Isolated ventricular septal defect in adults

Clinical and haemodynamic findings

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SUMMARY Clinical and haemodynamic findings were reviewed in 109 consecutive patients in whom an isolated ventricular septal defect was diagnosed after the age of 15 years (range 15-65 years). Most patients had no or minor cardiac symptoms. Based on the left to right shunt size and pulmonary pressure, 32 (29%) patients had large and 75 (69%) small ventricular septal defects, whereas in two (2%) patients data were insufficiently complete for determining the size. The anatomical location was membranous in 92% and muscular in 8% of the 51 patients in whom this could be assessed from a left ventricular angiogram or the surgeon's report of a subsequent operation, or both. Nine (8%) patients had developed the Eisenmenger syndrome, 12 had aortic regurgitation, and 16 (15%) had bacterial endocarditis, the incidence of the latter being 5.7 per 1000 patient years. Of the 34 (31%) patients who underwent surgery, five (15%) died while in hospital.

In contrast with reports from paediatric series our study in adults showed a predominance of small ventricular septal defects and a high frequency of irreversible pulmonary hypertension and serious complications, such as aortic regurgitation and bacterial endocarditis. Thus ventricular septal defects in adults should—regardless of symptoms—be looked on as potentially serious.

Ventricular septal defect is the most common congenital disorder of the heart with an incidence of 2/1000 live births.¹ Our present knowledge of the clinical and haemodynamic consequences of ventricular septal defect is mainly derived from studies of children,²⁻⁸ despite the fact that nearly 40% of infants with ventricular septal defect born alive and untreated are still alive at the age of 15 years.⁹ For this reason we have analysed the clinical and haemodynamic findings in our patients with ventricular septal defect who had reached adulthood at the time when the correct diagnosis was first established.

Patients and methods

The study population comprised the total number of patients seen in the years 1959-78 who were over the age of 15 years when the diagnosis of isolated ventricular septal defect was made. Of the total of 109, 56 were men and 53 women (Table 1). Table 2 gives the main clinical reasons for referral for surgery. Of the 59 patients with cardiac symptoms, 37 complained of ill defined chest sensations, palpitations or precordial

pain invariably related to physical exercise or both, and eight had recently had endocarditis (within a year of referral). Seven patients were admitted with a history of progressive dyspnoea, radiological evidence of cardiac enlargement, and auscultatory signs suggesting pulmonary congestion indicating the presence of heart failure. Of the 50 patients without cardiac symptoms, 32 were referred after a heart murmur had been detected during a routine medical examination and 18 had had murmurs detected during examination for extracardiac disease.

The diagnosis of ventricular septal defect was based on findings during right heart catheterisation in 77 patients, combined right and left heart catheterisation in 30 (routinely performed in all cases of ventricular

Table 1 Age and sex distribution in 109 adults with a late diagnosis of congenital isolated ventricular septal defect

Age (years)	Men	Women
15-24	24	28
25-34	13	16
35-44	8	6
45-54	9	2
55-65	2	1
Total	56	53

septal defect since 1970), and a left ventricular angiogram in one. One patient was operated on after incomplete catheterisation had indicated a large left to right shunt and a severe increase in pulmonary artery pressure. The diagnosis of ventricular septal defect was confirmed at operation. She died postoperatively from pump failure and necropsy showed a large ventricular septal defect and irreversible pulmonary arteriolar changes compatible with severe pulmonary hypertension. In all cases of clinically suspected aortic regurgitation an aortic root angiogram was performed. The degree of aortic regurgitation was graded as mild, moderate, or severe according to standard criteria.¹⁰

