Further Observations on the Natural History of Isolated Ventricular Septal Defects in Infancy and Childhood

Serial Cardiac Catheterization Studies in 75 Patients

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In the past few years several reports on the physiologic changes in ventricular septal defect with increasing age, based on serial cardiac catheterization studies, have appeared in the literature.\(^1\)\(^-\)\(^10\) The results of these investigations have not been uniform, and variable conclusions have consequently evolved. A number of workers\(^1\)\(^-\)\(^4\)\(^-\)\(^6\) suggested that progressive pulmonary hypertension and rapidly increasing pulmonary vascular obstruction hardly occur in childhood, whereas others\(^7\)\(^-\)\(^9\) indicated that these changes are not uncommon at this age. Recently, Lucas et al\(^10\) demonstrated varying hemodynamic changes in large ventricular septal defects, which they related to variations in the maturation process of the pulmonary vascular bed.

This paper is a continuation of previous communications from this Department on the serial hemodynamic findings in ventricular septal defect. To date, a total of 75 patients with isolated ventricular septal defect have had serial cardiac catheterization studies. The results confirm our previous observation that there is a distinct tendency for the elevated pulmonary artery pressure and pulmonary blood flow to fall in the first few years of life. By the second half of the first decade or later, these changes are rarely observed, and severe pulmonary hypertension at this time persists and may be accompanied by gradually increasing pulmonary vascular obstruction.

Material and Methods

The data in this report are based on two or more cardiac catheterization studies on 75 patients with isolated ventricular septal defect. Three patients with other intracardiac anomalies previously included in an earlier paper\(^1\) have been excluded in order to maintain homogeneity of material. Similarly, patients previously reported to have “transformed” from a ventricular septal defect into tetralogy of Fallot\(^1\)\(^-\)\(^8\) have been excluded in this series. There were 36 males and 39 females. At the time of the initial cardiac catheterization, the age varied from 1 month to 17 years. There were 39 children under 1 year of age, 19 between 1 to 3 years, and 14 between 3 to 10 years. Only three patients were over 10 years of age at the time of the first catheterization. The interval between the first and second cardiac catheterization was 1 to 7 years. In seven patients, a third procedure was done 2 to 5 years following the second. The subjects in this study were obtained at random, except for seven children in whom the typical auscultatory findings were noted to have subsequently disappeared. Infants diagnosed clinically to have a ventricular septal defect underwent cardiac catheterization and angiocardiography before their discharge to the cardiac clinic, where they were seen at regular intervals. In those that did have surgery later, a repeat hemodynamic examination was obtained prior to the operation. In the others, in whom surgery was not performed because the defect was functionally small and clinically benign, or inoperable due to presence of severe pulmonary vascular obstruction, repeat cardiac catheterizations were similarly obtained several years later.

The catheterization and angiocardiographic diagnosis of isolated ventricular septal defect was confirmed by surgery in 18 and by necropsy in five. The cardiac catheterization procedure has
been described in detail in a previous report. In the past three years oxygen saturations were determined with the aid of Wood's cuvette and double scale oximeter (Waters Corporation), and pressures were obtained and recorded by use of Sanborn transducers and Sanborn 150 direct-writing photographic recorder, respectively. Dye-indicator studies were obtained routinely with the aid of a Colson densitometer. Except in the older children or adolescents, in whom oxygen consumption was actually determined with the use of a Tissot spirometer with Scholander apparatus for gas analysis, normal oxygen consumptions based on the normal basal metabolic rates at different ages were used for calculating blood flow. In order to permit valid comparison at different ages, flows and resistances were calculated and expressed in relation to body surface area. Total pulmonary resistance index, rather than pulmonary arteriolar resistance, was used since pulmonary "capillary" wedge pressures could not be obtained in all patients. In spite of some questions as to the use of total pulmonary resistance instead of arteriolar resistance, we believe that for a comparative-study of this type there should be no significant, if any, difference in the results whether one uses arteriolar or total resistance indices. It has been our experience that the pulmonary "capillary" wedge pressure is usually in the upper limits of normal in ventricular septal defect, and rarely does it become higher than twice its normal value. In the presence of severe pulmonary hypertension, therefore, slight differences in left atrial pressure between the first and second cardiac catheterization will not appreciably alter the significance of the estimated pulmonary vascular resistance.

