The Natural History of Isolated Ventricular Septal Defect
A Serial Physiologic Study

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The advent of curative surgery for the patient with ventricular septal defect has emphasized the need for a more precise knowledge of the natural history of this anomaly. Despite numerous studies in the last few years, many factors relating to the natural history of ventricular septal defects remain incompletely defined.

The diversity in clinical course of patients with isolated ventricular septal defect is particularly enigmatic. This problem has been partially clarified by clinical, physiologic, and pathologic studies by many workers, including Dammann and Ferencz1 and Adams and associates,2 who related the clinical symptomatology to the changes in the pulmonary vascular bed. Work by Edwards,3 and Ferguson and associates,4 and Wagenvoort5 has more precisely defined the structural changes occurring in the lung subjected to the stress of increased flow and pressure. Understanding was further advanced by these workers through their assessment of the postnatal changes occurring in the pulmonary vascular tree in normal infants.4-7

A consideration of the hemodynamic consequences of an isolated ventricular septal defect should begin with a brief review of certain characteristics of fetal and neonatal circulatory systems. In the fetal state, pulmonary blood flow approximates only 10 per cent of the total cardiac output. Since pressures in the two ventricles are believed to be equal, the total pulmonary resistance must therefore substantially exceed the total systemic resistance.8 At birth, total pulmonary resistance drops immediately and profoundly following expansion of the chest and replacement of the intra-alveolar fluid with air.9 These mechanisms reduce the extramural pulmonary vascular pressure, permitting intramural pressure to distend the arterioles of the pulmonary vascular bed. This distention is largely responsible for the immediate fall in the total pulmonary resistance. To be sure, the neonatal pulmonary arteriole still characteristically possesses a marked degree of medial thickening.9,7

Anatomic studies reveal that with time, and in the absence of cardiovascular anomalies, the prominent media of these thick-walled arterioles atrophies and the diameter of the lumina concomitantly increases. This transition is thought to be largely complete in the normal infant at 2 to 6 months of age.6,7 As a result of these anatomic changes (i.e., maturation), a further fall in total pulmonary resistance occurs. Studies by Wagenvoort and associates,10 Ferguson et al.,4 and Lucas and associates11 suggest, however, that the maturation of the pulmonary vascular bed is not complete at 1 year, but continues through the first 4 years of life. The corresponding fall in total pulmonary resistance mirrors this histologic maturation of the pulmonary vascular bed during the period from birth through 4 years.11

An isolated ventricular septal defect imparts a stress, in the form of increased pulmonary arterial pressure and increased pulmonary blood flow, that may alter the normal

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Table 1

Incidence of Associated Defects

<table>
<thead>
<tr>
<th>Defect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated ventricular septal defect</td>
<td>40</td>
</tr>
<tr>
<td>Ventricular septal defect + coarctation of aorta</td>
<td>5</td>
</tr>
<tr>
<td>Ventricular septal defect + patent ductus arteriosus</td>
<td>7</td>
</tr>
<tr>
<td>Ventricular septal defect + corrected transposition</td>
<td>4</td>
</tr>
<tr>
<td>Ventricular septal defect + &quot;acquired&quot; pulmonary stenosis*</td>
<td>5</td>
</tr>
<tr>
<td>Ventricular septal defect + atrial septal defect</td>
<td>2</td>
</tr>
<tr>
<td>Multiple ventricular septal defects</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
</tr>
</tbody>
</table>

*The precise mechanism of this phenomenon of "acquired" pulmonary stenosis in ventricular septal defect is not known. Hence, these patients are considered separately, though they may represent yet another possible response in the patient with an isolated septal defect.

maturation of the pulmonary vascular bed. Clinical and physiologic observations at many cardiac centers indicate the benignity of the small defect; hence we can conclude that the small lesion imposes minimal stress. But the effect on the primary vascular bed of a large ventricular septal defect, and the very definition of a "large" defect, are not so easily determined.

In the neonate with a "large" defect, the initial fall in pulmonary resistance allows massive pulmonary blood flow, and indeed many of these infants succumb from the resultant failure of the left ventricle. Should the infant survive this critical period, his condition may spontaneously improve toward the end of the first year of life. Damann and Ferenez, on the basis of careful correlation of clinical, anatomic, and physiologic data, have demonstrated a stage of severe congestion followed by a period of relative absence of symptoms. After varying intervals, cyanosis developed in some of their patients. The pulmonary vascular bed, in the opinion of these authors, is responsible for this triad of clinical stages. They have concluded that the normal initial increase in the diameter of the pulmonary arteriole allows massive pulmonary blood flow and results in severe congestion. With time, anatomic alterations (medial hypertrophy and intimal proliferation) decrease the lumen of the pulmonary arteriole. The resultant decrease in the pulmonary blood flow brings about the period of relative freedom from symptoms. If the lumen diameter of the pulmonary arterioles decreases to the point at which pulmonary resistance exceeds systemic resistance, right-to-left shunting and cyanosis occur.

