CONGENITAL HEART DISEASE

Symptomatic atrial arrhythmias and transcatheter closure of atrial septal defects in adult patients

C K Silversides, S C Siu, P R McLaughlin, K L Haberer, G D Webb, L Benson, L Harris

Objective: To determine whether transcatheter device closure of a secundum atrial septal defect (ASD) will reduce the risk of developing subsequent atrial arrhythmias.

Design: The incidence and predictors of symptomatic atrial tachyarrhythmias (AT) were examined in adults undergoing transcatheter closure of ASDs.

Setting: Toronto Congenital Cardiac Centre for Adults.

Patients: 132 consecutive patients, mean (SD) age 44 (16) years; 74% female.

Main outcome measure: Sustained or symptomatic atrial arrhythmias at early follow up (six weeks; n = 115) and intermediate follow up (last clinic visit 17 (11) months post surgery; n = 121).

Results: 15% of the patients (20 of 132) had AT before the procedure (14 paroxysmal, six persistent). Patients without a history of arrhythmia had a low incidence of AT during early follow up (6%) and intermediate follow up (11%/year), while all patients with persistent AT before closure remained in atrial fibrillation or flutter. Of patients in sinus rhythm but with a previous history of AT, two thirds remained arrhythmia-free at follow up, with overall incidences of paroxysmal and persistent AT of 17%/year and 11%/year. A history of AT before closure (risk ratio (RR) 35.0, 95% confidence interval (CI) 7.2 to 169.0) and age > 55 years at the time of device insertion (RR 5.6, 95% CI 1.2 to 25.0) predicted AT after closure.

Conclusions: Device closure of an ASD before the onset of atrial arrhythmias may protect against the subsequent development of arrhythmia, in particular in patients less than 55 years of age.

Atrial tachyarrhythmias (AT) are common among adult patients with secundum atrial septal defects (ASD) and contribute to substantial cardiac morbidity. Surgical closure of an ASD, available for nearly five decades, has been shown to improve long term cardiac mortality and morbidity, but atrial arrhythmias remain an important determinant of late cardiac morbidity in this population. Recently, transcatheter device closure of an ASD has been shown to be a safe and effective alternative to surgery in appropriately selected patients. While early surgical closure of an ASD may reduce the long term risk of developing AT, the impact of transcatheter device closure on atrial arrhythmias is unknown. This needs to be explored, as the procedure may lead to changes in the threshold for closure and to a trend towards earlier closure. It is widely accepted that delay in surgical closure can lead to irreversible cardiac changes that prevent successful restoration of sinus rhythm. Transcatheter device closure of an ASD results in regression of structural changes, beginning as early as one month after closure. The purpose of this study was to determine whether transcatheter device closure of an ASD would reduce the risk of subsequent atrial arrhythmias. To accomplish this, we examined the incidence and predictors of AT after transcatheter device closure of ASDs.

METHODS
This was a cohort study of patients undergoing transcatheter device closure of an ASD at the University Health Network, Toronto, Canada. We included consecutive patients referred for closure of a secundum ASD between April 1997 and June 2001. Patients with a patent foramen ovale or those who did not have a device insertion were not included in the study. The institutional ethics board at the University Health Network approved the study.

Baseline clinical data
Baseline clinical data included age at the time of device insertion, sex, presence of symptoms, New York Heart Association (NYHA) functional class, cardiac drug treatment, and a history of sustained or symptomatic atrial arrhythmias, stroke or transient ischaemic attacks, or clinical right heart failure. The type of occluder device (Amplatzer or Cardioseal) and the size of the device were recorded.

Echocardiographic data
Maximum diameter of the ASDs and the number of defects were determined by transoesophageal echocardiography. Right ventricular dimensions were estimated from transthoracic right ventricular inlet measurements made at end diastole from the apical four chamber view. The right ventricle was considered enlarged when the inlet measurement was > 45 mm. Right and left ventricular systolic function were assessed visually as normal or impaired. The degree of tricuspid regurgitation was determined by colour Doppler. All echocardiograms were interpreted by experienced echocardiographers.

Primary outcomes
The primary outcomes of interest were sustained or symptomatic AT at the time of early (six week) follow up, and at intermediate follow up (the most recent clinical visit). Arrhythmias were documented by standard 12 lead ECGs or 24 hour ambulatory Holter monitors.

