PATHOPHYSIOLOGY AND NATURAL HISTORY

CONGENITAL HEART DISEASE

Isolated atrial septal defect with pulmonary vascular obstructive disease — long-term follow-up and prediction of outcome after surgical correction

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ABSTRACT We examined the cases of 702 patients found to have isolated atrial septal defect of the secundum or sinus venosus type at catheterization from 1953 to 1978. Forty patients (6%), 34 women and six men, had pulmonary vascular obstructive disease, with a total pulmonary resistance greater than 7 U/m²; of these patients 26 (mean age 47 years) underwent surgical closure and 14 (mean age 44 years) received medical treatment. All patients were followed for at least 4 years, with a median follow-up of 12 years. At the most recent follow-up, 17 of the 40 patients were dead. Of the 22 surgically treated patients with total pulmonary resistance less than 15 U/m², 19 were alive with significant regression of symptoms. All four surgically treated patients with total pulmonary resistance greater than or equal to 15 U/m² were dead. Of the five medically treated patients with total pulmonary resistance less than 15 U/m², four had died, and one was alive with significant progression of symptoms. Of the nine medically treated patients with total pulmonary resistance greater than or equal to 15 U/m², six had died and the three survivors had progression of symptoms. In the surgically treated group, the following variables correlated with survival: total pulmonary resistance (p < .00001), pulmonary arteriolar resistance (p < .00001), pulmonary-to-systemic resistance ratio (p = .004), systemic arterial oxygen saturation (p = .005), and pulmonary arterial oxygen saturation (p = .007). In conclusion: (1) Atrial septal defect with high total pulmonary resistance is uncommon and predominates in adult female patients. (2) Total pulmonary resistance (or pulmonary arteriolar resistance) is the best predictor of surgical outcome. In patients with total pulmonary resistance less than 15 U/m², surgical treatment is advised. (3) In patients with borderline total pulmonary resistance, the systemic arterial oxygen saturation provides a good prediction of surgical outcome.


PATIENTS with moderate or large congenital ventricular septal defects become symptomatic and develop pulmonary hypertension with an increased pulmonary vascular resistance in childhood. In contrast, patients with an isolated atrial septal defect (of ostium secundum or sinus venosus type) usually do not become symptomatic until middle or old age. A fraction of these patients go on to develop pulmonary vascular obstructive disease.1,2 Surgical correction, in patients with isolated atrial septal defect, is usually recommended when there is a significant shunt (pulmonary-to-systemic flow ratio of at least 1.5:1) and no evidence of severe pulmonary vascular obstructive disease.3 Furthermore, in the absence of significant pulmonary vascular obstructive disease, many studies have reported good surgical results even in the elderly.4 It has often been stated that the risks and benefits of surgery depend mainly on the presence of pulmonary hypertension,2,5,6 but the point at which surgery should be avoided remains uncertain. No large studies have reported on the long-term follow-up of patients with atrial septal defect and pulmonary vascular obstructive disease and the effect of surgery. This study addressed that question with particular reference to the prediction of outcome after surgical correction.

Methods

Study patients. Between 1953 and 1978, 702 patients at the Mayo Clinic were found to have isolated atrial septal defect of the ostium secundum or sinus venosus type at cardiac catheterization Of these 702 patients, 40 (6%) had pulmonary vascular obstructive disease, defined as a total pulmonary resistance of
7 U/m² or greater (total pulmonary resistance [U/m²] = mean pulmonary arterial pressure/pulmonary index).

Pulmonary arteriolar resistance (U/m²), defined as

Mean pulmonary arterial pressure – Mean left atrial pressure

Pulmonary index

was also elevated.

All 40 patients were followed until death, or for at least 4 years. The range of follow-up was 4 to 29 years (median 12 years). Follow-up information was obtained in all patients from repeated examinations at the Mayo Clinic and from telephone calls to the patients or relatives and to the referring physicians.