Only some patients progress through all three of these stages. As noted, many fail to survive the period of congestion. Others appear to maintain a high pulmonary resistance from birth, with early and persistent cyanosis. Edwards has suggested that these patients have failed to achieve any normal maturation of their pulmonary arterioles. Occasional patients become cyanotic in later childhood without appreciable prodromal symptoms.

Alternative explanations have also been advanced for the spontaneous improvement in congestive symptoms seen in infancy. Gasul and associates observed development of "acquired pulmonary stenosis" in patients with ventricular septal defect. It has been suggested that the relative size of the ventricular septal defect may decrease. These phenomena could, of course, allow clinical
improvement without a change in the pulmonary vascular bed. The variety of clinical courses, and the different theories advanced to explain these variations have led to conflicting opinions about the natural history and treatment of isolated ventricular septal defect.

This report attempts through serial studies to define the physiologic courses followed by a group of patients with isolated ventricular septal defects.

Material and Methods

Table 1 lists the cardiac defects present in 64 patients who underwent two or more physiologic studies prior to surgical intervention. This report is limited to the 40 patients who gave evidence of isolated ventricular septal defect. To eliminate complicating variables we have excluded from consideration the other 24 patients who presented a variety of cardiac anomalies in addition to this defect. The age of the patients with isolated ventricular septal defect at the time of right-sided heart catheterization ranged from 3 months to 16 years. The interval between catheterizations varied from 6 months to 7 1/2 years. All catheterizations at the University of Minnesota were performed without premedication and with local anesthesia only. Pressures were obtained by means of the Statham strain-gage model no. P23G and were electronically integrated. Oxygen determinations were performed by the method of Van Slyke.

In patients older than 5 years of age oxygen consumption was measured by means of a Benedict-Roth spirometer. In younger patients, the oxygen consumption was calculated by an assumed basal value of 172 ml of oxygen per square meter per minute. Pulmonary blood flow was computed with the Fick principle, and total pulmonary resistance was calculated as follows:

\[
TPR = \frac{\text{mean pulm. pressure in mm. Hg} \times 1332}{\text{pulmonary flow in ml. per second}}
\]

Thirty-two of the patients with isolated ventricular septal defect have undergone operation for complete surgical correction of the anomaly. In nine of these patients at autopsy, and for the remainder at the time of operation, the location and size of each defect were carefully noted. In the eight remaining cases, the diagnosis of isolated ventricular septal defect has not been confirmed surgically or at necropsy.

Heart catheterization was performed in nine patients at a postoperative interval of 7 to 24 months, with an average of 13 months.

Values for total pulmonary resistance, pulmonary blood flow, and pulmonary pressure obtained from catheterization studies on normal infants and children are shown in figures 1 to 3. These values, which appear also in subsequent figures as points of reference, form the basis of the physiologic groupings devised for these patients with isolated ventricular septal defect.

Results

The patients with isolated ventricular septal defect have been grouped initially according to the level of total pulmonary resistance at each catheterization. They have been di-

![Figure 2](image_url)
Pulmonary blood flow in normal infants and children in ml per second. A gradual increase occurs with increasing age. (From Lucas and associates. Reproduced with permission.)

![Figure 3](image_url)
Total pulmonary resistance in normal infants and children. Note the rapid decrease in total pulmonary resistance in the first 2 years and achievement of essentially "normal" adult values at about 4 years of age. (From Lucas and associates. Reproduced with permission.)
Relation of defect size to the ratio of pulmonary and systemic systolic pressures. In general, the larger the defect, the greater the ratio of pulmonary to systemic pressure. Those patients with defects measuring less than 1 cm. per M.\(^2\) of body surface area have the lowest ratio of pressure, and all fall in group IA. When the defect size is greater than 1 cm. per M.\(^2\) of body surface area, the pressure ratio appears almost independent of defect size. The physiologic group into which the patient falls also appears to depend on other factors than size, once the defect is greater than 1 cm. per M.\(^2\) of body surface area.

Provided further on the basis of pulmonary flow and pressure. These classifications are shown in table 2.

In figure 4, the ratio of systolic pulmonary arterial pressure to systolic systemic pressure has been plotted against the diameter of the defect per square meter of body surface area.\(^*\) A general correlation exists between relative defect size and relative pulmonary arterial pressure. Among patients in group IA (normal total pulmonary resistance, low flow and pressure) each defect was less than 1 cm. in diameter per M.\(^2\) of body surface area, and the systolic pulmonary arterial pressure ratio was less than 0.33. All patients with the defect greater than 1 cm. per M.\(^2\) of body surface area had a higher systolic pressure ratio, but the magnitude of the defect beyond this point did not relate precisely to the pressure ratio. Likewise, the variable physiologic responses among the patients with defect size greater than 1 cm. per M.\(^2\) of body surface area suggested that factors other than ventricular septal defect size alone were operative.