Results

The changes in pulmonary artery pressure and in the magnitude of pulmonary blood flow, the latter expressed in the form of pulmonary-systemic flow ratio, are demonstrated in figure 1.

Patients with Normal Pulmonary Pressure on Initial Cardiac Catheterization

In 25 patients with normal pulmonary artery pressure on initial cardiac catheterization, the pressure remained essentially unchanged, except in one child who at the age of 10 months had a pressure of 26/16 mm. Hg, and at the age of 4 years a pressure of 45/25 mm. Hg. The shunt flow across the defect remained the same, with the pulmonary-systemic flow ratio 2.2 and 2.4 in the first and second studies, respectively. The total pulmonary vascular resistance has correspondingly increased from 205 to 416 dynes sec. cm.⁻²/M.². In the other 24 patients, the estimated pulmonary vascular resistance was normal in both examinations.

Patients with Mild Pulmonary Hypertension on Initial Cardiac Catheterization

In 28 patients with mild pulmonary hypertension initially, i.e., with pulmonary artery pressures over 30 mm. Hg but less than 60 mm. Hg, 17 revealed a drop in pulmonary

Figure 1

Changes with increasing age in pulmonary artery systolic pressure and in pulmonary blood flow (expressed in pulmonary-systemic flow ratio) in 75 patients with isolated ventricular septal defect. The patients have been classified into three groups based on the pulmonary artery pressure at the time of the first cardiac catheterization: (A) with normal pressure, (B) with systolic pressure between 31 and 59 mm. Hg, (C) with systolic pressure of 60 mm. Hg or over.
artery systolic pressures ranging from 11 to 35 mm. Hg. In 10 patients there was no significant change in pressures, and in one there was a rise from 53/33 mm. Hg at the age of 1.7/12 years to 73/35 mm. Hg at the age of 3 years. There was no significant change in pulmonary blood flow in this particular case, and the calculated total pulmonary vascular resistance rose from 375 to 570 dynes sec. cm.\(^{-5}\)/M.\(^2\). In the 27 patients where the pulmonary artery pressure either dropped or remained unchanged, the pulmonary-systemic flow ratio diminished in 21 cases and remained essentially the same in six. The total pulmonary resistance in 25 patients remained in the normal range. In three children the slightly elevated pulmonary vascular resistance noted at the initial study dropped to normal levels at the time of the second cardiac catheterization.

**Patients with Severe Pulmonary Hypertension on Initial Cardiac Catheterization**

There were 22 patients who had severe pulmonary hypertension initially, i.e., with pulmonary artery systolic pressure of 60 mm. Hg or more. Of these, 10 had normal or slightly elevated pulmonary vascular resistance, seven had moderately elevated pulmonary resistance, and five had markedly elevated pulmonary resistance. In only one of the latter five cases, however, was the pulmonary vascular resistance greater than that of the systemic resistance, resulting in a larger right-to-left than left-to-right shunt. This was in a 17-year-old girl with typical hemodynamic features of Eisenmenger's complex at the time of the first examination. In the other four cases only a left-to-right shunt was noted.