Cardiac output was calculated according to the Fick principle. A rise in oxygen saturation in the pulmonary artery of $\geq 5\%$ of the mean of three values from the right atrium was accepted as a major shunt and that of $< 5\%$ as a minor shunt.¹¹ A positive hydrogen test result¹² or left ventricular angiography, or both, confirmed the diagnosis of ventricular septal defect. The size of the left to right shunt was taken as the difference between pulmonary flow (Q_p) and systemic flow and expressed as a percentage of Q_p . The upper normal limit for systolic right ventricular pressure was 30 mmHg,¹¹ and values above 95 mmHg were considered to be severely increased. The upper normal values of pulmonary artery mean pressure (PAMP) and pulmonary capillary vein mean pressure (PCVMP) were 18 and 10 mmHg respectively.¹¹ Pulmonary arteriolar resistance (PAR) was calculated according to the following formula:

$$\text{PAR} = \frac{\text{PAMP} - \text{PCVMP}}{Q_p \text{ (l/min)}} \times 80 \text{ (dyn s/cm}^{-5}\text{)}$$

with an upper normal value of 250 dyn s/cm⁻⁵.

Since the size of the defect is reflected by the size of the left to right shunt as well as by pulmonary artery pressure and resistance the following criteria were used to separate small from large defects:

Small defect—left to right shunt $< 50\%$, normal or moderately increased systolic right ventricular pressure, and PAR < 250 dyn s/cm⁻⁵.

Large defect—left to right shunt size $\geq 50\%$ and a normal or moderately increased systolic right ventricular pressure together with a normal or moderately increased PAR (< 800 dyn s/cm⁻⁵) or left to right shunt size $< 50\%$ with systolic right ventricular pressure > 95 mmHg and increased PAR. Patients with PAR > 800 dyn s/cm⁻⁵ combined with a bidirectional shunt (aortic oxygen saturation less than 95% in the absence of pulmonary disease) were classified as having the Eisenmenger syndrome.¹³

For the patient with a large defect at necropsy and two others, haemodynamic data were insufficiently complete either to determine the size of the shunt or

to estimate pressures. Thus the size of the defect could be assessed in all but two patients and the size of the left to right shunt as well as pulmonary pressures in all but three patients.

The anatomical location of the defect was based on left ventricular angiograms in the 31 patients in whom this technique was performed. In the 20 patients who underwent surgery on the basis of the findings of right heart catheterisation, the anatomical site was taken from the surgical report. The available data allowed a differentiation between membranous and muscular defects, the latter being subdivided into defects located in the middle or apical regions of the ventricular septum. The crista supraventricularis was not clearly visualised in the available angiograms. It was not possible, therefore, to differentiate positively between a membranous defect and a supracristal or infundibular septal defect.

No patient with either infundibular or valvular pulmonary stenosis (pressure gradient > 25 mmHg between distal parts of the right ventricle and pulmonary artery³), or both, was included in the present study.

Results

AGE AND SEX

Table 1 shows the age and sex distribution of the study population. The mean age was 29 (range 15–65) years. Young adults predominated, but 28 (26%) patients were aged more than 35 years. The proportions of men and women were similar.

SHUNT SIZE

The left to right shunt size varied from minor to 85%. In total, 84 (77%) patients had a left to right shunt size $< 50\%$. This group also included 33 patients with minor shunts. Twenty two (20%) patients had a shunt size $\geq 50\%$. In three patients the exact size could not be determined because data were incomplete.

SYSTOLIC RIGHT VENTRICULAR PRESSURE AND PULMONARY ARTERY RESISTANCE

Sixty six (60%) patients had normal systolic right ventricular pressures and 40 (37%) had increased systolic right ventricular pressures which exceeded 95 mmHg in 12 cases. Ten patients had increased pulmonary artery resistance. Five of 33 (15%) patients with minor shunts had raised systolic right ventricular pressure compared with 17 of 51 (33%) patients with major shunts ($< 50\%$) and with 18 of 22 (82%) with shunts $\geq 50\%$. When those patients with increased pulmonary artery resistance are excluded a tendency towards an increase in systolic right ventricular pressure with increasing shunt size was found (Fig. 1).