**Group IA.** Normal Pulmonary Vascular Maturation. Small Ventricular Septal Defect. Minimal Physiologic Abnormality

Figure 5 summarizes the physiologic data relating to these seven patients. The total pulmonary resistance at each catheterization study was at the normal level. The absolute pulmonary flow was slightly elevated and paralleled roughly the expected increase with...
Table 2

Summary of Classification of Isolated Ventricular Septal Defect

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Normal pulmonary vascular maturation (normal fall in total pulmonary resistance with age)</td>
</tr>
<tr>
<td></td>
<td>IA Small ventricular septal defect (less than 1 cm./M.²)</td>
</tr>
<tr>
<td></td>
<td>IB Apparent decrease in relative size of ventricular septal defect</td>
</tr>
<tr>
<td></td>
<td>IC Large ventricular septal defect</td>
</tr>
<tr>
<td>Group II</td>
<td>Delayed maturation of pulmonary vascular bed (delayed fall in total pulmonary resistance)</td>
</tr>
<tr>
<td></td>
<td>Large ventricular septal defect</td>
</tr>
<tr>
<td>Group III</td>
<td>Failure of pulmonary vascular maturation (no fall in total pulmonary resistance from fetal level)</td>
</tr>
<tr>
<td></td>
<td>Large ventricular septal defect</td>
</tr>
<tr>
<td>Group IV</td>
<td>Normal or delayed maturation of pulmonary vascular bed followed by evidence of progressive pulmonary vascular changes. (Increasing total pulmonary resistance after normal or nearly normal decrease from the fetal level)</td>
</tr>
<tr>
<td></td>
<td>Large ventricular septal defect</td>
</tr>
<tr>
<td>Group V</td>
<td>Cyanotic patients. Pathway to high pulmonary vascular resistance unknown</td>
</tr>
<tr>
<td></td>
<td>Large ventricular septal defect</td>
</tr>
</tbody>
</table>

age. The mean pulmonary arterial pressure was only slightly elevated (under 25 mm. Hg) and did not increase with time. As shown in figure 4, the defect size was less than 1 cm. per M.² of body surface area in each of the four patients in whom the defect was measured at the time of operation. The average age of these patients was 6 years at the first catheterization and 11.6 years at the second.

Wood²⁰ has suggested that a ventricular septal defect larger than 1 cm. per M.² of body surface area can allow a common ventricular ejection force to the pulmonary trunk and aorta. The defect size in this group lends support to this approximate value as the critical orifice area below which abnormal physiologic responses are minimal. The clinical course followed by these patients, who had virtually no symptoms and essentially normal thoracic roentgenograms and electrocardiograms, was compatible with the nearly normal physiologic values.

The normality of total pulmonary resistance in this group of patients at each study suggests that the pulmonary vascular bed had achieved normal maturation. No progressive vascular changes developed during the period of observation.

One patient (case 6) had had a bacteriologically proved (Streptococcus viridans) subacute bacterial endocarditis that was successfully treated medically. At operation 3 years later, the severe scarring observed in the septal leaflet of the tricuspid valve required plastic repair. While these patients exhibit minimal physiologic changes, their cardiac malformations cannot be considered completely benign.

Group IB. Normal Pulmonary Vascular Maturation. Large Ventricular Septal Defect. Apparent Decrease in Relative Size of Defect

These five patients (fig. 6) underwent initial catheterizations before 1 year of age. The total pulmonary resistance fell along the normally expected path. Pulmonary flow was moderately elevated. The mean pulmonary arterial pressures initially were considerably above the level seen in group IA, but at the time of the second study they had decreased in four of the five patients. This pressure drop without concomitant fall in the systemic pressure was noted in only two other patients in our series (group III).

Figure 7 is representative of the ratio of systolic pulmonary arterial pressure to systolic systemic pressure at each catheterization of the patients in group IB. This fraction, we believe, indicates the degree of communication between the two ventricles. Hence the fall in this ratio noted in all cases suggests decrease in the relative size of the ventricular communication.
ISOLATED VENTRICULAR SEPTAL DEFECT

Group IB. All five of these patients were under 1 year of age during the first physiologic study. Total pulmonary resistance had fallen along the normal expected pathway. The mean pulmonary artery pressure had fallen sharply in two patients and slightly in two more. This pressure change is further amplified in figure 7.

Three of these five patients showed symptoms from infancy onward, with frequent severe respiratory infections, pneumonia, and growth failure. Two patients (cases 9 and 11) were operated upon at 13 and 19 months, respectively. A third patient (case 10) spontaneously improved at age 2 and remained symptom-free; she was operated on at age 5. The remaining two patients (cases 8 and 12) had minimal symptoms.