In this group of 22 patients, 10 showed a fall in pulmonary artery systolic pressure ranging from 16 to 55 mm. Hg, 10 did not reveal any significant change in pressure, and two showed a systolic pressure rise of 20 to 25 mm. Hg. The pulmonary blood flow depicted by the pulmonary-systemic flow ratio diminished in 13, remained unchanged in eight and increased in one. The calculated total pulmonary vascular resistance increased in five, remained in the same range in nine, and diminished in seven (table 2). In five patients who had moderately severe pulmonary vascular obstruction initially, two showed considerable increase in the pulmonary vascular resistance. One of these already had the hemodynamic features of Eisenmenger's complex initially. The other, at the age of 7 years, had a left-to-right shunt accounting for a pulmonary-systemic flow ratio of 1.3, and no definite right-to-left shunt, the systemic arterial oxygen saturation varying from 98 per cent at rest to 88 per cent on crying. At the age of 14 years the pulmonary artery systolic pressure increased by 20 mm. Hg, and a right-to-left shunt, which was now greater than the left-to-right shunt, was observed. In other words, pulmonary vascular resistance became greater than systemic resistance, thus constituting a true example of progression to Eisenmenger's complex. Another child, who at the age of 7 years had severe pulmonary hypertension and moderate pulmonary vascular obstruction, also revealed increasing pulmonary vascular resistance, from an initial 550 dynes sec. cm.\(^{-5}\)/M.\(^2\) to 800 and 1200 dynes sec. cm.\(^{-5}\)/M.\(^2\) at the age of 10 and 15 years, respectively.

Increasing pulmonary vascular resistance was, however, not a usual feature in our cases, even in those with initially severe pulmonary hypertension and moderate pulmonary vascular obstruction. Thus, in seven patients with these hemodynamic findings on first cardiac catheterization, a significant fall in pulmonary vascular resistance was observed, with or without associated fall in pulmonary artery pressure, at the second catheterization (fig. 2).

The hemodynamic changes in 50 patients with initially elevated pulmonary artery pressure are analyzed according to the age of the patient during the first catheterization. In table 1 are grouped those patients with pulmonary artery pressure between 31 and 59 mm. Hg, and in table 2 are those with 60 mm. Hg or more. A similar table of the 25 pa-
patients with initially normal pulmonary artery pressure was not prepared, since, with the exception of a single case showing a 19 mm. Hg rise in pulmonary artery systolic pressure, there were no significant hemodynamic changes observed in this group.

The most striking findings in table 1 consist of the decline in pulmonary artery pressure, reduction in pulmonary blood flow, and maintained normal pulmonary vascular resistance in the majority of children in whom the initial cardiac catheterization was performed in the first 2 years of life. The elevated pulmonary artery pressure was accompanied by abundant pulmonary blood flow, the pulmonary-systemic flow ratio in the majority being more than 2.5, and normal pulmonary resistance. Of 21 subjects first studied at this early age, 15 (71 per cent) showed a drop in pulmonary artery pressure, and five (24 per cent) revealed no significant change in pressure in the subsequent cardiac catheterization. In 17 cases (81 per cent), there was associated reduction in pulmonary blood flow. In contrast, no significant hemodynamic changes were observed in the four children who were first studied after the age of 4 years.

Table 2 reveals a similar hemodynamic phenomenon, namely, a fall in pulmonary artery pressure and blood flow in the majority of children whose initial cardiac catheterization was conducted in the first 2 years of life. The elevated pulmonary artery pressure in these very young children was accompanied by abundant pulmonary blood flow that was three or more times the systemic flow in most of them. Pulmonary vascular resistance was,

![Graph](image)

**Figure 2**
Pulmonary artery systolic pressure plotted against total pulmonary vascular resistance in the first and subsequent cardiac catheterizations of patients with pulmonary vascular resistance. Note increasing pulmonary vascular resistance in six patients (upper graph) and decreasing pulmonary vascular resistance in seven patients (lower graph).

