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# Intermediate-Term Results of Phase I Food and Drug Administration Trials of Buttoned Device Occlusion of Secundum Atrial Septal Defects

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***Objectives.*** **This study was conducted to evaluate the intermediate-term results of the multi-institutional U.S. trial of the buttoned device for transcatheter closure of atrial septal defects (ASDs).**

***Background.*** **The trial was conducted in three centers (University of Arizona, University of Michigan and University of Wisconsin) under a Food and Drug Administration (FDA)-approved clinical trial with investigational device exemption. Only short-term follow-up is known.**

***Methods.*** **All 46 patients who had successful implantation of the device were prospectively followed up. Patients were evaluated at 1, 6 and 12 months after device occlusion and yearly thereafter.**

***Results.*** **This cohort was followed up from 51 to 68 months (mean 60.8, median 62). Patient ages ranged from 1 to 62 years (median 4); weights ranged from 10 to 105 kg (median 18); and stretched ASD sizes were 14 ± 4 mm (left to right shunts) and 10 ± 3 mm (right to left shunts). Of the 46 patients, 45 (98%) had effective occlusion of their ASD, and 34 (74%) had complete ASD closure. The incidence of residual shunts decreased from 65% (30 of 46 patients) at 1 month after device placement to 27% (12 of 45 patients) at last follow-up. All residual shunts were quantitated as trivial. Only two patients (4%) required reintervention for significant residual defects. There were no cases of endocarditis or thromboembolism in 224 patient-years of follow-up.**

***Conclusions.*** **In up to 5.5 years of follow-up, the buttoned device provided effective closure in 98% of patients in whom the device was successfully implanted. The incidence of residual shunts decreased during follow-up, and no instances of endocarditis or thromboembolism were observed.**

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Although the safety, feasibility and effectiveness of transcatheter occlusion of secundum atrial septal defects (ASDs) with the buttoned device have been demonstrated, only short-term follow-up is known (1,2). The purpose of this study was to evaluate the intermediate-term results of the multi-institutional U.S. trial of the buttoned device for transcatheter closure of ASDs.

## Methods

The trial was conducted in three centers (University of Arizona, University of Michigan and University of Wisconsin) from March 1991 to August 1992. The trial was approved by the U.S. Food and Drug Administration (FDA) and sponsored by Custom Medical Devices, which supplied the devices. The buttoned device, occlusion procedure and occlusion protocol have been previously described (1,2).

**Patient selection.** The criteria for patient selection has been previously reported (1). In brief, patients were eligible for inclusion in this study if they had ostium secundum ASD or a history of presumed paradoxic arterial embolism through a small ASD or patent foramen ovale (no other source identified) and all patient defects were thought to warrant surgical closure. Forty-six of 57 patients had successful implantation of the device. The characteristics of the 11 patients in whom ASD closure was attempted but failed have been previously described (1). These patients were removed from the cohort for analysis because their defects were surgically closed. Therefore, this cohort represents the 46 patients who had successful implantation of the device.

**Follow-up protocol.** Patients were evaluated at 1, 6 and 12 months after device occlusion and yearly thereafter. Evaluations consisted of a history and physical examination, chest X-ray film, electrocardiogram and Doppler echocardiographic

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**Abbreviations and Acronyms**

ASD = atrial septal defect
FDA = Food and Drug Administration
RV = right ventricle, right ventricular

studies. Chest X-ray films were studied for wire fractures and device displacement. Doppler echocardiographic studies were performed to assess for right ventricular (RV) volume overload, device position in relation to adjacent structures and residual shunts. Right ventricular volume overload is defined as an enlarged RV (>95th percentile for the patient's body surface area) and flat to paradoxic interventricular septal motion. Relief of the right heart from volume overload represents clinically effective treatment. Therefore, in patients with left to right shunts, we considered there to be effective ASD closure if there was no residual shunt or if the residual shunt was quantitated as trivial and there was resolution of RV volume overload, a normally split $S_2$ and absence of a diastolic rumble in the tricuspid area. In patients with stroke and presumed paradoxic emboli, effective closure was defined as disappearance of the right to left atrial level shunt by a sensitive method. Transesophageal contrast echocardiographic study with the Valsalva maneuver was performed 3 and 6 months after device implantation, and transthoracic echocardiograms were performed yearly thereafter. Residual shunts were quantitated as previously described (2), as outlined in Table 1. Electrocardiograms were studied for conduction disturbances, arrhythmias and evidence of RV hypertrophy.