Clinical evaluation. The clinical course from the time of diagnosis in all surviving patients was evaluated in terms of progression or lack of progression of at least two of the following clinical features: (1) symptoms (invariably shortness of breath and fatigue), (2) a change in the size of the main pulmonary artery as assessed subjectively by the frontal chest x-ray, or (3) a change in the degree of right ventricular hypertrophy, as assessed by the 12-lead surface electrocardiogram (an increase in the size of R wave in lead V₁ of at least 2 mm or an increase in the sum of the R wave in V₁ plus the S wave in V₅ₑ₆ of at least 5 mm was regarded as progression of right ventricular hypertrophy). For those patients who died during the follow-up period, the clinical cause of death was determined.

Evaluation at cardiac catheterization. At the time of entry into the study all 40 patients underwent cardiac catheterization. The procedure included (1) measurement of pressures in the inferior vena cava, superior vena cava, right atrium, right ventricle, pulmonary artery, pulmonary artery wedge, and a systemic artery, (2) determination of oxygen saturation by cuvette oximetry of blood samples drawn from the above-named positions, (3) determination of cardiac index and pulmonary index by the oxymetric principle of Fick, (4) determination of left-to-right and right-to-left shunts by the indicator-dilution technique with indocyanine green.

Repeat cardiac catheterization was performed in nine patients in the surgically treated group 6 months to 18 years after operation, and in three of the patients in the medically treated group 7 to 24 years after the index study.

Operation. The defect was repaired by direct suture in 16 patients and by insertion of a patch (either Dacron, Teflon, or Ivalon sponge) in 10 patients. In five early patients the repair was performed by the atrial-well technique described by Gross and Watkins, while in the remaining 21 patients cardiopulmonary bypass was used.

Statistics. Significance of univariate analysis of prognostic factors was tested with Student’s t test or the chi-square test. Multivariate analysis of prognostic factors was done with the Cox stepwise proportional-hazards general linear model procedure. Actuarial analysis of survival was done with the Kaplan-Meier method. A probability value of less than .05 was considered indicative of a significant difference.

Results

Baseline: clinical and hemodynamic characteristics. There were 34 women (85%) and six men (15%). Of the 40 patients, 26 underwent surgical correction of their defect, while 14 received only medical treatment. Twenty of the surgically treated patients had an ostium secundum defect and six had a sinus venosus defect. The mean age in the surgical group was 47 years (range 27 to 71) and in the medical group it was 44 years (range 19 to 75). No patient below the age of 19 presented with atrial septal defect and pulmonary vascular obstructive disease. In the surgical group, two patients were in New York Heart Association class I, six were in class II, 17 were in class III, and one was in class IV. In the medical group, two were in class II, 10 were in class III, and two were in class IV.

The hemodynamic variables measured at cardiac catheterization in the medically and surgically treated patients are listed in Table 1. The mean value for each variable (except mean pulmonary arterial pressure) was significantly different in the two groups. Specifically, the medically treated group had more advanced pulmonary vascular obstructive disease. Of the 26 surgically treated patients, 10 had a total pulmonary resistance between 7 and 9 U/m², 12 had a total pulmonary resistance between 10 and 14 U/m², and four had a total pulmonary resistance of 15 U/m² or greater. Of the 14 medically treated patients, two had a total pulmonary resistance between 7 and 9 U/m², three had a total pulmonary resistance between 10 and 14 U/m², and nine had a total pulmonary resistance of 15 U/m² or greater. Figure 1 depicts the relationship between the age of the patient at the time of the index catheterization and the total pulmonary resistance. Essentially, there is no simple relationship between increasing age and pulmonary resistance.

Follow-up: clinical and hemodynamic characteristics. The clinical course, in terms of progression or lack of progression of the clinical features previously defined,
is shown for each patient in figure 2. Using the total pulmonary resistance as a measure of the degree of pulmonary vascular obstructive disease, we correlated the clinical course with the total pulmonary vascular resistance.