### Table 1

<table>
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<tr>
<th>Age (yr.)</th>
<th>No. cases</th>
<th>Pressure drop (mm. Hg)</th>
<th>Pressure rise (± 10)</th>
<th>Changes in P/S flow ratio</th>
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<td>11-20 21-35 (± 10)</td>
<td>11-20 21-35</td>
<td>Increased (± 30%) Diminished</td>
<td>Increased† Normal limits Diminished‡</td>
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<td>.. 7 21 2 22 3 ..</td>
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*Pulmonary artery systolic pressure of 30 to 59 mm. Hg.
†Resistance increased from normal to abnormal levels.
‡Resistance dropped from high to normal levels.
§Pulmonary artery not entered in one patient.
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therefore, normal or only slightly elevated in these cases. In the 12 children studied initially in the first 2 years of life, eight (66 per cent) showed a drop in pulmonary artery systolic pressure ranging from 18 to 55 mm. Hg, and the rest did not have any significant change in pressure. The pulmonary blood flow diminished in eight (66 per cent), remained essentially unchanged in three (25 per cent), and increased in one (9 per cent). The total pulmonary vascular resistance dropped significantly in four (33 per cent), and remained unchanged in seven (58 per cent). Only one showed an increase in total pulmonary vascular resistance from 310 dynes sec. cm.⁻⁵/M.² at 11 months to 620 dynes sec. cm.⁻⁵/M.² at 2 years of age.

The hemodynamic changes in five children first studied after the age of 5 years were distinctly different. Of these five patients, three revealed no significant change in pulmonary artery pressure, and two showed increase in systolic pressure of 20 and 25 mm. Hg. These pressure alterations were accompanied by either no significant change in or by reduction of pulmonary blood flow, and by correspondingly increasing total pulmonary vascular resistance in three and unaltered high pulmonary resistance in two patients. No consistent hemodynamic changes were observed in the children first studied between the ages of 3 and 5 years. Of the five patients in this category, three revealed no significant change in pulmonary artery pressure, pulmonary blood flow, or pulmonary resistance. In the other two cases, the pulmonary artery pressure dropped by 20 and 25 mm. Hg, with no accompanying significant change in pulmonary resistance in one, and a drop in resistance to about 60 per cent of its original value in the other.

In 14 children, varying in age from 1 month to 2 ½ years at the initial catheterization, the previously demonstrated left-to-right shunt at the ventricular level was no longer notable by oxygen saturation studies of the right heart at the time of second catheterization 13 months to 6 years later. Selective dye-

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### Table 2

<table>
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<th>Changes in pulmonary pressure (mm. Hg)</th>
<th>Changes in P/S flow ratio</th>
<th>No.</th>
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<td></td>
<td></td>
<td></td>
<td>20-30</td>
<td>40-50</td>
</tr>
</tbody>
</table>

*Pulmonary artery systolic pressure of 60 mm. Hg or more.*

*In one other patient the pulmonary artery was not entered, but there were no significant changes in right ventricular pressure and pulmonary blood flow.*

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indicator studies and left ventricular angiocardiography, however, demonstrated minimal left-to-right shunts in six patients. In seven of the other eight patients with hemodynamic and angiocardiographic evidence of functional closure of the defect, the original typical holosystolic murmur was replaced by a soft ejection systolic murmur at the pulmonary area in five, and no murmur in two. The clinical and hemodynamic data in this group of 14 children are outlined in another report.15 Initial pulmonary artery systolic pressure in the range of 35 to 56 mm Hg was observed in three patients, and pulmonary blood flow more than twice the systemic flow in six. In the eight children where functional closure of the defect was probably complete, the second cardiac catheterization was performed before the age of 2 years in four, by the age of 3 years in two, and by 6 and 7 years in the other two children.

Discussion

Some differences in opinion regarding the natural history of ventricular septal defect still prevail. The disparity apparently stems from diverse results of serial hemodynamic studies conducted by various investigators. The diversity of these results may be attributed to several factors, such as differences in age groups studied, selection of case material, inclusion of cases with associated intracardiac anomalies, insufficient material or period of observation, etc. The most controversial problem seems to be the question of progressive pulmonary vascular obstruction. Some authors1, 4-6, 11 have indicated its extreme rarity in early childhood or even during the pediatric age, whereas others7-9, 13, 14 have suggested that this sequela is not uncommon at this age and should be a strong argument for very early corrective surgery. Weidman and associates12 have demonstrated seven cases with clinical proof of progressing pulmonary vascular obstruction in children with this lesion, and have emphasized that early surgery should be attempted in cases of this type.

