Surgical Treatment for Secundum Atrial Septal Defects in Patients >40 Years Old
A Randomized Clinical Trial

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OBJECTIVES
We prospectively examined whether surgical treatment of secundum atrial septal defects (ASDs) in patients ≥40 years old improves their long-term clinical outcome.

BACKGROUND
Surgical treatment of secundum ASDs in adults >40 years old is a subject of controversy because of the perception of good long-term clinical outcomes in patients with unrepaired ASDs and the lack of data from randomized trials.

METHODS
We recruited 521 patients >40 years old with secundum ASDs referred for treatment; 48 were excluded. Patients were randomly assigned to surgical closure (n = 232) or medical treatment (n = 241). The primary and secondary end points were a composite of major cardiovascular events (death, pulmonary embolism, major arrhythmic event, embolic cerebrovascular event, recurrent pulmonary infection, functional class deterioration or heart failure) and overall mortality, respectively. We assessed possible prognostic markers. The analysis was performed on an intention-to-treat basis.

RESULTS
The median follow-up period was 7.3 years (range 2 to 13). The risk of having the primary end point was significantly higher in the medical group, which had a univariate hazards ratio of 1.99 (95% confidence interval [CI] 1.23 to 3.22) and a multivariate hazards ratio of 1.85 (95% CI 1.08 to 3.17). Although the survival analysis did not reveal differences in overall mortality between the surgical and medical treatments (hazards ratio 1.71, 95% CI 0.76 to 3.86), the multivariate analysis, adjusted by age at entry, mean pulmonary artery pressure and cardiac index, demonstrated significant differences between the study groups (hazards ratio 4.09, 95% CI 1.41 to 11.89).

CONCLUSIONS
Surgical closure was superior to medical treatment in improving both the composite of major cardiovascular events and overall mortality in patients >40 years old with secundum ASDs. This superiority was related to the mean pulmonary artery pressure, age at diagnosis and cardiac index. Because of the higher risk of morbidity and mortality, we believe that anatomic closure should always be attempted as the initial treatment for ASDs in adults >40 years old with pulmonary artery systolic pressure <70 mm Hg and a pulmonary/systemic output ratio ≥1.7. The operation must be performed as soon as possible, even if the symptoms or the hemodynamic impact seems to be minimal.

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Manuscript received April 2, 2001; revised manuscript received July 26, 2001, accepted August 20, 2001.

Surgical treatment of atrial septal defects (ASDs) is the most common cardiac surgery performed for congenital heart disease in adults; however, the long-term survival of patients operated on after age 40 years remains controversial (1–7). Comparisons between medical and surgical management in adults have been based on retrospective data (4,5,8,9). Lamentably, the presence of several biases in these series is a common finding. Life expectancy may be shortened in some patients, but still long in others, regardless of surgical treatment. Therefore, the excellent outcome reported in some patients included in the surgical groups might not necessarily be surgery-related. The identification of strong predictive risk factors to select adult patients who may benefit from anatomic closure remains to be demonstrated. The aim of this open, prospective, randomized clinical trial was to analyze the impact of surgical treatment on long-term clinical outcome, as well as to identify possible predictive factors related to a good long-term prognosis when surgical repair is performed.