Not surprisingly, during the follow-up period all of the 14 medically treated patients showed progression of clinical features; all patients became more symptomatic and almost invariably developed more pronounced right ventricular hypertrophy on their electrocardiogram. All but one of the medically treated patients increased their New York Heart Association class by one grade. The two patients who were class IV remained as such. Three medically treated patients underwent repeat cardiac catheterization. All three patients showed progression of their pulmonary vascular obstructive disease, but the rate of progression was variable: the total pulmonary resistance increased from 12 to 13.5 U/m² over 7 years in one patient, from 14 to 30 U/m² over 7 years in another, and from 7 to 56 U/m² over 24 years in the third patient.

In contrast, in the surgically treated group, apart from two perioperative deaths, 18 patients improved by at least one NYHA class, four remained the same, and two increased to class IV. Of the 10 surgically treated patients who had total pulmonary resistance between 7 and 9 U/m², none showed progression of clinical features. In fact, there was regression of symptoms, of electrocardiographic evidence of right ventricular hypertrophy, and of radiologic evidence of main pulmonary arterial enlargement. All 12 surgically treated patients with a total pulmonary resistance between 10 and 14 U/m² also showed lack of progression of clinical features during the follow-up period. However, all four patients with a total pulmonary resistance of 15 U/m² or greater did poorly; two died within 24 hr of surgery, and the other two showed significant progression of clinical features. Nine surgically treated patients underwent a repeat cardiac catheterization. In seven of the nine the total pulmonary resistance was the same or less. In two of the nine, it had increased significantly: from 26 to 56 U/m² over 1 year in one patient, and from 17 to 30 U/m² over 10 years in the other.

Survival. At the most recent follow-up, 17 of the 40 patients were dead (figure 2). Of the 26 surgically treated patients, seven were dead. All four patients with a total pulmonary resistance of at least 15 U/m² had died; 2 within 24 hr of technically uncomplicated operative repair and two from cardiac failure at age 31 (2.3 years after repair) and 54 (13.6 years after repair). The three remaining surgically treated patients who died each had a total pulmonary resistance of less than 15 U/m², and were 65, 72, and 74 years old at the time of death. These deaths occurred at 6, 9, and 17 years (respectively) after repair, and two of the deaths were

![FIGURE 1](image1.png)  
**FIGURE 1.** Relationship between the age of the patient and the total pulmonary resistance (TPR), in Wood units, at diagnostic catheterization.

![FIGURE 2](image2.png)  
**FIGURE 2.** Relationship between the clinical course during the follow-up period and the total pulmonary resistance (TPR) at diagnostic catheterization in the 26 surgically treated patients and the 14 medically treated patients. In parentheses next to the point representing each patient who died is the length of the follow-up period in years. Two surgical patients died of noncardiac (N.C.) causes.
due to noncardiac causes. Of the 14 medically treated patients, 10 were dead at recent follow-up, with a mean age of 54 years at death (range 28 to 77 years) and a mean interval from diagnosis to death of 9 years (range 1 to 27 years). Cardiac failure was the cause of death in all 10 patients. Histologic analysis of lung tissue was available from the autopsy of three patients. All three specimens were described as showing intimal thickening. No specific measure of medial hypertrophy was described.

The survival of the surgically treated patients was good, with 85% and 80% of patients remaining alive after 5 and 10 years, respectively (figure 3). The survival curve for the medically treated group is shown in figure 4. Gradually declining survival is demonstrated, with 70% and 41% of patients remaining alive after 5 and 10 years, respectively.

**Prognostic factors.** In surgically treated patients, univariate analysis of the ability of several variables obtained at diagnosis cardiac catheterization and age in predicting survival is shown in table 2. As has been suggested from the clinical course (figure 2), the total pulmonary resistance and pulmonary arteriolar resistance were highly predictive of outcome: the higher the resistance, the greater the probability of death. A total pulmonary resistance of 15 U/m² appeared to be a good discriminative level. Of 18 surgically treated patients who had been followed for at least 10 years, only one of 14 patients with a total pulmonary resistance of less than 15 U/m² died, whereas three of the four patients with a total pulmonary resistance of greater than or equal to 15 U/m² had died (figure 5). Systemic arterial oxygen saturation and pulmonary arterial oxygen saturation were also predictive of survival, and they varied inversely with pulmonary vascular resistance. A systemic arterial oxygen saturation of 92% appeared a good discriminative value. Of 18 surgically treated patients who had been followed for at least 10 years, only one of 12 patients with a systemic arterial oxygen saturation value of 92% or greater died, whereas three of the six patients with a systemic arterial oxygen saturation of less than 92% had died (see figure 5). Stepwise multivariate analysis of data from the surgically treated patients, revealed that only total pulmo-