Just as in any other distinct entity, the natural course of ventricular septal defect must encompass a spectrum depending, among other things, on the functional size of the defect and the response of the pulmonary vascular bed to the hemodynamic stress resulting from the defect. Recently, Lucas and co-workers10 have demonstrated different serial physiologic patterns in 40 patients and classified them into five groups accordingly. The various patterns were interpreted to be closely related to the size of the defect, as well as to the response of the pulmonary vascular bed consisting of normal maturation (normal regression of fetal state), delayed maturation, or failure of maturation to occur. Our findings are essentially in agreement with theirs.

In a previous report based on a study of 32 patients,1 we have pointed out the distinct tendency for the increased pulmonary artery pressures and pulmonary blood flow in infants with ventricular septal defect to decrease during the early years of life. Severe pulmonary hypertension and pulmonary vascular obstruction were observed in a small minority, and only three showed increase in pulmonary vascular resistance at the second cardiac catheterization, although no significant reversal of the shunt flow across the defect was observed in that series. Recently, one of these patients was studied by us for the third time, and the findings revealed unquestionable progression in pulmonary vascular obstruction. This is discussed in more detail below.

In this present series of 75 patients, we have observed normal pulmonary artery pressure in one third of the cases at the time of the first cardiac catheterization. Except for one case that showed slight rise in pressure, the pulmonary artery pressure as well as the total pulmonary vascular resistance remained normal in all. Left ventricular angiographic studies in this type of case reveal that the defect is generally small with a diameter usually of only a few millimeters.16 The small size of the defect evidently limits, not only the transeptal flow of arterial blood into the lesser circulation, but also inhibits transmis-
sion of left ventricular ejective force into the right ventricle. The relatively small shunt and the normal pulmonary artery pressure evidently do not constitute enough stress to promote pulmonary vascular reaction leading to obstruction during childhood. Whether a similar benign course is maintained during adulthood is not known at the present time.

Our previous finding of a distinct tendency for the elevated pulmonary artery pressure and pulmonary blood flow to decrease during the first 2 or 3 years of life is again corroborated in this report. We have observed this finding in approximately three fourths of the children who were noted to have mild pulmonary hypertension in the first or second year of life, and in two thirds of those with moderate or severe pulmonary hypertension at this early age. The drop in pulmonary artery pressure does not appear to be related to a reduction in pulmonary resistance, since there is no accompanying increase in the pulmonary blood flow. In fact, the pressure elevation in the pulmonary artery observed initially is generally unrelated to any significant pulmonary vascular obstruction. The hypertension occurs in association with abundant pulmonary blood flow (so-called hyperkinetic pulmonary hypertension), and pulmonary vascular resistance is often in the upper limits of normal, or only slightly elevated. Of the 33 cases with elevated pulmonary artery pressure during the first 2 years, only one revealed a significant increase in pulmonary vascular resistance. Whether the pulmonary vascular response would have continued if the defect was not closed is a matter of conjecture. It is possible that pulmonary vascular obstruction may have progressed in this case, as is sometimes observed in older children with large defects and elevated pulmonary resistance.

The only valid explanation for the frequently observed drop in pulmonary artery pressure and pulmonary blood flow during the first 2 or 3 years would appear to be a relative reduction in the functional size of the defect. As the heart normally increases in size, most rapidly during the first and, to a lesser extent, second year of life, the defect probably remains the same or fails to undergo a corresponding increase in size. It is possible that other factors, such as normal maturation of the pulmonary vascular bed resulting in diminished pulmonary vascular resistance, also play some role in this striking hemodynamic improvement, but, if they do, they are probably masked by the effect of relative reduction in the functional size of the defect. In cases where the auscultatory, hemodynamic, and angiocardiographic evidence of the defect has disappeared, an actual diminution, rather than a relative reduction in the size of the defect, must have occurred. It is most likely that these ventricular septal defects were of the low muscular variety which, according to Edwards, is usually oval-shaped in infancy and tends to become smaller and linear with age, until finally the margins may coapt, resulting in anatomic closure. A number of recent accounts of spontaneous functional closure of ventricular septal defect have appeared in the literature. It is of interest that the "closure" generally occurs in early childhood, not uncommonly during the first 3 years, and usually not later than 6 years of age.

