Prognosis for Patients with Ventricular Septal Defect and Severe Pulmonary Vascular Obstructive Disease

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SUMMARY
The status of 58 patients, 3 to 57 years of age, with ventricular septal defect and a marked increase in pulmonary vascular resistance (pulmonary obstructive disease) was determined 5 years or longer after diagnostic catheterization. Forty-six (80%) were alive 5 years after this study. The probability of living 5 years was 95% for patients aged 10 through 19 years and 56% for those 20 years of age or older. The dissimilarity of actuarial curves between these two groups is consistent with the hypothesis that pulmonary vascular obstructive disease develops under age 20. Calculated pulmonary resistance increased with age of patient on admission to the study, suggesting its progressive nature. Hemoptysis was rare under age 20, and its presence over this age indicated a poor prognosis. The most common causes of death were “sudden” or “unknown.” Most surviving patients were gainfully employed or attending school without severe symptoms.

Additional Indexing Words:
Cardiac catheterization
Five-year survival probability
Pregnancy
Hemoptysis
Pulmonary artery pressure
Age

In some patients with ventricular septal defect, pulmonary vascular changes develop and result in obstruction to flow of blood in the small muscular arteries and arterioles and, in some, these changes progress so that pulmonary resistance equals or exceeds systemic resistance. The obstructive changes will be referred to as pulmonary vascular disease. Surgical experience at the Mayo Clinic indicates that closure of the ventricular septal defect in patients with severe pulmonary vascular disease carries a high mortality rate and the survivors are often not benefited. In a recent study,1 nine (69%) of 13 surgically treated patients with ventricular septal defect and severe pulmonary vascular disease were dead 5 years after operation, and of the four living patients two had evidence of progressive pulmonary vascular disease.

Much less is known regarding the prognosis for those patients for whom operation has not been recommended because of the marked elevation of pulmonary resistance. Information on 65 such patients seen at the Mayo Clinic in the years 1950 through 1962, with follow-up of 5 or more years on 58, forms the basis of this report.

The time of onset of pulmonary vascular disease and its progression vary among patients with ventricular septal defect. In most
cases in this study we were unable to define the age at which significantly obstructive pulmonary vascular changes had developed. Consequently, all observations were begun at the time of diagnosis by cardiac catheterization. For the purpose of this study, pulmonary vascular disease was defined as severe when the ratio of calculated pulmonary resistance to systemic resistance measured traditionally as mean pressure-flow ratios exceeded 0.70. The authors realize that hemodynamic measurements do not always correlate with pathological changes, but usually patients with severely elevated pulmonary vascular resistance will have pathological evidence of severe disease.

Methods
Selection of Patients
Only those patients whose pulmonary artery was entered at cardiac catheterization were included in the study. A diagnosis of ventricular septal defect was based on one or more of the following findings: (1) an abnormal indicator-dilution curve, indicative of a right-to-left shunt, recorded from a systemic artery following injection of dye into the right ventricle, but not following injection of dye into the main pulmonary artery; (2) an increase in oxygen saturation from right atrium to right ventricle, of 10 percentage points in one series or 5 percentage points in two series; (3) passage of the catheter from the right ventricle to the aorta with normally oriented great vessels; (4) demonstration of a ventricular septal defect and normally related great arteries by selective angiocardiography from either ventricle; and (5) postmortem demonstration of a defect.

The diagnosis of severe pulmonary vascular obstructive disease was made when the ratio of total pulmonary vascular resistance to total systemic vascular resistance was greater than 0.70 and the pressure in the pulmonary artery was equal to or nearly equal to the systemic pressure. Patients with known additional congenital cardiac defects were not included.

The 65 patients who fulfilled these criteria and had not had surgical closure of the ventricular septal defect ranged in age from 3 to 57 years at the time of cardiac catheterization. They were divided into three groups according to age at cardiac catheterization, as shown in table 1. The data hereinafter presented are based on the 58 patients whose status was determined on follow-up.

Clinical Features at Time of Initial Cardiac Catheterization
The 58 patients, regardless of age, were remarkably similar on clinical examination at the time of cardiac catheterization. None had a definite history of cardiac failure in infancy, although seven had a history of "pneumonia" during the first 2 years of life. None had had brain abscess, bacterial endocarditis, or cerebrovascular accident. All but three complained of fatigue and dyspnea but none was severely disabled. Thirty-five patients were cyanotic at rest and another five were cyanotic only after exertion. No patients in groups 1 and 2 (less than 20 years old) had a history of hemoptysis on admission, but 11 of the 23 in group 3 (20 years old or older) had hemoptysis. No patients in groups 1 and 2 had had syncope or angina, but four in group 3 had a history of syncope and two complained of exertional pain of an anginal type. Only two patients were born and lived at an altitude greater than 5,000 feet above sea level.

