Ventricular septal defect in children born in Liverpool 1960 to 1969

Evaluation of natural course and surgical implications in an unselected population

D F DICKINSON, R ARNOLD, J L WILKINSON

From the Regional Paediatric Cardiothoracic Unit, Royal Liverpool Children's Hospital; and Institute of Child Health, Alder Hey Children's Hospital, Liverpool

SUMMARY We have reviewed data on all patients born between 1960 and 1969 and registered in the Liverpool Registry of Congenital Malformations as having congenital heart disease. There were 385 with a ventricular septal defect as their sole or main cardiac lesion. Analysis of the available follow-up data showed that 50 of these were subsequently assigned to other diagnostic categories and a further 41 failed to fulfil our diagnostic criteria for a ventricular septal defect, leaving 294 patients for study. In view of the high incidence of small defects in asymptomatic infants and children not subjected to cardiac catheterisation, clinical criteria for the acceptance of the diagnosis were defined and 190 patients were included on these grounds alone. The clinical course, associated cardiac and non-cardiac defects, and surgical implications were analysed.

The majority of defects were small and 31% closed spontaneously. Fifty per cent of the deaths in infancy were unrelated to the ventricular septal defect. We estimate that by present criteria only 15% of an unselected population of patients with a ventricular septal defect are likely to require surgical treatment.

Ventricular septal defect is the most common of all congenital cardiac malformations, and its epidemiology has been the subject of a number of detailed reviews.¹⁻³ These studies have compared the relative frequency of the defect in infancy with its rarity in adult life. The tendency of some defects to close spontaneously has been noted, as has the relatively high mortality during the first year of life. Other authors⁴⁻⁶ have studied selected groups of patients, the selection providing a bias usually towards the larger, haemodynamically more significant defects. These studies, in which a high proportion of cases was investigated by cardiac catheterisation, have yielded much information about the particular groups studied.

There remains, however, a number of unanswered questions about the natural history of ventricular septal defect in the population as a whole. Epidemiological studies have repeatedly shown a high early mortality and the reason for this needs to be elucidated. The proportion of patients with large defects causing

symptoms and possibly requiring operation is not well documented. In order to answer these questions there is a need to link epidemiological data from a large unselected group of patients with detailed clinical and follow up data. So far, no such study has been reported.

The object of our study therefore was to present the detailed long term follow up of such a large unselected group of patients who were part of an earlier epidemiological study of congenital heart disease.⁷ We hope that these data will help to span the gap between previous epidemiological studies and the detailed follow up studies of selected populations of patients, and will give a clearer picture of the heterogeneous group of patients who appear in epidemiological tables in the category of ventricular septal defect.

Patients and methods

The Liverpool Registry of Congenital Malformations contains information on all children found to have a congenital malformation who were born to residents of the registry area. The methodology of the registry has

been described in detail previously.^{7, 8} Patients are entered in the registry if a congenital malformation is identified in the neonatal period or later in childhood. Information is obtained from the neonatal units, children's hospitals, school medical clinics, and necropsy records within the registry area. A member of the registry staff regularly checks the register of new inpatients and outpatients in the children's hospitals, including those referred specifically to the heart clinic and neonatal surgical unit.

From January 1960 to December 1969 there were 163 692 births, including 3212 stillbirths, within the registry area. Among these, 1120 were registered as having congenital heart disease. The registry records and hospital case sheets of all these patients were reviewed in detail in order to confirm the presence of congenital heart disease and to place each patient in one of 17 diagnostic categories.⁹ Those appearing under the heading of ventricular septal defect are the subject of this report.

For such a study to be relevant to previously published epidemiological data, it is essential that diagnostic groupings of the various studies should correspond as closely as possible. For this reason, the selection of patients has to be based on the presence of a ventricular septal defect as the sole (or major) cardiac defect. Epidemiological studies, of necessity, limit the number of diagnostic categories and it is frequently necessary when placing a patient with more than one defect (for example ventricular septal defect plus persistent ductus) to opt for one or other category on the basis of which defect is judged to be the more important. Thus, within the category of ventricular septal defect are not only patients with isolated septal defects but also a heterogeneous group with associated "lesser" cardiac defects and others with major non-cardiac malformations, including those with Down's syndrome.

While accepting that the inclusion of such patients complicates the study, we are convinced that their exclusion could invalidate any comparison with other epidemiological studies.

DIAGNOSTIC CRITERIA

The diagnosis of a ventricular septal defect was accepted on the basis of three grounds, necropsy in 48 cases, cardiac catheterisation or open heart surgery in a further 56, and clinical features only in another 190, a total of 294 cases in all.