The clinical and hemodynamic improvement which may be observed in early childhood is exemplified by patient T.J., whose serial chest roentgenograms are shown in figure 3. This child was diagnosed to have a large ventricular septal defect in infancy. The heart was markedly enlarged, and congestive heart failure, repeated pulmonary infections, and failure to gain weight characterized the first and second years of life. At the age of 2 years (fig. 3A), cardiac catheterization revealed pulmonary artery pressure of 93/51 mm. Hg, pulmonary blood flow of 19.8 L./min./M.\(^2\), systemic blood flow of 5.8 L./min./M.\(^2\), and total pulmonary vascular resistance of 215 dynes sec. cm.\(^{-5}\)/M.\(^2\). At the age of 5 years, the heart size was remarkably diminished (fig. 3B), and a repeat study revealed pulmonary artery pressure of 47/36 mm. Hg, pulmonary blood flow of 9.4 L./min./M.\(^2\), systemic blood flow of 6.3 L./min./M.\(^2\) and,
similarly, normal pulmonary vascular resistance. At 7 years the heart was essentially normal in size (fig. 3C), and a third cardiac catheterization revealed pulmonary artery pressure of 38/12 mm. Hg, pulmonary blood flow of 6.4 L./min./M.², systemic blood flow of 3.7 L./min./M.² and normal pulmonary vascular resistance. In summary, the severe pulmonary hypertension noted in very early childhood rapidly disappeared in a few years, accompanied by considerable reduction in shunt flow and improvement in clinical status. These changes are most likely related to progressive functional closure of the ventricular septal defect, such as may occur in low-lying muscular defects. Unfortunately, we have not performed left ventricular angiocardiograms in this case to permit localization of the defect with reasonable certainty.

The opposite physiologic course, namely, that characterized by persistent or increasing pulmonary hypertension and progressive pulmonary vascular obstruction, may occur in a minority of patients with ventricular septal defect. We have observed this phenomenon in six patients (fig. 2). This represents 8 per cent of the total 75 patients in this series, 12 per cent of those with elevated pulmonary artery pressure at the initial examination, or 27 per cent of those who had pulmonary artery pressure of 60 mm. Hg or more at the time of initial study. Except for an 11-month-old infant who had relatively normal pulmonary resistance initially, all had elevated pulmonary vascular resistance at least twice the normal on first catheterization. One patient was 3 years of age, and four others were over 6 years at the time of initial examination. Two patients who had Eisenmenger’s physiology, with pulmonary vascular resistance definitely higher than systemic vascular resistance, were 14 and 17 years of age.

These findings lend support to the assumption that increasing pulmonary vascular obstruction does occur during childhood in some patients with isolated ventricular septal defect. It appears, however, to be less common than others have suggested.7, 8, 13, 14 It seems more likely to be observed in the latter part of the first decade in patients whose pulmonary hypertension has been, right from the beginning, accompanied by significantly elevated pulmonary vascular resistance. Presumably, maturation of the pulmonary vascular bed has been incomplete, or has failed to occur in these cases for reasons as yet unknown.10 If the defect remains uncorrected, progressive pulmonary vascular obstruction...
leading eventually to Eisenmenger's syndrome may follow.