METHODS

Study group. Between November 1985 and August 1998, the National Institute of Cardiology of Mexico “Ignacio Chávez” recruited 521 patients ≥40 years old, who were referred for ASD treatment, from major national medical centers; 48 patients were excluded. After obtaining written informed consent and a medical history and reviewing the most recent echocardiogram, the patients underwent right heart catheterization. For the purposes of this study, inclusion criteria were isolated ASD (only ostium secundum [88.2%] or sinus venosus defect [11.8%]), age ≥40 years at
diagnosis, pulmonary/systemic output (Qp/Qs) ratio ≥1.7 and pulmonary artery systolic pressure <70 mm Hg. Exclusion criteria were a contraindication for cardiac surgery, severe comorbid disease, previous cardiac surgery, complex congenital cardiac malformation, rheumatic valve disease, coronary artery disease at diagnosis, mitral or aortic regurgitation, left ventricular dysfunction and fixed pulmonary vascular resistance. Patients were randomly assigned on a 1:1 basis to surgical treatment of the defect or to continued medical surveillance. A randomization procedure was performed within six months after the first cardiac catheterization by an independent researcher who verified the eligibility criteria. For data analysis, we compared the outcomes for both surgical and medical treatment groups according to the intention-to-treat principle. The cross-over group comprised patients randomly assigned to receive medical therapy who met any of the following criteria: onset of new symptoms or worsening of existing symptoms at the discretion of the primary physician, refusal of the patient to continue in the medical therapy group and a new unsuspected comorbid disease; these patients were then scheduled for surgery. To avoid a waiting-time bias, surgically treated patients underwent anatomic closure within six months after randomization.

Data collection. Because the overall follow-up period began on the date of right heart catheterization (time zero), all clinical, demographic, radiographic, electrocardiographic, echocardiographic and laboratory data were obtained from the medical records within three months before cardiac catheterization; otherwise, the studies were repeated. Data were collected by two different researchers and compared afterward. Another researcher performed a third review if any discordance was detected. Discrepancies were solved by consensus. Postoperative cardiovascular events were further classified as early (≤30 days) or late (>30 days). The information was entered in a computer-designed format to facilitate analysis by using the Statistical Package for the Social Sciences (SPSS, version 8.0 for Windows) (10).

Follow-up and clinical decisions. All patients were advised to appear for clinical and echocardiographic follow-up evaluations at six- or eight-month intervals, or as soon as either new symptoms appeared or the previous clinical state deteriorated. Although the echocardiographic study was used as one of the main markers to evaluate the hemodynamic impact of ASD during follow-up in the medical group, the primary physician required complete clinical and hemodynamic evaluations, including right and left catheterizations before deciding to submit a patient to surgery.

End points. The primary end point was a compound index of major cardiovascular events (assessed as time to first event) of cardiac-related death, heart failure, pulmonary or systemic embolism, recurrent pulmonary infection, sustained ventricular tachyarrhythmia and progression of pulmonary hypertension (elevation ≥20% from baseline). Secondary end points were the median time of survival, overall mortality and incidence of atrial fibrillation or flutter.

Statistical analysis. Based on parametric data analysis from previous studies in adults (1–9), we estimated a mean frequency of 37% of the compound index used as a primary end point in adult patients without surgical intervention after the age of 40 years at the end of five-year follow-up. For the primary end point, we considered a 15% difference between surgical and medical groups as clinically relevant. With 416 patients (208 per group), the study was designed to have a power >80% for a two-tailed test at a 5% level of significance.

Continuous variables are expressed as the mean value ± SD. Comparisons between the two groups were conducted by using the Student t test for normally distributed continuous variables or the Mann-Whitney U test for those variables without normal distribution. For comparisons among three or more groups, analysis of variance, or its equivalent nonparametric test, was used. The chi-square or Fisher exact test was used for categorical variables. The association between individual variables and the clinical outcome was initially assessed by bivariate analysis. Survival was estimated using the Kaplan-Meier method, and differences among groups were assessed by the log-rank test (11).

Seven demographic, clinical and hemodynamic variables were assessed by Cox hazards regression to identify predictors of death and to examine the adjusted independent effect of the relative hazards associated with factors measurable at clinical presentation, while controlling for possible confounding variables. The seven variables were age at entry, cardiothoracic ratio (CTR), previous atrial arrhythmia, mean pulmonary artery pressure (mPAP), Qp/Qs ratio, cardiac index and treatment group. Significant continuous variables were selected for categorical analysis, and cut-off points were determined to define subgroups for maximal comparison with the log-rank statistic. Cox proportional hazards ratios were estimated for each categorical variable, using the most favorable category as the reference. For multivariable analysis, first we explored all variables in a forced model, and second, the independent factors associated with reduced time to the end point in stepwise forward Cox proportional hazards modeling (12,13). The validity of the proportionality assumption was verified graphically. Checks for possible interactions were explored. Statistical significance was inferred at p < 0.05.
RESULTS