Fig. 1 Size of left to right shunt expressed as percentage (%) of pulmonary flow correlated with systolic right ventricular pressure (SRVP) in 106 adults with isolated ventricular septal defect (VSD). ●—patients with normal pulmonary arteriolar resistance ($<250 \text{ dyn s/cm}^{-5}$); ○—patients with raised pulmonary arteriolar resistance. Vertical line denotes a shunt size of 50%. Lower horizontal line denotes upper normal value for SRVP (30 mmHg), upper line (95 mmHg) denotes the arbitrarily chosen level for systemic blood pressure. A shunt size of $<50\%$ and an SRVP of $<95 \text{ mmHg}$ represent small VSDs.

SIZE OF DEFECT

Fig. 1 shows the individual data for left to right shunt size and for systolic right ventricular pressure. Of three patients who were not reported because of incomplete data, one had histological evidence of severe pulmonary hypertension most probably due to the Eisenmenger syndrome. If this patient is included, 32 (29%) patients had large and 75 (69%) small defects; in two (2%) patients the size could not be determined. Nine (8%) patients fulfilled the criteria for the Eisenmenger syndrome.

SYSTOLIC MURMUR

The intensity grade of the systolic murmur (0–6) was available in the 101 patients in whom the left to right shunt size was determined. Fig. 2 shows the correlation between systolic murmur intensity and shunt size. High grade murmurs with a thrill (grades 5 or 6) were found in patients with shunts of all sizes including the minor ones. In 82 patients a murmur $\geq$ grade 4 was heard; of 12 patients with systolic right ventricular pressure $>95 \text{ mmHg}$, seven had a murmur $\leq$ grade 3.

AORTIC REGURGITATION

All patients were carefully investigated to detect aortic regurgitation. In each patient in whom this condition was clinically suspected, an aortic root angiogram was

Fig. 2 Intensity grade of systolic murmur and size of left to right shunt expressed as percentage (%) of pulmonary flow. ●—patients with systolic right ventricular pressure (SRVP) $<95 \text{ mmHg}$; ○—patients with SRVP $\geq 95 \text{ mmHg}$. Horizontal line denotes a shunt size of 50%.

performed to confirm the diagnosis. Aortic regurgitation was found in 12 (11%) patients (seven men and five women; mean age 36 (range 20–58) years. Five patients had had bacterial endocarditis and one rheumatic fever, in six patients the cause was unknown.

BACTERIAL ENDOCARDITIS

Sixteen (15%) patients (eight men and eight women; mean age 36 (range 16–64) years) had a history of bacterial endocarditis, and two had experienced two episodes. The incidence of bacterial endocarditis was thus 5.7/1000 patient years. Six had had bacterial endocarditis several years before admission, and in 10

Table 2 Clinical reasons for admission in 109 adult patients with isolated ventricular septal defect

Reason for admission	No. of patients
Cardiac symptoms	
Palpitations and atypical chest pain	37
Recent endocarditis	8
Heart failure	7
Angina pectoris	3
Haemoptysis	3
Paroxysmal atrial fibrillation	1
Total	59 (54%)
No cardiac symptoms	
Routine examination	32
Murmur heard during examination for non-cardiac disease	18
Total	50 (46%)

Fig. 3 Size of left to right shunt expressed as percentage (%) of pulmonary flow correlated with systolic right ventricular pressure in 22 adult patients with VSD with aortic regurgitation, a history of bacterial endocarditis, or both. Horizontal and vertical lines as in Fig. 1. ●—patients with aortic regurgitation; ■—patients with a history of bacterial endocarditis; ○—patients with aortic regurgitation and endocarditis.

this complication had occurred within the past year. In eight of these patients a recent episode was the main clinical indication for admission (Table 2); two had developed severe aortic regurgitation, with heart failure being the main reason for referral.

SHUNT SIZE AND SYSTOLIC RIGHT VENTRICULAR PRESSURE IN AORTIC REGURGITATION AND/OR BACTERIAL ENDOCARDITIS

Fig. 3 shows the haemodynamic findings in 22 patients with either aortic regurgitation or bacterial endocarditis, or both. There was considerable variation in shunt size and systolic right ventricular pressure. Apparently the haemodynamic pattern in this subgroup did not differ significantly from that of the total group. This indicates that neither the size of the

shunt nor the degree of pulmonary hypertension were important factors in the occurrence of these two serious complications in isolated ventricular septal defect of adults.