The sequence of hemodynamic events is illustrated by the serial clinical and cardiac catheterization findings in patient J.H., who at the age of 6 years was noted to have a loud pansystolic murmur and thrill along the left sternal border, marked cardiomegaly and pulmonary hypervascularity (fig. 4A). Cardiac catheterization at this time revealed pulmonary artery pressure of 77/47 (femoral artery 99/52) mm. Hg, pulmonary blood flow of 9.3 L./min./M.2, systemic blood flow of 3.3 L./min./M.2, and total pulmonary resistance of 550 dynes sec. cm.−5/M.2. At the age of 10 years, the murmur was noted to have become shorter and not so loud, the heart was smaller, the pulmonary artery segment was prominent, and pulmonary vascularity was reduced (fig. 4B). Cardiac catheterization revealed pulmonary artery pressure of 103/66 (femoral artery 115/77) mm. Hg, pulmonary blood flow 7.7 L./min./M.2, systemic blood flow 3.2 L./min./M.2, and total pulmonary resistance of 800 dynes sec. cm.−5/M.2. A systemic arterial sample yielded 90 per cent oxygen saturation. By 15 years she started to manifest clinical cyanosis. The murmur became very faint and short, and the heart further reduced in size. The pulmonary trunk and main branches, however, appeared dilated in contrast to the narrow peripheral branches (fig. 4C). Cardiac catheterization revealed pulmonary artery pressure of 100/63 (descending aorta 110/62) mm. Hg, bidirectional shunt flow consisting of 2.9 L./min./M.2 left-to-right and 1.8 L./min./M.2 right-to-left, pulmonary-systemic flow ratio of 1.3, and total pulmonary resistance of 1,200 dynes sec. cm.−5/M.2. This case definitely illustrates progressive pulmonary vascular obstruction leading toward Eisenmenger's physiology. It is indeed unfortunate that surgical correction of the defect could not be performed after the first or even second cardiac catheterization because of the stubborn refusal of the parents to submit the child to surgery.

It is of interest to note that an almost equal number of cases with practically identical pulmonary hypertension and pulmonary vascular obstruction during the first catheterization did reveal a significant fall in pulmonary vascular resistance by the second examination (fig. 2). In four of the seven cases this was
associated with a drop in pulmonary artery pressure by 18 to 30 mm. Hg. The initial catheterization was performed in four cases before the age of 2 years, and repeated not later than the age of 5. The reduction in pulmonary resistance may be related to delayed onset of maturation of the pulmonary vascular bed, although in those cases where a significant pressure drop was observed, relative reduction in the functional size of the defect must have occurred also.

In this series we have purposely excluded patients who during the first year had hemodynamic features of a large ventricular septal defect with pulmonary hypertension and minimal pulmonary stenosis, and subsequently developed findings of tetralogy of Fallot a few years later. At the time of surgery these patients had morphologically abnormal outflow tracts consistent with tetralogy. We presently consider these cases to be variants of tetralogy of Fallot showing delayed progression of the pulmonary infundibular stenosis, thus accounting for the relatively prolonged precyanotic phase of the disease.

The results of this study suggest that the natural course of ventricular septal defect may be expressed in a spectrum with one extreme showing relative reduction or even functional closure of the defect, and the opposite extreme consisting of progressive pulmonary vascular obstruction leading to Eisenmenger’s complex. There appear to be several factors responsible for the varying physiologic courses, the most important being the size of the defect, the age of the patient, and the individual response of the pulmonary vascular bed to the hemodynamic stress from a large defect. It appears that in children with normal or mildly elevated pulmonary artery pressure significant pulmonary vascular obstruction does not occur during childhood, and the pulmonary artery pressures do not increase. In the first 2 or 3 years of life relative reduction in the functional size of the defect is common, and occasionally functional closure of the defect may occur at this early age. This accounts for the widely known clinical improvement often observed after the infancy period in patients with isolated ventricular septal defect. Increasing pulmonary vascular obstruction may occur in some patients, particularly in those in the latter part of the first decade who had severe pulmonary hypertension associated with moderately elevated pulmonary vascular resistance. Progressive pulmonary vascular changes in these cases may eventually terminate in the development of frank Eisenmenger’s syndrome with higher pulmonary than systemic vascular resistance, and reversal of the shunt flow across the defect.