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**FIGURE 3.** Observed survival to 10 years in 26 surgically treated patients with atrial septal defect and pulmonary vascular obstructive disease. Parentheses enclose number of living patients under observation at 3, 5, and 10 years.

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**FIGURE 4.** Observed survival to 10 years in 14 medically treated patients with atrial septal defect and pulmonary vascular obstructive disease. Parentheses enclose number of living patients under observation at 3, 5, and 10 years.

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**TABLE 2**  
Univariate analysis of prognostic variables in surgically treated patients (n = 26)

<table>
<thead>
<tr>
<th>Factor</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pulmonary resistance</td>
<td>.0001</td>
</tr>
<tr>
<td>Pulmonary arteriolar resistance</td>
<td>.0001</td>
</tr>
<tr>
<td>Ratio of pulmonary to systemic resistance</td>
<td>.004</td>
</tr>
<tr>
<td>Systemic arterial oxygen saturation</td>
<td>.005</td>
</tr>
<tr>
<td>Pulmonary arterial oxygen saturation</td>
<td>.007</td>
</tr>
<tr>
<td>Ratio of pulmonary to systemic flow</td>
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</tr>
<tr>
<td>Mean pulmonary arterial pressure</td>
<td>.17</td>
</tr>
<tr>
<td>Age</td>
<td>.53</td>
</tr>
</tbody>
</table>
PATHOPHYSIOLOGY AND NATURAL HISTORY–CONGENITAL HEART DISEASE

FIGURE 5. Outcome (solid dots indicate alive patients, dots with a slash indicate dead patients) in 18 surgically treated patients followed for at least 10 years. Relationship to total pulmonary resistance (TPR, a) and systemic arterial oxygen saturation (SAO2, b) obtained at diagnostic cardiac catheterization.

In the medically treated groups, no variables were found to be of prognostic significance. Of the nine patients who had a total pulmonary resistance above 15 U/m², survival ranged from as short as 1 year to as long as 10 years.

Discussion

This study has confirmed that, among patients with isolated atrial septal defect, pulmonary vascular obstructive disease is uncommon, being present in only 6% of patients with this condition seen at the Mayo Clinic from 1953 to 1978. Despite this, it has been well established that pulmonary vascular obstructive disease markedly influences the natural history and operative mortality in these patients.2, 5, 9 However, because of the low prevalence, there have been very few reported series on such patients. We have investigated a group of 40 patients with atrial septal defect and clearly defined pulmonary vascular obstructive disease and followed them for a median period of 12 years (range 4 to 29) without any loss of follow-up.

Causes. It seems clear from the data presented above that pulmonary vascular obstructive disease rarely occurs in children with isolated atrial septal defect.10–12 Haworth10 described a small series of nine patients younger than 9 years of age with isolated atrial septal defect and pulmonary vascular obstructive disease, but she also indicated that this subset constituted a small fraction of the population with atrial septal defect seen at the Hospital for Sick Children in London. A more recent analysis of 709 patients with isolated secundum atrial septal defect in Vellore, India, found that 9% of this population already had the Eisenmenger reaction with shunt reversal, and a significant number of these patients were less than 20 years of age.11

Earlier observations1, 13 have suggested that pulmonary hypertension increases progressively with advancing age. In our study, no simple relationship between age at time of presentation and vascular resistance was observed. However, in the three medically treated patients who underwent serial hemodynamic studies, all three showed progression of disease with time. The interesting feature, however, was that the rate of progression was quite variable. Quite similar observations were made in a large French study on isolated atrial septal defect that included 34 patients who underwent two cardiac catheterization procedures before surgical correction a mean of 6.4 ± 4.7 years apart.14 The majority of patients had an increase in their pulmonary vascular resistance over time, but the rate of progression was variable. Thus, although there may be an age-related “wear and tear” effect on the pulmonary vasculature due to increased flow alone, it appears that patients who develop moderate-to-severe pulmonary vascular obstructive disease do so because of a multifactorial cause.