SURGERY

A total of 34 (31%) patients with a mean age of 25 (range 15–51) years underwent surgery. Table 3 summarises the shunt size, symptoms, and clinical reasons for surgery. Of 22 (22%) patients with shunt sizes $\geq 50\%$, 18 underwent surgery. Of the remaining four patients, three with systolic right ventricular pressure >95 mmHg had inoperable defects, and one (aged 51 years) with a shunt size of 51% and moderate symptoms was treated medically. Of the 84 patients with shunt sizes $<50\%$, 14 underwent surgery despite the small size because of (a) severe aortic regurgitation needing aortic valve replacement or conservative repair (4); (b) history of recent bacterial endocarditis, normal pulmonary artery pressures, and as prophylaxis against recurrent bacterial endocarditis (3); (c) a moderate rise in systolic right ventricular pressure (40–45 mmHg) (2); and (d) various degrees of dyspnoea on exertion without evidence of pulmonary disease or rise in pulmonary artery pressure (5).

The ventricular septal defect was closed in 27 patients by direct suture and in six by patch. In one 34 year old man with severe aortic regurgitation due to bacterial endocarditis a thoracotomy showed severe dilatation of the ascending aorta, which was grossly underestimated by the angiograms. A suitable prosthesis was not available at the time of surgery (in 1967). He subsequently died from pump failure. Table 3 shows that a further three patients with severe aortic regurgitation and small defects died; one of ventricular fibrillation immediately after operation, one of heart failure related to a paravalvular fistula, and one of a thrombus on the prosthesis (Starr-Edwards) three months after the operation, the diagnosis being verified at necropsy. As mentioned above

Table 3 Left to right shunt size, symptoms, clinical reasons for surgery, and hospital mortality rate in 34 adults with isolated ventricular septal defect

Shunt size	Symptoms	n	Clinical reason for surgery	n	Postoperative deaths
Large (n=18)	Dyspnoea	11	Shunt size and symptoms	10	
	Atrial fibrillation	1	Shunt size solely	6	
	No symptoms	6	Severe aortic regurgitation	2	
Small (n=14)	Dyspnoea	11	Severe aortic regurgitation	4	4
	No symptoms	3	Prophylaxis against recurrent endocarditis	3	
			Pulmonary hypertension	2	
Undetermined (n=2)	Dyspnoea	1	Various dyspnoea and astheniform symptoms	5	
	No symptoms	1	Possibly large shunt and evidence of severe pulmonary hypertension	1	1
			Questionable	1	
Total				34	5 (15%)

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Table 4 Anatomical localisation of ventricular septal defect in 51 adults in whom this could be determined from a left ventricular angiogram or the surgical report or both

Localisation	Concomitant aortic regurgitation				
	Severe	Moderate	Mild	None	Total
Membranous defect	6	2	3	36	47
Muscular defect (region)					
Middle				1	1
Apical			1	2	3

one girl (aged 15 years) with severe pulmonary hypertension died of pump failure one week after the operation. The hospital mortality was thus 15% (5/34). Of the four patients with aortic regurgitation who died, the valvular damage was caused by bacterial endocarditis in three.

ANATOMICAL LOCATION OF DEFECT

Table 4 shows that of 51 patients in whom the anatomical location could be determined, 47 (92%) had membranous defects. Of the 12 patients with aortic regurgitation, 11 (92%) had membranous defects including those with severe regurgitation and a history of bacterial endocarditis. In one patient with mild aortic regurgitation of unknown origin, a small apical defect was found.

Discussion

Medical care in Norway offers medical examinations at birth, during infancy, and at school. Despite this, ventricular septal defect in the present series of patients had remained unrecognised until adolescence. The fact that most patients had moderate symptoms, or none at all, may explain why they had undergone several medical examinations during childhood without having been referred for complete cardiac evaluation. The purpose of our study was to increase our knowledge of the clinical and haemodynamical status of patients with a late diagnosis of congenital isolated ventricular septal defect.