The therapeutic significance of these findings is obvious. In the patients with normal or only slightly elevated pulmonary artery pressure there is no justification for early surgery for fear of progressive pulmonary vascular changes. Similarly, in the presence of pulmonary hypertension, surgical closure of the defect need not be attempted in the first 2 years of life due to the danger of rapid development of progressive pulmonary vascular obstruction. The hypertension at this age is usually unaccompanied by high pulmonary resistance, and the pulmonary artery pressure tends to fall somewhat as the child grows older. If surgery is necessary at this very early age, it is generally due to excessive shunt flow across the defect, with marked overloading of the heart chambers and intractable congestive heart failure not responsive to medical management. In pre-school or school-age children with significant pulmonary hypertension, especially those with evidence of pulmonary vascular obstruction, early surgical repair of the defect should be attempted. Functional closure of a ventricular septal defect may occur in a minority of cases; if it does, it tends to occur in the first 3 to 6 years of life.

Summary

Serial cardiac catheterization has been performed in 75 patients with isolated ventricular septal defect. At the time of the first cardiac catheterization, 39 were under 1 year
of age, 19 were between 1 to 3 years, 14 between 3 to 10 years, and three over 10 years. In 68 patients the second catheterization was performed 1 to 7 years after the first, and in seven patients a third cardiac catheterization was performed 2 to 5 years after the second.

Normal pulmonary artery pressure was observed at the initial study in 25 patients. Of these, only one revealed a slight rise in pulmonary artery systolic pressure by 19 mm. Hg; the rest revealed no significant hemodynamic changes.

Mild pulmonary hypertension (31 to 59 mm. Hg systolic pressure) was noted in 28 patients at first catheterization, at which time moderate or severe pulmonary hypertension (60 mm. Hg or more systolic pressure) was present in 22 patients. In 33 of these 50 cases, the initial investigation was done during infancy and not later than the second year. In three fourths of the cases with mild pulmonary hypertension, and in two thirds of those with moderate or severe hypertension studied at this very early age, a significant drop in pulmonary pressure and flow was observed at the subsequent catheterization. This was interpreted to indicate most likely relative reduction of the functional size of the defect during early childhood. In eight patients hemodynamic and angiocardiographic evidence of the ventricular septal defect disappeared, indicating probable functional closure.

Progressive pulmonary vascular obstruction was observed in six patients, one of whom already had Eisenmenger’s complex at the initial examination. All but one, an 11-month-old infant, had significantly elevated pulmonary vascular resistance already present during the first cardiac catheterization. In seven patients with similar findings at the initial examination, striking reduction in pulmonary vascular resistance was observed. The progressive pulmonary vascular obstruction is interpreted to indicate failure of the pulmonary vascular bed to undergo maturation, whereas the diminution in pulmonary resistance observed in the other group is interpreted to indicate delayed onset of pulmonary vascular maturation.

The therapeutic significance of these findings is discussed.

References


The Experimental Method

Reasoning will always be correct when applied to accurate notions and precise facts; but it can lead only to error when the notions or facts on which it rests were originally tainted with error or inaccuracy. That is why experimentation, or the art of securing rigorous and well-defined experiments, is the practical basis and, in a way, the executive branch of the experimental method as applied to medicine. If we mean to build up the biological sciences, and to study fruitfully the complex phenomena which occur in living beings, whether in the physiological or the pathological state, we must first of all lay down principles of experimentation, and then apply them to physiology, pathology and therapeutics. Experimentation is undeniably harder in medicine than in any other science; but for that very reason, it was never so necessary, and indeed so indispensable. The more complex the science, the more essential is it, in fact, to establish a good experimental standard, so as to secure comparable facts, free from sources of error. Nothing, I believe, is to-day so important to the progress of medicine.—Claude Bernard, M.D. An Introduction to the Study of Experimental Medicine. New York, The Macmillan Company, 1927, p. 2.
Further Observations on the Natural History of Isolated Ventricular Septal Defects in Infancy and Childhood: Serial Cardiac Catheterization Studies in 75 Patients

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