Statistical analysis
Statistical analysis was undertaken using SPSS version 10.0 (SPSS Inc, Chicago, Illinois, USA). Comparisons between patients with and without arrhythmias were done using the Pearson χ² test, Fisher’s exact test, or Student’s t test as appropriate. Comparisons between multiple groups were made with the Kruskal–Wallis test or pairwise testing with...
RESULTS

In all, 132 consecutive patients underwent device closure of a secundum ASD between June 1997 and April 2001 (table 1). Amplatzer devices were used in 80% of cases and Cardioseal patches in 20%. The mean age at the time of device insertion was 44 (16) years. Of the 15% of patients who had persistent atrial fibrillation or flutter, 14 had paroxysmal atrial fibrillation and one had persistent atrial fibrillation. Indications for device closure included: right ventricular dilatation (83%), functional limitation (50%), arrhythmias (15%), right heart failure (7.6%), and transient ischaemic attack or stroke (6.1%). Indications were not mutually exclusive.

The mean size of the defects was 15 (5) mm (range 4–37 mm). Nine per cent of the patients (12 of 132) had more than one ASD. Echocardiographic assessment of the right ventricular dimension (n = 127) and function (n = 113) showed that most patients had evidence of right ventricular dilatation (81%), whereas fewer had evidence of right ventricular dysfunction (15%).

Compared with patients without AT, those with paroxysmal or persistent AT were older at the time of the procedure (42 (15) v 54 (17) v 67 (10) years, p < 0.001), were more often symptomatic (63% v 93% v 100%, p = 0.02), and had worse NYHA functional class (37% v 62% v 83%, p = 0.02) (table 2).

Arrhythmic events in early follow up

No arrhythmic events occurred at the time of device insertion or in the 24 hour postprocedure observation period. Seventeen patients referred from outside the province of Ontario did not return for the six week follow up visit. Six week clinical visits were available in the remainder of the patients (115 of 132). Palpitations (26%) and migraine headaches (16%) were commonly reported at the time of this visit. One patient had a transient sensory deficit, but there were no strokes.

Fifteen patients (13%) experienced early AT. None of the six patients with persistent AT was in sinus rhythm at the six week visit, while nine patients experienced paroxysmal atrial fibrillation. Of the latter group, six had not had documented AT before the procedure; three of these patients had complained of palpitations before the procedure.

The prevalence of AT at the time of the six week visit is shown in table 3. Early paroxysmal AT was uncommon in patients with no previous history of arrhythmias compared with those with paroxysmal or persistent AT (6% v 33% v 100%, respectively, p < 0.001). A history of persistent AT compared with no AT (100% v 7%, p < 0.001), age > 55 years (47% v 18%, p = 0.02), and female sex (79% v 53%, p = 0.02) were associated with early arrhythmic events. A history of paroxysmal AT was not associated with arrhythmias events (20% v 6%, p = 0.09).

Arrhythmic events in intermediate follow up

Follow up data were available in 92% (121 of 132 patients). Complete follow up data were available for 121 patients, with a mean follow up time of 17 (12) months. Eleven per cent of these patients (13 of 121) had AT during follow up.

Of the 14 patients with paroxysmal AT before the procedure, nine (64%) did not have arrhythmias during follow up (fig 1). Three patients (21%) had a recurrence of paroxysmal atrial flutter and two (14%) developed persistent atrial fibrillation. The first patient had a history of surgical closure of an ASD as a child and had a device insertion for patch dehiscence. The recurrence of arrhythmias occurred two years after the device insertion. The second patient initially stopped antiarrhythmic treatment and remained arrhythmia-free until one year after the procedure, at which time his atrial fibrillation returned and persisted. Two patients who had been free of arrhythmias before the procedure developed paroxysmal atrial flutter. Both these patients had experienced palpitations and one had a stroke before referral for device closure. Of the eight patients (fig 1) with persistent atrial fibrillation during follow up, six did not undergo subsequent cardioversion and were managed with antiplatelet therapy; one underwent cardioversion but reverted to atrial fibrillation during follow up; and the remaining patient’s atrial flutter was successfully treated by catheter ablation two years after the ASD device closure.