Fall of the total pulmonary resistance in these patients along the curve followed by normal patients suggests that normal maturation of the pulmonary vascular bed was achieved. The fall in the ratio of pulmonary arterial systolic pressure to systemic systolic pressure supports the hypothesis of a decrease in the relative size of the ventricular septal defect. If the defect size had been unchanged, a decrease in total pulmonary resistance unaccompanied by a decrease in systemic resistance would have allowed an increase in pulmonary blood flow (left-to-right shunt). This increase did not occur in these patients. It is noteworthy that despite this presumed decrease in size, all defects were still larger than 1 cm. per M.² of body surface area at the time of surgical intervention.

Group IC. Normal Pulmonary Vascular Maturation Despite High Pulmonary Blood Flow and Elevated Pulmonary Arterial Pressure. Large Ventricular Septal Defect

The total pulmonary resistance of these five patients (fig. 8) was at the normal level for the age at each study. The absolute pulmonary blood flow, however, was greatly elevated. The mean pulmonary arterial pressure was moderately elevated and did not change appreciably during the interval between studies. In each of these cases (fig. 4) the diameter

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of the ventricular septal defect was between 1.5 and 3.5 cm. per M.² of body surface area. Each patient in this group had a ratio of systolic pulmonary arterial pressure to systolic systemic arterial pressure that was greater than 0.5.

Clinically, four of these five patients (cases 13 to 16) were severely handicapped by frequent respiratory infections, pneumonia, and congestive heart failure. These problems persisted until operations were performed when the patients were 9 to 13 years of age.

Each patient in this group had a large ventricular septal defect and apparently normal maturation of the pulmonary vascular bed; as a consequence, elevated right ventricular pressure was maintained in each case by means of an exceedingly high pulmonary blood flow (hyperkinetic pulmonary hypertension). Despite these cardiac stresses persisting over several years, none of these patients exhibited pulmonary changes tending to limit such a volume, although four of the five had severe symptoms.

We regard the normality of pulmonary vascular maturation in this group of patients as unique, since patients in subsequent groups with apparently similar stresses followed quite different courses.

**Group II. Delayed Maturation of the Pulmonary Vascular Bed. Large Ventricular Septal Defect**

These 10 patients (fig. 9) evidenced delayed fall in total pulmonary resistance, with an approximation of normal levels during the interval between the two catheterizations. Pulmonary blood flow approached normal value for age at the first study, and it had increased to levels considerably above the normal value for age by the second study. Three patients showed rises in mean pulmonary arterial pressure without comparable rises in mean systemic pressures.

Six of these patients had rather large defects, the diameter measuring more than 4 cm. per M.² of body surface area. In no other group of patients were defects of this relative magnitude observed. Nine patients exhibited symptoms of moderate congestion and growth failure; the exception was the patient with the smallest defect (case 26). None was cyanotic. These patients' ages covered the entire childhood span (6 months to 12 years) at the time of the first catheterization.

The fall in total pulmonary resistance in these patients occurred later and with a more gradual slope than the fall seen in normal infants; this suggested a delay in the normal maturation of the pulmonary vasculature. Since normal maturation was the initial response of the lung to the stress of a large ventricular septal defect, this group illustrates the effects of a second initial response. Although six patients had very large defects, among the total group (fig. 4) defect size does not appear to have been primarily responsible for this difference. Since we know of no other factors that might bring about this delay of pulmonary vascular maturation, we continue to hold that inherent differences in the vas-
cilar bed may be responsible for the apparent differences in response to similar stress.

Defect size did appear, however, to influence surgical mortality. Surgical correction had been attempted in all 10 of these patients. Five of them died within 48 hours, apparently from failure of the left side of the heart; four of these fatalities occurred in patients with very large ventricular septal defects, in at least two of which the size of the defect was definitely a contributory factor. In one (case 22) the membranous septum was virtually absent, and the sutures had pulled out at the superior margin of the patch; in the other (case 24) the large Ivalon patch used in the repair buckled and partially occluded blood flow to both the pulmonary artery and aorta. No specific cause of death was determined in the other three cases.

Group II. In these patients the normally expected decrease in total pulmonary resistance was delayed. Pulmonary blood flow increased beyond normal levels. Despite the fall in total pulmonary resistance, the mean pulmonary pressure remained stable or increased slightly in nine of the 10 patients.

Group III. The total pulmonary resistance in these two young infants did not change from the initial high values. A decrease in mean pulmonary artery pressure occurred. These patients may possibly represent an early stage prior to a delayed fall in resistance as seen in group II. They might also reach the end state depicted in group V (fig. 13).

Group III. Failure of Pulmonary Vascular Maturation. Large Ventricular Septal Defect

In two patients (fig. 10) total pulmonary resistance did not fall significantly below the fetal level with the lapse of time. The absolute pulmonary blood flow remained low and did not increase with age, and when computed on the basis of square meters of body area, it decreased. The mean pulmonary pressure fell in both patients, as did the ratio of systolic pulmonary arterial pressure to systolic systemic arterial pressure. The one defect measured was quite large (3.5 cm. per M.² of body surface area). Both patients had severe symptoms (recurrent pneumonia and congestive heart failure) in infancy. They improved somewhat in the interval between studies, but because of the persistent high total pulmonary
resistance, they were treated surgically. Both survived operation and later showed moderate improvement clinically. The roentgenograms in these patients were of unusual interest in that normal peripheral pulmonary markings were associated with a pronounced increase in the proximal vascularity at the earliest roentgenographic examination, and the disparity in the pulmonary markings persisted to the time of operation (fig. 11).