**Event-free rates.** Actuarial event-free rates are shown in Figure 1. Surgical or transcatheter intervention for removal or inspection of the device with or without closure of the ASD, or recatheterization for residual ASD with additional device placement, was considered an event. The actuarial event-free rate is 96% at 68 months of follow-up.

**Table 1.** Quantification of Atrial Shunts by Echocardiography

| Grade | Criteria |
|---|---|
| None | No defect by two-dimensional echocardiography<br>No shunt detected with color flow mapping on right atrial side of device<br>No RV volume overload |
| Trivial | No defect by two-dimensional echocardiography<br>Minimal color disturbance on right atrial side of device (<1-mm width at origin of color Doppler jet)<br>No RV volume overload |
| Small | No defect by two-dimensional echocardiography<br>(1- to 2-mm width of color Doppler jet either in center or in periphery of device) |
| Moderate | Defect visualized on two-dimensional echocardiography (>2-mm width of color Doppler jet); RV volume overload may be present |
| Large | Defect visualized by two-dimensional echocardiography; large and/or multiple color Doppler jets; RV volume overload |

RV = right ventricular. Modified from Rao et al. (2).

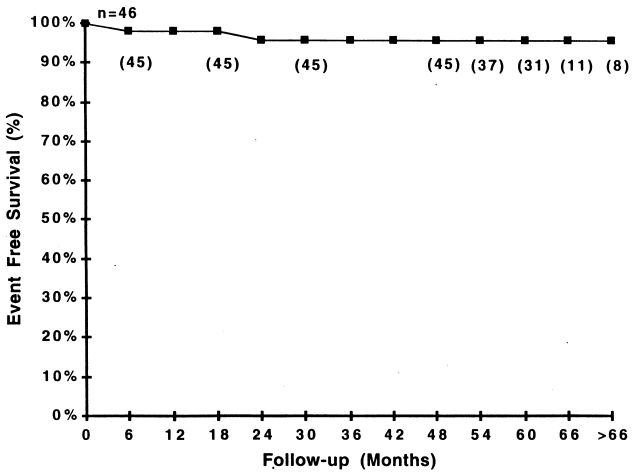


**Figure 1.** Actuarial event-free rates after transcatheter occlusion of secundum ASD with buttoned devices.

**Data analysis.** Data are expressed as the mean value ± SD for continuous, normally distributed variables. Median values and ranges are given for data with skewed distribution. Actuarial analysis of event-free rates was performed using the Kaplan-Meier method.

## Results

**Study group.** All 46 patients with successful implantation of the device were prospectively followed. Patient ages at the time of device implantation ranged from 1 to 62 years (median 4), and weights ranged from 10 to 105 kg (median 18). Devices were implanted in 38 patients with significant left to right shunts, stretched ASD size (14 ± 4 mm) and Qp/Qs before occlusion (1.8 ± 0.6), and in eight patients with presumed paradoxic embolism and stretched ASD size (10 ± 3 mm). This cohort has been followed from 51 to 68 months (mean 60.8, median 62). Nineteen patients have been followed from 61 to 68 months and 26 patients from 51 to 60 months.

**Residual shunts in follow-up.** At most recent follow-up, 45 (98%) of 46 patients had effective occlusion of their ASD: all patients with ASD and seven of eight patients with stroke and patent foramen ovale. Thirty-four (74%) of 46 patients had complete ASD closure. This represents a decrease in the incidence of residual shunts from 65% (30 of 46 patients) at 1 month after device placement to 27% (12 of 45 patients) at the last follow-up. None of these residual shunts were clinically significant; they were all quantitated as trivial.