### Table 1 Baseline characteristics of all patients undergoing transcatheter closure of secundum atrial septal defects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n = 132)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>97 (74%)</td>
</tr>
<tr>
<td>Age at the time of closure (years)</td>
<td>44 (16)</td>
</tr>
<tr>
<td>Range</td>
<td>15–78</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>17 (11)</td>
</tr>
<tr>
<td>Range</td>
<td>3–59</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>53 (40%)</td>
</tr>
<tr>
<td>Presyncope</td>
<td>19 (14%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>66 (50%)</td>
</tr>
<tr>
<td>NYHA functional class &gt;2</td>
<td>55 (42%)</td>
</tr>
<tr>
<td>History of atrial arrhythmias</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>112 (85%)</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>14 (11%)</td>
</tr>
<tr>
<td>Persistent</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>History of stroke or transient ischaemic event</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>History of right heart failure†</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>Cardiac drug treatment</td>
<td>32 (24%)</td>
</tr>
<tr>
<td><strong>Echocardiographic data</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Range</td>
<td>4–37</td>
</tr>
<tr>
<td>Right ventricular dilatation (n = 127)</td>
<td>105 (83%)</td>
</tr>
<tr>
<td>Right ventricular systolic dysfunction (n = 113)</td>
<td>20 (18%)</td>
</tr>
<tr>
<td><strong>Procedural data</strong></td>
<td></td>
</tr>
<tr>
<td>Type of device</td>
<td></td>
</tr>
<tr>
<td>Amplatzer</td>
<td>105 (80%)</td>
</tr>
<tr>
<td>Cardioseal</td>
<td>27 (20%)</td>
</tr>
<tr>
<td>Size of device (mm) (mean (SD))</td>
<td></td>
</tr>
<tr>
<td>Amplatzer</td>
<td>23 (6.5)</td>
</tr>
<tr>
<td>Range</td>
<td>11–40</td>
</tr>
<tr>
<td>Cardioseal</td>
<td>39 (2.4)</td>
</tr>
<tr>
<td>Range</td>
<td>33–40</td>
</tr>
</tbody>
</table>

*Clinical evidence of right heart failure.
†Includes: digoxin, β adrenergic antagonists, calcium channel antagonists, or antiarrhythmic drugs.
Table 3 shows the annual incidence rates of AT. Patients without a history of AT had a lower annual incidence of paroxysmal AT than those with a history of previous paroxysmal AT (1%/year vs 17%/year, p = 0.003). The incidence of development of persistent AT in patients with a history of paroxysmal arrhythmias was 11%/year.

Based on the results of the univariate analysis, variables entered into the multivariate model included: age at the time of the procedure (entered as a categorical variable), sex, history of palpitations, history of AT, and NYHA class > 2. History of AT before the procedure (risk ratio (RR) 35.0, 95% confidence interval (CI) 7.2 to 169.0; p < 0.001) and age ≥55 years at the time of device closure (RR 5.6, 95% CI 1.2 to 25.0; p = 0.03) were independent predictors of arrhythmias during follow up. Secondary analysis (n = 113) in which data on the echocardiographic measures of both right ventricular dimension and function were available did not identify additional predictors.

The probability of remaining arrhythmia-free at one year was 88%. Arrhythmia-free survival was significantly longer in patients who underwent closure before the age of 55 years (fig 2). Similar improvements in arrhythmia-free survival were seen in patients who underwent closure of the ASD before the age of 55 years (fig 3).

Of the 11 patients lost to follow up, none had a history of AT. The mean age of the patients lost to follow up was 41 (15) years, eight were female, one had more than one defect (the mean diameter of the defect was 15 (4) mm), seven had evidence of right ventricular dilatation, and one had right ventricular dysfunction. Other than differences in the baseline history of arrhythmias, all other characteristics were similar to the group of patients with intermediate term follow up data.

DISCUSSION
In this study we examined the incidence of early and intermediate term AT after device closure of secundum ASD in adult patients. In this cohort, 15% of the population had documented AT before the procedure. Patients with no history of AT and those undergoing closure before the age of 55 years had a high likelihood of remaining arrhythmia-free in intermediate term follow up. Despite closure of the ASD, patients with persistent atrial fibrillation or flutter at the time of closure were unlikely to be in sinus rhythm in follow up.

Early postoperative AT has been documented in many surgical series following ASD closure. Postoperative AT are probably multifactorial and relate to the techniques of surgery, catecholamine stimulus, and drugs given in the postoperative setting. Rates of AT vary between 4–40% in the early postoperative period. In our study, we report a prevalence of early AT of 13% after transcatheter device closure.