As expected, our data indicate that most cases (69%) had small defects; large defects were found in only 29% and the size of the defect could not be determined in 2%. About one third of those with large defects had developed the Eisenmenger syndrome. The haemodynamic patterns found in our series of adults with ventricular septal defects apparently differ from the findings usually reported in studies of ventricular septal defects in younger age groups. In infancy small defects are found in less than 50% of cases and the Eisenmenger syndrome is rare.^{4,6} On the other hand, Keith *et al.*⁴ in their study of teenage/adult groups of patients with ventricular

septal defects found a distribution in size more similar to that in our study, with 80% having small defects and 20% large ones; the prevalence of 10% for the Eisenmenger syndrome was comparable to that of 8% in our series. Although different criteria were used, Weidman *et al.*⁷ found that 59% of 228 patients aged 12–21 years had small defects and 51% of 75 patients over 21 years had small defects.¹⁴ The percentage of cases with the Eisenmenger syndrome was 13.5% and 24% in the two groups. Thus the prevalence of the Eisenmenger syndrome is higher in adults than in infants and children. Several factors may explain this shift of haemodynamic pattern from infancy to adulthood. Of small defects detected in infancy 15–30% have closed by the age of 15 years.⁹ Furthermore, young patients with the largest defects are referred to paediatricians and evaluated for surgery. Surgical correction or mortality from heart failure, therefore, tend to eliminate cases with large defects in adulthood. Nevertheless, in accordance with those of others our study shows that in patients with untreated large defects the development of the Eisenmenger syndrome is not uncommon.^{7,14} It should be emphasised that the prognosis of the Eisenmenger syndrome in adults is poor.¹⁵ In keeping with this, four of nine patients with the Eisenmenger syndrome in the present series were admitted because of overt cardiac failure.

An important finding in our study was the high number of cases with aortic regurgitation (12/109, 11%). In mainly paediatric series the incidence of aortic regurgitation varied between 1.7% and 6.3%.^{3,9,16} Aortic regurgitation has not been reported, however, in patients with defects aged less than 1–2 years.^{3,16} Whether aortic regurgitation is due to longstanding haemodynamic stress or whether ventricular septal defect in some patients is only part of a more severe developmental defect in the atrioventricular connective tissue skeleton is uncertain. The anatomical location of ventricular septal defect was identical in patients with and without aortic regurgitation, but adequate differentiation between membranous and supracristal or infundibular defects was unfortunately not possible. Long term follow up may be helpful in identifying patients with defects at risk of developing aortic regurgitation as adults. The incidence of aortic regurgitation caused by bacterial endocarditis was 41% (5/12) in our study compared with 8% and 10% in the studies of Keane *et al.*¹⁶ and Corone *et al.*³ respectively. The main reason for admission in three of the patients with aortic regurgitation was overt cardiac failure; two of these had recently had bacterial endocarditis.

The incidence of bacterial endocarditis of 5.7 per 1000 patient years in our study is comparable to 7.1 per 1000 patient years between the ages 15 and 20

years in Corone's series.³ In patients aged less than 15 years figures of 0.5–2.1 per 1000 patient years have been reported.^{9,17} Gersony and Hayes¹⁸ found an incidence in patients over 20 years to be six times that in the younger ones. Since this complication is relatively easy to diagnose retrospectively, we (like others^{3,17,18}) have calculated the incidence of bacterial endocarditis as if all cases had been followed since birth.

According to the findings in the present series, we recommend surgery for ventricular septal defects in adults with: (a) large defects but without the Eisenmenger syndrome; (b) small defects with concomitant aortic regurgitation and needing valvular replacement; and (c) small defects and increasing pulmonary artery pressures. Surgery is otherwise rarely recommended, although such a policy may have to be reconsidered when follow up data are available. In particular it may prove necessary to operate on patients who have had bacterial endocarditis without evidence of associated aortic regurgitation.

The present study shows that ventricular septal defects which escape detection until adulthood—even in countries with a well developed medical care system—should be considered to be clinically serious. Severe complications often develop even when cardiac symptoms have been absent for a long time.

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