These two patients with large ventricular septal defects appear to have achieved little or no maturation of the pulmonary vasculature. The maintenance of the total pulmonary resistance at or above fetal levels, and the absolute limitation of the pulmonary blood flow support this thesis. This pattern, then, constitutes a third type of initial response of the pulmonary vascular bed in a patient with a large ventricular septal defect. One may legitimately ask, however, if these patients would show a subsequent fall in total pulmonary resistance similar to that demonstrated in group II. Another potential pathway available to these patients is seen in group V, in which three cyanotic older patients with initial total pulmonary resistance above fetal levels showed the following pattern: continuing increases in total pulmonary resistance; increasing pulmonary arterial pressure; and pulmonary blood flow of less than 50 ml. per second. This pattern is precisely what might be anticipated if failure of pulmonary vascular maturation occurred and persisted to this older age. It is impossible to ascertain which course these patients in group III might have followed without surgical intervention.

Group IV. Apparent Normal Pulmonary Vascular Maturation Followed by Progressive Pulmonary Vascular Changes. Large Ventricular Septal Defect

Figure 12 summarizes studies on four patients whose total pulmonary resistance initially fell to nearly normal values. This initial drop was followed by an increase in total pulmonary resistance. For case 31 this was precisely revealed during the course of three cardiac catheterizations. In the other three patients the fall was assumed, and significant increases in total pulmonary resistance were demonstrated in a later examination. The wide variation in age at which the total pulmonary resistance rose among patients in this group (6 months to 11½ years) is of interest. The mean pulmonary artery pressure increased in three patients and decreased slightly in one, but these changes in the mean pulmonary pressure were associated with comparable changes in the mean systemic pressure.

All four patients in the group had symptoms of severe congestion during infancy. For one of them (case 30) these symptoms were interrupted by an operation at age 18 months. The other three showed a dramatic "spontaneous" improvement in symptoms of
CONGESTION DURING THE PERIOD OF OBSERVATION.
Cyanosis developed in two of them subsequent to this clinical change (cases 31 and 33); since they were then considered operable only at an enhanced risk, they were not referred for surgical correction of their defect.

These patients represent a group in which maturation of the pulmonary vascular bed proceeds in a normal or nearly normal fashion. This process is then interrupted (at varying ages) by a progressive rise in the total pulmonary resistance. The two cyanotic patients have followed the clinical pattern suggested by Dammann and Ferencz. 

The physiologic data support their hypothesis that this clinical course is secondary to pulmonary vascular changes.

- The marked disparity in the ages at which the various stages of disease were manifested suggest a complex etiology and renders precise prognosis difficult.

**Group V. High Pulmonary Vascular Resistance and Cyanosis. Large Ventricular Septal Defect**

The seven patients in this group (fig. 13) all gave evidence of cyanosis before the initial studies were made. Therefore, the data have not been very helpful in explaining the etiology and development of cyanosis in these persons with ventricular septal defect. We have included them in order to describe better the course of this affliction once cyanosis has taken place. They ranged in age from 3½ to 9 years when first seen by us. These cyanotic patients can be separated into two groups on the basis of the initially measured total pulmonary resistance and the response of the total pulmonary resistance with time:

**A. Patients with Initially High Pulmonary Resistance that Continued to Rise**

These were all obviously cyanotic when first seen by us (cases 34, 35, and 36). The onset of cyanosis was 6 weeks, 6 years, and 10 years, respectively. Total pulmonary resistance in these three patients significantly increased over time. In these cases the absolute pulmonary blood flow was limited to about 50 ml. per second, despite differences in size and age. (Limitation of pulmonary blood flow to this level was noted in the two patients in group III who achieved no pulmonary vascular maturation.) All had moderate exertional dyspnea and growth retardation, but were otherwise without symptoms. They were considered to represent substantially increased operative risks and therefore were not referred for surgical correction. Anatomic confirmation of the diagnosis of ventricular septal defect has not been made in these patients. Some may actually represent a different congenital anomaly. We have included them because these cases suggest a potential course followed by patients with failure of pulmonary vascular maturation.

**B. Patients with Lesser Initial Pulmonary Resistance and with a Slight Decline in This Value Occurring with Growth**

In these four patients (cases 37 to 40) the
pulmonary blood flow was somewhat above normal and increased slightly. Thus, each had a small left-to-right shunt in addition to the right-to-left flow. Pulmonary arterial pressures in these patients increased with age. These four patients were quite different clinically from the cyanotic patients described above. Although one was minimally cyanotic at rest (case 39), the other three were cyanotic only on exertion. The age of onset of cyanosis was recorded as 4, 5, 7, and 8 years, respectively. The patients were somewhat small for their ages and were characterized by exercise intolerance, which had developed concomitantly with the onset of cyanosis.