On physical examination all 58 patients had findings of pulmonary hypertension, particularly reflected by accentuation of the pulmonary-valve-closure sound. X-ray examination of the chest showed a cardiothoracic ratio less than 0.55 in all but eight patients; the size of the main pulmonary artery, the central vascular markings, or both were increased in all; and the peripheral vascular markings were judged to be either normal or reduced in all. The electrocardiograms showed evidence of right ventricular hypertrophy in all but a 14-year-old patient who had unusual

| Table 1 |
| Status of Patients by Groups 5 Years after Initial Cardiac Catheterization |

<table>
<thead>
<tr>
<th>Group</th>
<th>Age at catheterization, years</th>
<th>Total patients</th>
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<th>Status unknown</th>
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<td></td>
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<td>13</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>65</td>
<td>58</td>
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VENTRICULAR SEPTAL DEFECT

Hemodynamic Studies

The ratio of pulmonary to systemic flow did not exceed 1.2 in any patient. All patients had either a right-to-left shunt demonstrated by abnormal indicator-dilution curves or systemic arterial oxygen desaturation. Although the lowest systemic arterial oxygen saturations were recorded in patients 20 years old or older, a wide range was found at all ages.

Survival Data

Table 1 shows the status of the 58 patients by groups 5 years after admission. It is seen that 46 patients (80%) were then alive. Figure 1 shows the survivorship curves for the three groups as determined by the actuarial method. The number of patients in group 1 is too small for statistical analysis; however, there was a significant difference between the survival curves of groups 2 and 3. The probability of surviving 5 years was 95% for patients in group 2 and 56% for those in group 3.

Group 1

Eleven of 12 patients were alive 5 to 12 years (average, 7) after diagnostic catheterization. Ages at follow-up ranged from 8 to 17 years (average, 14). All were cyanotic with effort and six were also cyanotic at rest. One of the 11 had hemoptysis and another syncopal episodes. One patient who had syncope at 4 years of age had no further episodes by 12 years of age. Two developed chest pain on exertion; all were dyspneic on exertion with some limitation of activity, but in none was this severe, and all were able to attend school. None had experienced heart failure, bacterial endocarditis, brain abscess, or cerebrovascular accident during the period of observation.

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Group 2

Whereas 22 of 23 patients were alive 5 years after catheterization, 19 survived for periods ranging up to 16 years (average, 8 years). Ages at follow-up ranged from 16 to 33 years (average, 21). Only three were not cyanotic at rest, and two of these became so with exertion. All were limited in activity, but only two so severely that they were unable to work or attend school. One had developed syncope and another hemoptysis. One patient recovered from bacterial endocarditis and brain abscess. Two had developed angina with exertion, and in one angina was related to periods of atrial dysrhythmia.

Group 3

Whereas 13 of 23 patients were alive 5 years after catheterization, 11 survived 5 to 14 years (average, 8) after catheterization. Of the 23 patients, 11 had had hemoptysis on admission and 12 had not. Seven (64%) of the 11 with hemoptysis were dead at follow-up; four deaths occurred less than 1 year after admission and an additional three within 7 years (average, 2.5). The remaining four were alive 6 to 14 years after admission (average, 10). Of the 12 who did not have hemoptysis, none died within a year, and five (42%) died within 7 years (average, 4.4). Seven were alive 5 to 9 years after admission (average, 7), and three of these had developed the symptom since admission. Only one of four patients with syncope on admission died during the follow-up period, and his death occurred 2 years after admission. One of two patients with angina on admission died 7 years later. Ages of the 11 living patients at follow-up ranged from 28 to 62 years (average, 41). Although limited in activity, seven patients were gainfully employed; the remaining four were severely disabled. Six were cyanotic at rest and four others only after exercise. Of the survivors, five had hemoptysis and four of these had had the symptom on admission. Four had syncopal attacks and two of these had had the symptom on admission. The one patient with angina had had the symptom from admission.

Three patients were alive 10 to 14 years after catheterization and all were severely disabled. The first had recovered completely from hemiplegia 9 years previously, but had been unable to work for 2 years. The second had had features of chronic heart failure for 10 years. The third was severely disabled and unable to work.

Pregnancy

Of 23 female patients more than 16 years old at the time of follow-up or death, two had been pregnant with uncomplicated delivery of normal children; one of these had had no difficulty during or after her one pregnancy, while the other, who had occasional hemoptysis, continued to have this symptom infrequently during her two pregnancies.

Causes of Death

Seventeen of the 58 patients died during the follow-up periods, which varied in duration from 5 to 16 years (average, 8). The one death in group 1 followed a respiratory infection diagnosed as influenza. Of the four deaths in group 2, two occurred suddenly without any obvious prior change in clinical status and without any findings at autopsy to explain the death, the third followed an operation for lung abscess, and the fourth followed an operation for brain abscess. Of the 12 deaths in group 3, five were sudden and unexplained, two were from unknown causes (no autopsy), two from cerebral vascular accident, two from congestive heart failure, and one following severe pulmonary hemorrhage.