Despite successful surgical closure of an ASD, AT continue to be a common cause of cardiac morbidity in late follow up. For example, in a study from our centre examining AT after surgical closure of ASDs, 60% of patients with pre-existing AT continued to have arrhythmias after closure of an ASD, and an additional 3% (five cases) developed new AT. In our present series, the incidence of AT during follow up was 11%, which is lower than in many surgical series; however, our follow up (for a mean of 17 (11) months) was shorter than the surgical series (mean duration ranging between 3.8–27.2 years). Little information is available about the incidence of AT after device closure of an ASD. In 61 patients (median age 12 years, 19 patients over 18 years) who had undergone device closure of an ASD, Berger and colleagues reported a 5% incidence (n = 3) of de novo AT (mean follow up seven months). Possible explanations for the higher incidence rates of AT in our population include the older age of our cohort, the inclusion of patients with a history of paroxysmal or persistent AT, and the longer duration of follow up. Furthermore, in our study we examined incidence rates stratified according to the presence of arrhythmias.
before device insertion and predictors of intermediate term arrhythmic events.

The presence of AT before surgical closure of an ASD has been shown to be a determinant of late arrhythmic outcomes. Right atrial dilatation caused by the interatrial shunting of blood results in structural changes that will provide a substrate for AT. Arrhythmogenic foci in the region of the pulmonary veins and vena caval junctions may contribute to the propensity to arrhythmias in this population. Once initiated, persistence of the arrhythmia may lead to further distension of the right atrium or pulmonary veins and more advanced and permanent electrical remodelling. As atrial remodelling is thought to be a potentially reversible process, early intervention may play a role in the prevention of persistent AT. Regression of right atrial dilatation and shortening of the QRS duration on the ECG has been shown to begin as early as one month after transcatheter device closure of an ASD. In keeping with this observation, two thirds of our patients with paroxysmal AT before closure were arrhythmia-free during follow up. Although the structural or cellular criteria distinguishing reversible from irreversible remodelling have not been defined, in this cohort we observed that once patients had persistent atrial fibrillation or flutter, spontaneous return to sinus rhythm was unlikely. From the available data, we were unable to determine whether cardioversion would be effective in maintaining sinus rhythm after there has been atrial remodelling secondary to device closure.

Surgical studies suggest that ASD should be considered for closure in patients before the age of 40 years in order to prevent late AT. In contrast, we found that device closure before the age of 55 years was associated with fewer arrhythmic events during follow up. Mean age at the time of procedure in our patients (44 (16) years), baseline prevalence of AT (15%), and symptom status were similar to those described in the surgical series and cannot account for this difference. The mean duration of follow up in our series (17 (11) months) was shorter than in most surgical series and may have been a factor in accounting for the difference in this predictor of arrhythmic events after closure.

For those patients with persistent AT, the Cox maze procedure has been proposed as an adjunctive intervention at the time of surgical ASD closure. In a series of 26 patients, Kobayashi and colleagues reported successful outcome during long term follow up in patients with ASD and atrial fibrillation undergoing concomitant Cox maze. This procedure remains an alternative treatment option for the patient with persistent AT, but the potential for associated surgical morbidity needs to be taken into account. Recent reports suggest that it may be possible to accomplish long term successful elimination of atrial fibrillation using a catheter ablation approach, while elimination of typical atrial flutter using radiofrequency ablation is already well established. For the patient with persistent AT, it is conceivable that a future approach to device closure may come to incorporate catheter ablation of the arrhythmia before closure.
Limitations
The referral pattern at our institution is such that patients are referred from various regions of the country. Despite the geographical variability, only 8% of patients were lost to follow up. In this study, patients with asymptomatic AT were not identified, as Holter monitoring was not available in most cases. Because of the increased prevalence of asymptomatic AT in the older age group, information about this may be of additional value in assessing the incidence of AT before and after device insertion. Although our study provides information on the intermediate term follow up in patients after device closure of an ASD, longer follow up data are needed.

Conclusions
The data from this intermediate follow up study suggest that device closure of an ASD before the onset of atrial arrhythmias may protect against the subsequent development of arrhythmia, in particular in patients less than 55 years of age. Furthermore, patients with a history of paroxysmal arrhythmias can anticipate a reduction in the incidence of arrhythmia post closure. New onset or paroxysmal atrial arrhythmia in a patient with a known ASD should prompt consideration of device closure, as those with persistent atrial fibrillation or flutter may remain in this rhythm. Further data are required to confirm whether these observations will be sustained in the long term.

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