They were considered to be reasonable surgical risks and were therefore operated upon. One patient died in the immediate postoperative period. At autopsy, it was observed that the surgical patch was intact and that complete closure of the defect had been achieved. The pulmonary arterioles were noted to have severe medial thickening and intimal proliferation. After surgical correction, the three surviving patients were without cyanosis at rest or on exercise. Their exercise tolerance increased considerably, and at catheterization 1 year later, one patient (case 39) revealed a fall in the pulmonary arterial pressure from preoperative values of 90/50 mm. Hg, with a mean of 60, to postoperative values of 60/12 mm. Hg, with a mean of 24.

It is not possible to identify the particular

**Figure 13**

*Group V.* These patients were cyanotic prior to the first heart catheterization. The three patients (cases 34, 36, 39) with the high and rising total pulmonary resistance had fixed, abnormally low pulmonary blood flows and rising pulmonary pressures. The other patients, while cyanotic, showed no increase in the total pulmonary resistance and had abnormally high pulmonary flows.

**Figure 14**

*Effect of surgical correction on the physiology in ventricular septal defects.* The open dot represents the first preoperative study and the closed dot, the second preoperative study. The open triangle represents the postoperative study. The broken line then represents the postoperative change. In all patients the postoperative pulmonary blood flow fell to normal or slightly below normal levels and the mean pulmonary arterial pressure dropped significantly to normal or near normal values. In case 9 the total pulmonary resistance increased, but in all others did not change appreciably during the year following surgical intervention.
physiologic course followed by these patients to their state of high pulmonary vascular resistance and cyanosis. This point in the natural history could be reached either by failure of pulmonary vascular maturation or by normal pulmonary vascular maturation followed by progressive pulmonary vascular changes. Some patients do reach this stage of severe pulmonary change and poorer prognosis.

Postoperative Studies

Knowledge of the influence of surgical correction on the natural history of a ventricular septal defect is important both in understanding the functional pathology and in determining the optimal time of treatment. The initial result of a "curative" surgical procedure upon the course of the lesion as defined physiologically is seen in figure 14.

Despite the dissimilarity of the patients' stages at the time of surgical intervention, and despite the number of courses potentially leading to a particular stage, the response to surgical correction was uniform: in the majority, physiologic study approximately 1 year after surgical intervention revealed essentially no change in total pulmonary resistance. The pulmonary blood flow was reduced, in many instances drastically, to normal levels. The mean pulmonary arterial pressure was decreased sharply to normal or nearly normal values.

These findings would suggest that the pulmonary arterioles show little change in the direction of more normal structure, at least in the first postoperative year. The dramatic changes in pulmonary pressure and flow depend on the elimination of the left-to-right shunt present before surgical therapy. Knowledge of the late response of the pulmonary vascular bed to closure of the ventricular septal defect must await restudies years or even decades after corrective surgery.

Comment

This group of cases may not be representative of all isolated ventricular septal defects. Many factors influence the type of patient seen at a particular institution and hence serve to bias the selection. The factors resulting in multiple catheterization studies will tend to influence the selection still further; but these appear minimal here, since this group experience parallels the total experience in patients with isolated ventricular septal defect seen at our institution during the last 6 years.

It is important to recall that this communication deals with patients having only isolated ventricular septal defect. Additional anomalies may profoundly alter the physiologic situation and also the resultant natural history of the lesion.

In the hemodynamics of ventricular septal defect, the location of the defect has been deemed to be of some importance. Abbott has proposed that a ventricular septal defect with a right-to-left shunt represents a specific entity arising out of the anatomic relationships between the ventricular septal defect and the aortic root. This hypothesis no longer seems tenable, for a large defect located anywhere in the membranous septums can be associated with a right-to-left shunt. In addition, certain defects in which the aorta overrides the right ventricle anatomically nevertheless shunt only left-to-right. Finally, in the defect characterized by origin of both great vessels from the right ventricle without pulmonary stenosis, either left-to-right or right-to-left shunting can occur. Location of the defect in various portions of the membranous septum in the patients in this series had no apparent influence on the course followed. No conclusion may be drawn from the course followed by the one patient with a muscular septal defect.

The size of the ventricular septal defect did appear to be of major consequence. Those patients with openings of less than 1 cm. per M.² of body surface area had minimally altered physiologic responses, were essentially without symptoms, and revealed no change during the period of observation.

Two specific influences of the large defect (greater than 1 cm. per M.² of body surface area) are worthy of note. In some infants, a relative decrease in defect size resulted in a definite alteration in physiologic response. Moreover, the very large defect (larger than 4 cm. per M.² of body surface area) influenced
the surgical mortality. Apart from these consequences, however, the precise size of the defect beyond 1 cm. per M.² of body surface area did not critically influence the physiologic course followed by the patient.