**Surgical retrieval of devices.** One patient had the defect occluded for prevention of recurrence of thromboembolic stroke. This patient had repaired tetralogy of Fallot and a pacemaker implanted; thrombi from the pacemaker site were presumed to paradoxically embolize, causing stroke. Four months after device implantation, the patient had a transient ischemic episode. She subsequently underwent surgical closure of a small residual defect and device explantation.

**Percutaneous device removal.** The one patient (1) with a persistent moderate residual shunt up to 20 months after device implantation underwent transcatheter retrieval of one arm of the occluder, which was protruding across the ASD into the right atrium, and she had placement of a second device (3), with only a trivial residual shunt at 32 months of follow-up after the second procedure. This patient's recatheterization was considered an event, but because placement of an additional device provided effective closure of her persistent moderate residual shunt, the final outcome was considered a success.

**Follow-up observations.** Physical examinations revealed no residual murmurs indicative of an ASD. M-mode echocardiographic images suggested resolution of volume overloading and a decrease in the size of the RV—from 2.3 ± 0.6 to 1.6 ± 0.46 cm at last follow-up. Two-dimensional echocardiography revealed stable position of the device. Electrocardiograms showed wandering atrial pacemakers in two patients, and persistence of RV hypertrophy in one patient with no residual shunt noted by echocardiography. The previously reported patient with atrial flutter (1) has been off medication for 2 years without recurrence. There were no wire fractures or changes in device position noted on the chest X-ray films. There have been no cases of endocarditis or thromboembolism in 224 patient-years of follow-up.

## Discussion

This study demonstrates an excellent 5.5-year clinical outcome of this group of patients after ASD occlusion with the buttoned device. Of the 46 patients, 45 (98%) had effective ASD closure and 34 (74%) had complete ASD closure; 12 (27%) of 45 patients had trivial residual shunts of no clinical significance. Only two patients (4%) required repeat intervention for ineffective ASD closure: surgery in one and catheter intervention in the other. These results compare favorably with the published intermediate-term follow-up data on the Bard Clamshell occluding device (4). In the study by Prieto et al. (4), with a mean follow-up of 41 months, effective ASD occlusion was achieved in 30 (97%) of 31 patients, although their complete ASD closure rate of 55% (17 of 31 patients) was lower than ours (74%), and their incidence of trivial residual shunts was higher than ours—12 (39%) of 31 patients versus 12 (27%) of 45 patients. The incidence of ineffective ASD closure was similar in both studies. Our higher rate of complete closure and lower rate of residual shunts may be attributable to our longer follow-up—mean 60.8 months versus mean 41 months—because it has been shown (1,2) that the incidence of residual shunts decreases with time.

It is of interest to note that the rate of effective ASD closure in our study and in the Bard Clamshell study (4) is similar to the recent surgical experience (5) where 2 (2%) of 104 patients had a significant residual ASD at long-term follow-up. The incidence of trace residual shunts in the surgical group is not known. Likewise, the intermediate-term implications of trace residual shunts in our patients and in the Bard Clamshell study are not known. Longer follow-up will be necessary to determine whether these trace residual shunts will become clinically relevant.

A large variety of devices for transcatheter closure of ASD have been developed (6). However, most of these devices require large-sized catheter delivery systems that may be problematic in infants and young children. The buttoned device can be implanted through an 8F or 9F sheath. Indeed, the buttoned device was implanted with relative ease in an infant weighing 3.6 kg (7).

Our cohort of 46 patients was derived from 57 attempted ASD occlusions (1), giving a successful implantation rate of 80%, similar to the international experience (2). With the introduction of the fourth-generation device and the over-the-wire delivery technique, implantation success rate has increased to nearly 99% (6); therefore, the intermediate-term success rate is likely to be substantially higher with the newer design.

At the present time, phase II FDA-approved clinical trials with the button device are under way. We believe that the current success rates and low incidence of complications certainly support the ongoing clinical trials.

**Conclusions.** The buttoned device provided safe and effective ASD closure in 98% of our patients up to 5.5 years after successful implantation. The incidence of residual shunts decreased during follow-up, and no instances of endocarditis or thromboembolism were observed in 224 patient-years of follow-up.

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