Forty-eight of the initial adult patients >40 years old with an isolated ASD were excluded: 22 (46%) who refused to enter the study (they underwent surgical or medical treatment without randomization); 10 (21%) whose pulmonary artery pressure was >70 mm Hg; and 16 (33%) whose Qp/Qs ratio was ≤1.5. The remaining 473 patients were randomly assigned to either surgical (n = 232) or medical (n = 241) treatment after right heart catheterization. There were 369 women and 104 men. All patients were followed for a mean period of 7.1 years (range 2.0 to 16.3). Only 32 patients (6.7%) discontinued follow-up: 20 due to change of residence and 12 for unknown reasons. The time before being lost to follow-up was 6 ± 3.2 years, and all were censored. During the follow-up, 22 patients initially assigned to medical treatment were crossed over to surgical treatment; however, they remained as part of the medical group until they were scheduled for surgical treatment (Fig. 1).

Age at the first right heart catheterization was similar for the surgical and medical groups. No clinical or statistical differences were found in mean follow-up, echocardiographic variables, incidence of arrhythmia and degree of cardiomegaly between the age groups. The clinical, echocardiographic and hemodynamic profiles of the study group are outlined in Table 1. Although the age at presentation was variable (range 40 to 69 years), age >60 years was not exceptional, and the mean (±SD) age at entry was similar in both treatment groups. Furthermore, the major clinical feature at presentation was age-related: palpitations, vertigo and/or incidental murmur were the most common presenting features in patients <50 years old; whereas dyspnea, palpitations, acute event of paroxysmal supraventricular arrhythmia and syncope were most common in patients ≥50 years old.

Arrhythmia was found in 125 patients at entry. A total of 101 patients (21.3%) had atrial fibrillation or flutter and received digoxin and long-term anticoagulant therapy. The most commonly referred symptoms were dyspnea and palpitations. During follow-up, 10 (2.1%) cerebrovascular embolic events occurred: 4 in the medical group and 6 in the surgical group; however, no fatal outcomes were observed.

The New York Heart Association (NYHA) functional class was II or I at entry in all patients; 15 (6.2%) patients in the medical group deteriorated to functional class III over a mean period of 6.1 ± 5.2 years. In contrast, overall NYHA functional class improved from class II to I in 18 patients (57%) in the surgical group. New-onset atrial fibrillation or flutter during follow-up was detected in 18 patients (7.4%) in the surgical group and in 21 patients (8.7%) in the medical treatment group.

All patients showed some degree of cardiomegaly, but extreme cardiomegaly (CTR ≥0.65) was uncommon. In this manner, 49 patients (21.1%) in the surgical group (mean age 52.3 ± 9.9 years) versus 51 patients (21.1%) in the medical group (mean age 59.7 ± 10.1 years) had a CTR ≥0.65. Furthermore, mPAP and the severity of tricuspid regurgitation were not associated with CTR. Tricuspid regurgitation was detected in 55 patients: 25 (10.7%) in the surgical group and 30 (12.4%) in the medical group. Extreme regurgitation was rare, occurring in only 3 (12%) of 25 surgically treated patients and 3 (10%) of 30 of medically treated patients. We did not find any relationship between the degree of tricuspid regurgitation and the advent of atrial fibrillation. Although tricuspid regurgitation and CTR were partially related, their impact on the survival rate was not significant (collinearity and interactions were explored).

According to the univariate analysis, the following risk markers were associated with the primary end point: age at presentation, medical treatment and mPAP ≥35 mm Hg. These variables remained as strong risk markers after the multivariate analysis (Table 2). Interestingly, the overall occurrence of the primary end point during follow-up was generally consistent across subsets, based on predefined baseline characteristics. Refusal of the patient to continue in the medical treatment group was the case in 22 patients.