The symptomatologic and physiologic status in a patient with a large ventricular septal defect is probably primarily influenced by the state of the pulmonary vascular bed. In the normal child during the first 4 years of life the pulmonary vasculature undergoes maturation from its fetal state to its normal adult condition.

In the presence of a large ventricular septal defect the following possibilities may occur: (1) the pulmonary vessels may develop normally (group IC), (2) maturation of the pulmonary vessels may be delayed (group II), or (3) maturation may fail to occur (group III). This concept of normal or altered pulmonary vascular maturation appears vital to an understanding of the natural history of ventricular septal defect.

A second phenomenon observed in patients with large defects was the series of changes indicative of progressive pulmonary vascular disease (group IV). The wide range in age of onset of these changes makes it difficult to predict the occurrence of progressive vascular disease in the individual patient.

An appreciation of the state of the pulmonary vascular bed is necessary in defining the stage of the disease process that a particular patient has reached. In our experience, knowledge of pressures in the pulmonary circuit has not provided this information. High pulmonary arterial pressures may be present in patients with normal pulmonary resistance. The high pressures may be maintained by greatly augmented pulmonary flow (hyperkinetic pulmonary hypertension), by high total pulmonary resistance (obstructive pulmonary hypertension), or by both.

As a prognostic sign, high pulmonary arterial pressure usually indicates a large defect but provides no information regarding the state of the lungs. Progressive pulmonary vascular disease does occur in the presence of a stable pulmonary arterial pressure. This is because in the case of a large ventricular sep-

tal defect free or nearly free communication exists between the two ventricles. If pulmonary resistance is less than systemic resistance, then the systemic resistance will determine the ventricular pressure necessary to maintain an adequate cardiac output. The lesser resistance in the pulmonary circuit necessitates the hyperkinetic effect of increased pulmonary blood flow (left-to-right shunt) to maintain the pressure in the ventricle at its obligatory level. As the pulmonary resistance approaches the level of systemic resistance, a lesser augmentation of pulmonary blood flow is required. If pulmonary resistance exceeds systemic resistance, then the pulmonary resistance determines the pressure in the ventricles necessary for an adequate cardiac output. Pressure in the pulmonary and systemic circuits will therefore rise as pulmonary obstructive disease progresses. Now the hyperkinetic effects are needed in the systemic circuit, and right-to-left shunting occurs. Until it exceeds the systemic resistance, however, a rising pulmonary resistance may not produce an increase in pulmonary arterial pressure.

On the other hand, an increasing pulmonary arterial pressure does not necessarily mean progressive pulmonary vascular disease. A normal increase in systemic resistance during childhood will necessitate a higher left ventricular pressure. In the presence of a large ventricular defect this increased pressure will be reflected in the pressure of the pulmonary artery. Pulmonary resistance may remain unchanged, and augmentation of pulmonary blood flow will result.

Thus a knowledge of pulmonary blood flow, as well as pressure, is essential in evaluating the patient with a ventricular septal defect. These two factors may be considered separately, or they may be combined as "resistance."

Measurements of total pulmonary resistance, while less accurate, have allowed assessment of the degree of pulmonary vascular maturation and an estimate of the progressive pulmonary obstructive lesions. The significance of a particular value of total pulmonary resistance depends on a large extent
on the age of the patient. For example, a value for total pulmonary resistance of 900 dynes second cm.\(^{-2}\) at 6 months of age is within normal range. The same value in the same patient at 4 years of age is abnormal. Even a decrease in total pulmonary resistance from the normal 6-month level if less than that achieved by normal children suggests abnormality of the vascular bed.

The crucial point of this concept is that in measurements recorded during physiologic and histologic maturation, failure of the total pulmonary vascular resistance to increase does not necessarily mean that the pulmonary vascular bed has continued to be normal. Failure or delay in maturation of the pulmonary vascular bed may be as important as, and probably more common than, progressive pulmonary vascular disease, at least during childhood. Viewed in this light, the apparently irreconcilable differences of opinion expressed in the literature are understandable. Those who report no observed increase in pulmonary arterial pressure or in total pulmonary resistance in the childhood years are in the main correct. On the other hand, the clinical and histologic evidence that severe pulmonary vascular disease exists in some patients despite stable physiologic values is not negated. In addition to the infrequently seen rising total pulmonary resistance, failure or delay in the normal fall of the pulmonary resistance indicates that the pulmonary vascular bed is abnormal.

**Surgical Consideration**

The physiologic consequences of a large ventricular septal defect, and normal pulmonary vascular maturation are incapacitating and frequently critical during infancy. In our institution, infants with isolated ventricular septal defects and with congestive heart failure ensuing prior to 6 months of age, suffer a 25 per cent mortality in the first 2 years of life when treated medically. Ideally, prompt surgical intervention in these patients should be the goal.