Discussion

It has long been known that the fate of children with a large ventricular septal defect associated with equivalent systolic pressures in the two ventricles is related to the resistance to blood flowing through the lungs, and this is reflected in adaptive structural differences in the small arteries and arterioles. To define "pulmonary vascular obstructive disease" remains a difficult and involved task and in this paper we have used the term arbitrarily from a hemodynamic viewpoint to
ventricular septal defect

Figure 2

Hemoptysis in groups 1, 2, and 3 showing low incidence under age 20 years.

indicate a severe limitation of pulmonary blood flow and have categorized this obstructive feature by relating it to systemic blood flow. The deficiencies inherent in classifying cases by the ratio of pulmonary to systemic resistance, particularly from one value for flow, and the need to use total pulmonary resistance rather than pulmonary "vascular" resistance because of lack of data on left atrial (wedge) pressure in some cases, are recognized by us. While our data indicate a progressive vascular obstructive process to be occurring over the years with severe pulmonary hypertension associated with a large ventricular septal defect, there is singular lack of evidence for progression in specific instances, and the situation is thus radically different from the primary (or idiopathic) pulmonary hypertension which runs its typical course within a few years. While mention has been made of the disappointing survival data on the group of patients with severe pulmonary vascular disease who recover from the surgical closure of their ventricular septal defect, there is still much to be learned about the proper management of the borderline case and the degree of involution possible in the pulmonary vascular obstruction in different age groups. Even a 12-year experience is not enough.

Beginning observations at the time of cardiac catheterization imposed certain limitations on analysis of the data, but despite these, some very interesting facts were apparent.

There was a statistically significant difference in longevity between the younger patients (group 2) and the older patients (group 3) (fig. 1). Age at the time of admission was the only difference in these two groups. The difference in survival curves is consistent with two main hypotheses, namely that patients develop progressive pulmonary vascular changes (or disease) at about the same age, or that young people tolerate the disease better than do adults. It is the opinion of the authors that both factors are operative but that early development of the disease is the more important one.

Hemoptysis is uncommon before the age of 20 years and less than 10% of patients developed the symptom during the follow-up period (fig. 2). Almost half the patients 20 years of age or older at the time of admission had hemoptysis, and 64% of these died within 7 years. Although at follow-up six patients...
age had angina, and only 15% of patients 20 years of age or older complained of exertional chest pain. It had no demonstrable effect on longevity.

Thirteen patients experienced syncopal attacks, slightly more patients being in group 3 than in the other two groups. There were no characteristics in these 13 patients which otherwise distinguished them from the others.

Pregnancy has been considered hazardous to the health and life of women with ventricular septal defect and pulmonary vascular disease. Only two women in the study became pregnant, and these were not adversely affected by the pregnancy.

The severity of pulmonary vascular disease may be defined from several variables measured during cardiac catheterization. Figure 3 shows the relation of age to pulmonary vascular resistance measured on admission catheterization. Calculated pulmonary resistance had a positive correlation with age of patient on admission, presumably as a result of increase in severity of pulmonary vascular disease. The increase in resistance was not apparently related to increasing mean pressure in the pulmonary artery, since pulmonary artery pressures did not differ significantly at different ages (fig. 4). Severity of pulmonary vascular disease on admission was not related to 5-year survival. Figure 5 relates the

in the three groups were alive despite having experienced hemoptysis for periods varying from 2 to 30 years, it was apparent that most of the patients who had hemoptysis did not have the life expectancy of those who did not have the symptom.

None of the patients less than 20 years of

Figure 4

Relation of mean pressure in pulmonary artery (PA) to age at time of initial cardiac catheterization and to clinical status at time of review.

Figure 5

Relation of ratio of pulmonary to systemic resistance \( R_p/R_s \) to age at time of initial cardiac catheterization and to clinical status at time of clinical review. Numbers adjacent to open circles indicate years between initial cardiac catheterization and death.

Figure 6

Relation of arterial oxygen saturation to age at time of initial cardiac catheterization and to clinical status at time of review.
status of the patients 5 years after catheterization to the ratio of pulmonary to systemic resistance. The absence of change in this ratio with increased age is the result of an increased systemic resistance in the older patients. There is no relation between 5-year survival and severity of pulmonary vascular disease as presented by a comparison of pulmonary and systemic resistance. Figure 6 shows the relation of age at the time of review to systemic arterial oxygen saturation at the time of initial catheterization. There is again no obvious relationship between prognosis and arterial oxygen saturation.

Acknowledgment
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Reference

Radical “Surgery” for Writers

In criticism, no faint praise. Take away from the author everything that is not his by right, take it as a surgeon takes away every last cell of morbid tissue, with a strict and relentless knife; then cauterize the wound and help the victim to his feet again and send him away with both hands filled with flowers.

An author whose tissue is so morbid that he cannot survive the operation should not to be subjected to it. He should be allowed to die in peace.—Van Wyck Brooks: From a Writer’s Notebook. New York, E. P. Dutton & Co., Inc., 1958, p. 111.
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