In the whole study group, the median survival time...
without a major cardiovascular event (primary end point) was 13.7 ± 0.2 years (95% confidence interval [CI] 12.9 to 14.9 years). Of the 473 patients included, 76 had a major cardiovascular event at 15 years, with an estimated cumulative overall event–free survival rate of 99% at 1 year, 89% at 5 years, 79% at 10 years and 58% at 15 years of follow-up. Significant differences for the primary end point were found when the analysis was performed according to the type of treatment and age at entry (Figs. 2A and 2B). The log-rank statistic showed differences between the three groups of age at entry in both the medical and surgical groups (Figs. 2C and 2D).

There were 50 events (20.7%) in the medically treated versus 26 events (11.1%) in the surgically treated patients (hazard ratio 2.0 [95% CI 1.20 to 3.2], p = 0.004). The total number of heart failures, strokes and embolic events did not differ significantly (Table 3). Using a forward multivariate Cox regression model to identify the best associated variables with the primary end point during follow-up, we found that age at diagnosis, mPAP ≥35 mm Hg and medical treatment were the main risk markers.

Although the overall mortality rate did not differ significantly in the surgical (5.8%) and medical (4.3%) groups (hazard ratio 1.6 [95% CI 0.76 to 3.86]), sudden death was more frequent in the medical than in the surgical group (2.9% vs. 0.9%, respectively), with a hazard ratio of 4.0 (95% CI 0.83 to 19.3; p = 0.08). Interestingly, when multivariate Cox regression analysis was adjusted by age at entry, mPAP >35 mm Hg, previous atrial fibrillation or flutter and cardiac index <3.5 l/m², a significant difference in mortality was found between the surgical and medical groups (Table 4).

**DISCUSSION**

Surgical repair is still the main therapy for ASDs. Thus, the life expectancy of patients with unrepaired ASDs is generally thought to be shortened (2,4,14–17). However, this conclusion is supported by the results of several retrospective studies that have mainly included young adult patients (16,18,19). The previous belief that only 50% of patients with unrepaired ASDs survive beyond the age of 40 years and <10% reach the age of 60 years, has not been confirmed in many other observational studies (5,8,20,21). Furthermore, although the surgical closure of ASDs is frequently...
performed in patients >40 years old, there is a lack of controlled follow-up studies comparing the long-term outcome between surgical and medical treatment (22). Selection bias is a common error of some observational studies that have attempted to describe the long-term outcome of congenital heart disease gone untreated or unrepaired. Thus, the inclusion of a small number of patients of specific age groups may lead to an unreal perception of the long-term outcome and misleading conclusions. This feature has been demonstrated in other congenital heart diseases (23,24).

Murphy et al. (2) pointed out that patients who have an operation after the age of 40 years are at increased risk of postoperative cardiovascular complications, whereas children and young adults have an excellent prognosis. Specific studies directed at exploring the clinical impact of the surgical treatment of ASDs in patients >40 years old have been called into question because of the multiple discrepancies found. These discrepancies are partly due to the heterogeneity of the study groups. To reduce this limitation, Konstantinides et al. (5) used multivariate analysis to assess 179 consecutive patients >40 years old at diagnosis of isolated ASD. They found a significant decrease in overall mortality after surgical repair of the defect, and the relative risk of death during the follow-up period was 0.31. These results are similar to those of other studies (25,26). In contrast, in our study, we found that the surgical treatment of ASDs in adult life does not significantly alter the prognosis in terms of mortality, whereas the risk for major cardiovascular complications was clearly elevated in this group. Nevertheless, several considerations must be pointed out. First, our study was designed to be prospective and randomized. Second, the clinical, demographic and hemodynamic profiles were defined to include patients >40 years old diagnosed with pulmonary artery pressure <70 mm Hg, without severe comorbid factors and with an excellent functional class (NYHA class II or I). Third, although mortality was analyzed, the primary end point of this study was a compound index of major cardiovascular events.