The preponderance of female patients (85%) in this study is striking and is more than expected (female-to-male ratio of 2:1 for atrial septal defect without pulmonary obstructive disease). This predominance of young to middle-age female patients underscores a similarity to primary pulmonary hypertension. It is highly unlikely, however, that the patients in this study had primary pulmonary hypertension as a coincidental disease because of the relative rarity of this condition and its more malignant clinical course. Perhaps there is a spectrum of predisposition to pulmonary hypertension regardless of the pathogenic mechanism, whether it is a hyperactive pulmonary vasculature, thromboembolic events, or some platelet-vessel wall abnormality.15 Patients at the far end of this spectrum would develop the overt clinical syndrome, whereas patients who were, for example, in the middle of the spectrum might only develop pulmonary vascular disease in response to some stress, e.g., high altitude or increased pulmonary flow.

Surgically treated patients. In this study, comparisons between the patients treated surgically versus those treated medically have to be made with caution since the two groups were different with regard to severity of disease (table 1). Overall, the surgically treated patients have done well — both in terms of clinical improvement (figure 2) and survival (figure 3), with
80% of patients remaining alive after 10 years. There are no other reported studies with as large a patient population for comparison with these data. Liddle et al. studied 15 patients with atrial septal defect and pulmonary systolic pressures above 50 mm Hg. The mortality approached 40% and interestingly they suggested that outcome was unrelated to preoperative pulmonary pressure. Pulmonary resistance was not calculated in their study. Saksena and Aldridge presented preoperative and postoperative hemodynamic data on patients undergoing atrial septal defect repair. However, only five of their patients had significantly increased pulmonary resistance. Of note in their study was the increase in pulmonary resistance postoperatively in 75% of their patients.

In the present study, total pulmonary resistance at diagnostic catheterization was highly predictive of outcome after operation (table 2). Patients with total pulmonary resistance values of 15 U/m² or greater did poorly and those with values less than 10 U/m² fared very well (figures 2 and 5). The 12 patients with values between 10 and 14 U/m² also did well, with the great majority showing clinical improvement, but the long-term outcome in this group is less certain because a number have not yet been followed for 10 years (figure 5).

Interestingly, the systemic and pulmonary oxygen saturations were both predictive of outcome. Thus, these easily measurable variables, reflecting the overall adequacy of the circulation in terms of cardiac output, oxygenation, and shunting, may be useful in deciding whether to operate — particularly if the total pulmonary resistance is borderline or there is some question as to the accuracy of the measurement for pulmonary index. A study of the natural history of patients with primary pulmonary hypertension also suggests that the systemic oxygen saturation is predictive of outcome.

Other approaches to deciding about operability could utilize data obtained during hemodynamic testing with pulmonary vasodilators to assess vascular reactivity. Alternatively, a recent study by Yamaki et al. suggested that analysis of lung biopsy material could be predictive of vascular reactivity.

Our observation that the outcome in medically treated patients was unpredictable is puzzling. Perhaps the outcome depends more on the pathogenetic mechanisms involved in each individual patient than on the hemodynamic status at the time of diagnosis.

**Clinical implications.** For patients with an atrial septal defect and pulmonary vascular obstructive disease with a predominant left-to-right shunt, our data suggest the following approach to management: All patients with a total pulmonary resistance less than 10 U/m² should proceed to operation; if the total pulmonary resistance is 15 U/m² or greater then operation is not advised; if the total pulmonary resistance is between 10 and 14 U/m², then operation should probably be performed, barring adverse findings with respect to systemic arterial oxygen saturation. The role of preoperative lung biopsy or the hemodynamic response to exercise in predicting outcome after surgery remains to be determined.

**References**

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