in a 46-year-old patient 2 weeks after device implantation. The patient was treated with digoxin and converted promptly to sinus rhythm. There have been no recurrences of atrial flutter over the subsequent 11 months. Other complications observed during followup were believed to be definitely unrelated to the device: A 63-year-old man had an acute myocardial infarction, proved by angiography to be due to progression of atherosclerotic disease of his right coronary artery. A 3-year-old patient was hospitalized for acutely altered mental status ultimately attributed to accidental drug ingestion; magnetic resonance imaging and computed tomography of the brain showed no evidence of cerebral thromboembolism. Notably, there have been no cases of endocarditis and no clinically evident embolic events in 350 patient-months of follow-up.

DISCUSSION

Design features of the buttoned device that were demonstrated in an animal model⁵ included a delivery system suitable for small children as well as adults and a device that could be repositioned or easily retrieved if in improper position. The 8Fr delivery sheath proved applicable to our patient population, with its median patient age of 4 years (including patients weighing as little as 10 kg), and successful application of the device to even smaller patients has been reported.⁷ Although the 45 and 50 mm devices, as well as larger devices,¹² require a 9Fr delivery sheath, they are generally used only in the adolescent or adult patient. Nevertheless, even the 9Fr delivery sheath compares favorably with the 11Fr sheath required to implant the Clamshell-occluding device.¹³

Device removal: Removal of unreleased devices was accomplished in the catheterization laboratory in 19 of 20 attempts (14 of 15 patients), and successful implantation of another device was achieved in 8 patients at the same procedure. One counteroccluder that had embolized to the left pulmonary artery was also retrieved in the catheterization laboratory. Transcatheter retrieval of released occluders was not attempted in this trial. The increased strength of the button loop and delivery wire loop in the second-generation buttoned device⁸ used in this trial made the device readily removable before release from the delivery wire, even after buttoning.

Buttoning and unbuttoning: The button in the second-generation device includes a radiopaque marker, which makes passage of the button through the counteroccluder more radiographically apparent. However, Figure 3 shows that unbuttoning can occur despite passage of the button marker to the right side of the counteroccluder before release. The radiopaque button marker makes the button more eccentric with respect to the axis of the delivery wire (Figure 1), which may have contributed to the observed frequency of unbuttoning (4 of 50 released devices, 8%). A third-generation device has been developed that includes a third small loop between the button loop and the delivery wire, creating a less eccentric button. Operator experience may also be an important factor in unbuttoning, as 3 of 4 cases of unbuttoning occurred in the first week of experience.

Efficacy of the buttoned device: For patients with left to right shunts, relief of the right heart from volume overload represents clinically effective treatment. We therefore believe that patients with no or only trivial residual shunts have been effectively treated. At last follow-up, 45 of 46 patients (98%) with successful device implantation have been effectively treated for left to right atrial shunting. We also observed that residual left to right shunting decreased significantly over time (Figure 4), and 81% of patients have no residual shunt after 12-month follow-up. At the most recent follow-up, 28 patients (61%) had no residual shunt, 17 (37%) had only a trivial residual shunt (9/11 of which were not confirmed at repeat cardiac catheterization) and only 1 patient (2%) had a clinically significant residual shunt.

These results compare favorably with the multicenter trial of the Clamshell-occluding device, in which 33% of patients had (by our criteria) small or moderate residual shunts at 12 months by transthoracic echocardiography.¹⁴

ASD closure to prevent systemic emboli is controversial,¹⁵ and judging efficacy for this indication is less straightforward. Although the number of patients we treated for this indication is small and the duration of follow-up has been relatively short, no patient has had a recurrent embolic event since device implantation. Bridges and co-workers¹⁶ demonstrated a reduction in the incidence of recurrent embolic events in a larger group of patients treated with the Clamshell-occluding device, and we hope that the buttoned device will prove similarly effective.

Safety of the buttoned device: All 57 patients tolerated the occlusion procedure well and remained hemodynamically stable, including the 5 patients requiring surgical device retrieval and ASD closure. The major clinical consequence for the 11 patients with unsuccessful device implantation was the need for surgical closure of their ASD. We speculate that increased operator experience and the improved third-generation buttoned device may reduce the incidence of unbuttoning and device embolization. There have been no instances of endocarditis or systemic embolism in 350 patient-months of follow-up. With 95% confidence, the upper bound for incidence of these 2 complications can be calculated at 1 case/100 patient-months. Enrollment of more patients and continued follow-up are necessary to further define the long-term consequences of transcatheter ASD occlusion with the buttoned device.

Conclusions: We conclude that the buttoned device can provide effective closure of ostium secundum ASD <25 mm in diameter, with effective clinical closure in 79% of cases attempted and 98% of patients in whom devices were successfully implanted. The prevalence and size of residual shunts decreased during follow-up, and no instances of endocarditis or thromboembolism were observed. Percutaneous device removal can be readily accomplished before release from the delivery wire. The major complications of attempted occlusion were device unbuttoning, device embolization and device entrapment, all of which were well tolerated and effectively treated by surgery. Continued trial of this de-

vice is warranted to determine whether use of the third-generation device can reduce or eliminate unbuttoning and to further document the longer term response to transcatheter ASD occlusion.

Acknowledgment: We wish to acknowledge the assistance of Paramjeet S. Chopra, MD, Hrair Garabedian, MD, Peter Lang, MD, and Allen D. Wilson, MD, and of Cathy Brown, RNC MSN, Amy Lindauer, RN, and Patricia Smith, RN CNS. We particularly wish to thank Rolando Zamora, MD, for providing continuing follow-up of patients enrolled at the University of Arizona.

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