Our study reports a large series of adults with ASDs (n = 473) assessed, during a mean period of 7.3 years, at a single center. Of these, 232 patients were assigned to surgical treatment. Early postoperative complications were observed in 24 patients; 14 had perioperative bleeding complications; 6 had transient ischemic attacks; 3 had complex arrhythmic events; 1 had implantation of a definitive pacemaker (injured sinus node of a patient with sinus venous ASD); 2 had mediastinitis; and 1 had a pulmonary embolic event. Nevertheless, all patients showed full recovery and were discharged without sequelae.

In contrast, the incidence of nonfatal cardiovascular complications during the follow-up period was reduced by surgical treatment of the defect. This finding was frequently related to a decreased incidence of recurrent pneumonia (hazard ratio 4.4 [95% CI 1.80 to 10.7]). Although recurrent pulmonary infections were seldom included in most previous studies, in the present study, 4 (28.5%) of 14 deaths in the medical treatment group were related to this complication.

During long-term follow-up, atrial fibrillation or flutter developed in 8% of all patients, although no difference was observed between the surgical and medical groups. However, the onset of this arrhythmia did, in fact, differ: in patients with surgical repair, most arrhythmic events began...
within two years after the operation; however, in the medical group, the mean onset of arrhythmia was seven years. Interestingly, mPAP was higher among patients with unrepaired ASDs who developed atrial fibrillation or flutter during follow-up, as compared with those patients who had surgical repair (39 ± 5 mm Hg vs. 31 ± 3 mm Hg, p < 0.05). These results are similar to those reported by Gatzioulis et al. (27). In contrast, the preoperative mPAP in the surgical group was not associated with the risk of developing arrhythmias in the long term. These results suggest that the mechanism responsible for triggering atrial fibrillation or flutter might be different. In addition, the onset of atrial fibrillation or flutter was related to long-term mortality in the medical group, but not in the surgical group. Finally,

Figure 2. Event-free probability for primary end point by type of treatment and age at entry.

Table 3. End Point Results

<table>
<thead>
<tr>
<th>End Point</th>
<th>Medical Treatment (n = 241)</th>
<th>Surgical Treatment (n = 232)</th>
<th>Hazards Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Totality of events</td>
<td>50 (20.7%)</td>
<td>26 (11.1%)</td>
<td>2.0 (1.20–3.20)</td>
<td>0.0046</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9 (3.7%)</td>
<td>5 (2.1%)</td>
<td>1.6 (0.52–4.97)</td>
<td>0.3982</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>4 (1.6%)</td>
<td>5 (2.1%)</td>
<td>0.9 (0.20–3.20)</td>
<td>0.8266</td>
</tr>
<tr>
<td>Peripheral embolism</td>
<td>1 (0.4%)</td>
<td>3 (1.3%)</td>
<td>0.4 (0.04–3.68)</td>
<td>0.4056</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (1.6%)</td>
<td>6 (2.6%)</td>
<td>0.5 (0.13–2.15)</td>
<td>0.3727</td>
</tr>
<tr>
<td>Recurrent pneumonia</td>
<td>24 (10.0%)</td>
<td>6 (2.6%)</td>
<td>4.4 (1.80–10.7)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Sudden death</td>
<td>7 (2.9%)</td>
<td>2 (0.9%)</td>
<td>4.0 (0.83–19.3)</td>
<td>0.0837</td>
</tr>
<tr>
<td>Secondary Total mortality</td>
<td>14 (5.8%)</td>
<td>10 (4.3%)</td>
<td>1.6 (0.76–3.86)</td>
<td>0.1934</td>
</tr>
</tbody>
</table>

CI = confidence interval.
embolic events were related to this arrhythmia in 63% of all patients. Therefore, our observations are consistent with the perception that repair of ASDs does not significantly reduce the risk of arrhythmias, but its long-term clinical impact may be different in each group.