In the patient with a large ventricular septal defect and with delayed or absent pulmonary vascular maturation, the earlier the surgical correction of the defect, the greater is the potential for reestablishing the normal maturational process. Although our contention is still subject to verification, we believe that early surgical intervention under these circumstances offers the most favorable prognosis. For whatever the initial response of the lung in a patient with a large ventricular septal defect, the potential for progressive pulmonary vascular disease always exists. Early surgical closure would prevent this serious complication.

The increased operative mortality among infants, however, does impose decided limits on surgical therapy. In our experience, this becomes minimal after age two. Moreover, if the defect is to decrease in size, it will have done so by that time. Other factors being equal, we believe 2 years of age or older to be the optimal time for surgical correction of a large ventricular septal defect. We make this recommendation on the basis of a currently low rate of surgical mortality (less than 5 per cent). A comparable mortality rate has been achieved at a number of other centers under the same circumstances.

For the severely ill infant under 2 years, selecting the wisest form of therapy is a vexing problem. While the mortality rate with medical therapy is considerable, surgical treatment has also resulted in high mortality rates. Our current practice has been to defer operations on these infants, if possible, and to extend surgical treatment only to those who appear unlikely to survive. Another approach to the patient in this category has been a two-stage procedure, banding of the pulmonary artery followed by closure of the defect at a later time. Clarification of the relative merits of medical treatment and the one-stage and two-stage surgical techniques will be achieved only through experience. The results of the application of each of these therapeutic methods leave a great deal to be desired. Substantial reduction in the mortality in this age group achieved through any of the above methods would, of course, alter our present therapeutic procedures.

The advisability of surgical intervention at the two extremes of the spectrum of disease remains at issue. Patients with small defects
undergo little or no physiologic change in the pediatric years. While the risk of subacute bacterial endocarditis and the possibility of pulmonary vascular disease in later years must be considered, the need for surgical intervention does not appear urgent. Under this circumstance, one should have a critical knowledge of the surgical mortality rate observed at the center proposing treatment. If it is truly minimal (i.e., less than 1 per cent for this good-risk category) then these patients would benefit from elective surgical correction of their defect.

No agreement has been reached about the appropriate therapy for the older child with high pulmonary resistance (severe pulmonary vascular disease). In those patients with right-to-left shunts and without any left-to-right shunting, no short-term benefits accrue from surgical correction that would justify the surgical mortality encountered. It is not known whether regression of the pulmonary vascular changes ultimately does or does not occur after closure of the defect.

Patients with residual left-to-right shunts as well as the right-to-left flow appear to benefit immediately from defect closure in proportion to the magnitude of the left-to-right flow. We therefore customarily advise surgical correction in these patients.

Conclusion

The natural history of the isolated ventricular septal defect is variable and as yet incompletely defined. In the varying responses of the pulmonary vascular bed to presumably identical stresses lies the key to further knowledge of this affliction. Advances in the understanding of pulmonary hypertension, similar to those advances made in the knowledge of systemic hypertension, are clearly required. Presently one can only recognize the several possible courses open to the patient with a large ventricular septal defect. This variability of response is in itself of major importance. It should alert the clinician and surgeon alike to the need for careful and precise evaluation of each patient presenting with a ventricular septal defect. Even more important, the very existence of several different adaptations to a presumably identical stress should serve as a warning against making any single generalization about the natural history and therapy of this disorder at the present time.

Summary

Forty patients with isolated ventricular septal defect were studied physiologically two or more times before they underwent surgical treatment. Utilizing baselines obtained by heart catheterizations of normal infants and children, we grouped patients with ventricular septal defect according to the magnitude of the total pulmonary resistance, pulmonary blood flow, and pulmonary arterial pressure, and according to changes in these values over time. The patients with small defects (less than 1 cm. per M.² of body surface area) were easily separable on the basis of physiologic findings. Patients with large ventricular septal defects (greater than 1 cm. per M.² of body surface area) exhibited one of three possible initial responses to the stress of high pulsatile pulmonary flow and increased pulmonary artery pressure: (1) normal regression of total pulmonary resistance; (2) delayed fall in total pulmonary resistance; (3) failure of the total pulmonary resistance to decrease with age.

These physiologic responses were thought to be related to normal maturation, delayed maturation, or failure of maturation of the pulmonary vascular bed. It was observed that a subsequent increase in total pulmonary resistance could be superimposed on any of the three initial responses at any time. Clinical evidence and catheterization data suggested that the relative size of the ventricular septal defect had decreased in five patients.

The variability of the physiologic courses, the importance of the pulmonary vascular bed in determining these responses, and our lack of understanding of the etiology of the pulmonary vascular changes were noted.

The indications for, and timing of surgical intervention in patients with isolated ventricular septal defects, are discussed in light of the above findings.

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The Natural History of Isolated Ventricular Septal Defect: A Serial Physiologic Study
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