In contrast to the distribution of age groups reported in previous studies, 70% of our patients were 40 to 60 years old at diagnosis. Konstantinides et al. (5) also included patients >55 years old, but most patients included in their surgical group had an operation before the age of 55 years. This may be considered as a selection bias, so that the real impact of age may be masked. Nevertheless, we confirm that age is an independent risk marker to develop major cardiovascular complications, even when adjusted by the clinical, hemodynamic and echocardiographic profile. Although we did not find significant differences in mortality, sudden death was more frequent in the medical group than in the surgical group (7 vs. 2), with a hazard ratio of 4.0 (95% CI 0.83 to 19.3).

Severe deterioration of functional class as a first finding at diagnosis is rare. In general, when a patient is in NYHA functional class IV or III at diagnosis, there is a comorbid factor, such as left ventricular failure or right ventricular dysfunction secondary to pulmonary hypertension or other early complications. For this reason, we did not include patients in NYHA functional class IV or III, as we believe they comprise a special subgroup that needs to be evaluated separately, and it is not possible to extrapolate our results to this group.

Conclusions. We conclude that surgical treatment of ASDs was superior to medical treatment in improving both the composite of major cardiovascular events and overall mortality in patients >40 years old. Superiority was related to the cardiac index, mPAP and age at diagnosis. Because of the higher risk of morbidity and mortality, we believe that anatomic closure should always be performed as the initial treatment for ASD in adults >40 years old, with a Qp/Qs ratio ≥1.7 and pulmonary artery systolic pressure <70 mm Hg. The operation must be performed as soon as possible, even when the symptoms and hemodynamic impact seem to be minimal.

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REFERENCES


Table 4. Forward Multivariate Cox Regression Analysis for Secondary End Point (Death)

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>SE</th>
<th>Wald's Statistic df</th>
<th>Sig*</th>
<th>R</th>
<th>HR</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical treatment</td>
<td>1.4088</td>
<td>0.5438</td>
<td>6.7122</td>
<td>1</td>
<td>0.0096</td>
<td>0.1357</td>
<td>4.0911</td>
<td>1.4092</td>
</tr>
<tr>
<td>CI &lt;3.5 l/m²</td>
<td>1.1329</td>
<td>0.4819</td>
<td>5.5259</td>
<td>1</td>
<td>0.0187</td>
<td>0.1173</td>
<td>3.1045</td>
<td>1.2072</td>
</tr>
<tr>
<td>Age at entry (years)</td>
<td>10.2493</td>
<td></td>
<td></td>
<td>2</td>
<td>0.0059</td>
<td>0.1562</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>1.1198</td>
<td>0.5975</td>
<td>3.5119</td>
<td>1</td>
<td>0.0609</td>
<td>0.0768</td>
<td>3.0643</td>
<td>0.9499</td>
</tr>
<tr>
<td>≥60</td>
<td>1.9799</td>
<td>0.6199</td>
<td>10.2021</td>
<td>1</td>
<td>0.0014</td>
<td>0.1790</td>
<td>7.2418</td>
<td>2.1489</td>
</tr>
<tr>
<td>Previous AF or flutter</td>
<td>1.2263</td>
<td>0.4856</td>
<td>6.3782</td>
<td>1</td>
<td>0.0116</td>
<td>0.1308</td>
<td>3.4087</td>
<td>1.3160</td>
</tr>
<tr>
<td>mPAP (&gt;35 mm Hg)</td>
<td>1.6636</td>
<td>0.4937</td>
<td>11.3531</td>
<td>1</td>
<td>0.0008</td>
<td>0.1911</td>
<td>5.2783</td>
<td>2.0055</td>
</tr>
</tbody>
</table>

*Model significance: overall score (6 df) = 49.13, –2LLR (6 df) = 207.105, p < 0.0001.

AF = atrial fibrillation; B = regression coefficient; df = degree of freedom; R = R-adjusted value; SE = standard error of B; other abbreviations as in Tables 1 and 2.