The clinical diagnosis of a ventricular septal defect was accepted only when the typical physical signs of such a defect were found on more than one occasion by a physician experienced in the management of congenital heart disease. The auscultatory physical signs required for the diagnosis were either the presence of a loud pansystolic murmur with a thrill maximal at the

left sternal edge or the presence of the clearly localised, high pitched murmur of the type which has been shown by Evans *et al.*¹⁰ and Vogelpoel *et al.*¹¹ to correlate well with the presence of a small ventricular septal defect. Disappearance of either of these typical murmurs was accepted as evidence of spontaneous closure of the defect.

Patients with certain additional cardiac defects were included in the study when the ventricular septal defect was judged to be the major defect present or when it was considered that ventricular septal defect was the most appropriate diagnostic category. These additional defects are shown in Table 1. Patients in whom the ventricular septal defect was part of a more complex congenital lesion, for example, Fallot's tetralogy or complete atrioventricular canal, were excluded. Patients with additional coarctation of the aorta were also excluded because the clinical course may be more dependent on the coarctation than on the ventricular septal defect.

Table 1 *Additional cardiac abnormalities in 42 patients with ventricular septal defect. Some patients had more than one additional lesion*

Persistent ductus arteriosus	19
Infundibular pulmonary stenosis	13
Ostium secundum atrial septal defect	7
Aortic regurgitation	5
Other	8

Results

The diagnosis of "ventricular septal defect" had been recorded in the registry at some time in childhood in 385 patients (23.5 per 10 000 livebirths). On the basis of repeated follow up examination and investigation by cardiac catheterisation when indicated, 50 patients were assigned to other diagnostic categories, including Fallot's tetralogy (nine patients), pulmonary stenosis (10 patients), aortic stenosis (six patients), persistent ductus arteriosus (five patients), atrial septal defect (six patients), and endocardial cushion defect (four patients). In a further 41 cases the recorded physical signs or other available data were insufficient to satisfy our criteria for acceptance on clinical grounds alone. These patients were excluded, leaving 294.

Thus the incidence of ventricular septal defect in the population under study was 18 per 10 000 births. In the liveborn infants the incidence was 17.5 per 10 000 births and in the stillbirths, 21.8 per 10 000 births. Associated cardiac abnormalities were present in 42 cases (Table 1). Major malformations outside the cardiovascular system were observed in 59 (20%)

Table 2 Major non-cardiac malformations in 59 patients with ventricular septal defects

Down's syndrome	20
Gastrointestinal	14
Urogenital	11
Skeletal	11
Eye and ear	8
Pulmonary	5
Central nervous system	3
Lip and palate	3
Chromosomal anomalies (excluding Down's syndrome)	3
Hepato biliary	2

Table 3 Age at presentation in 277 patients with clinical evidence of a ventricular septal defect

	<3 mth	3 mth-1 y	>1 y	Total
Symptomatic	53 (19%)	5 (2%)	4 (1%)	62 (22%)
Asymptomatic	129 (47%)	33 (12%)	53 (19%)	215 (78%)
Total	182 (66%)	38 (14%)	57 (20%)	

Table 4 Cause of death in 24 cases where death was unrelated to presence of ventricular septal defect

Major gastrointestinal malformation	6
Prematurity with major respiratory problem	5
Birth asphyxia	3
Diaphragmatic hernia	3
Trisomy E	1
Biliary atresia	1
Renal agenesis	1
Gastroenteritis	1
Choanal stenosis and pneumonia	1
Haemophilia	1
Multiple major malformations (small ventricular septal defect)	1

patients, including 20 children with Down's syndrome. Malformations were frequently multiple and their distribution according to the major organ systems involved is given in Table 2.

At the age of 10 years complete follow up data (defined as continuing follow up, or follow up until previous death or spontaneous closure of the defect) were available in 91% of cases. Thereafter the data was less complete (Fig. 1) since many patients born after 1965 and still being followed up were last reviewed at an age of less than 15 years.

CLINICAL PRESENTATION

Two hundred and fifteen (73%) patients presented with the discovery of a systolic murmur in a symptom-free infant or child. In 62 (21%) patients, the presentation was with symptoms of congestive cardiac failure, requiring treatment with digoxin and diuretics.

Seven cases were found at necropsy in stillborn

Fig. 1 Course of follow up over a 15-year period of 287 liveborn patients with a ventricular septal defect. The shaded area represents those patients born after 1965 whose follow up had not extended to the close of this period at the time of their most recent review.

Patients who died after operation are included under the category of "operation".

"Died" indicates those patients who died primarily as a result of the VSD (excluding operative deaths).

infants, and in 10 cases the diagnosis was made at necropsy, the cardiac lesion being unsuspected during life. The ages at presentation of the 277 patients with clinical evidence of a ventricular septal defect are given in Table 3. Of these 277 patients, 75 developed symptoms related to their cardiac defect at some time during childhood. The remaining 202 children were symptom free throughout the period of observation.

DEATHS

Fifty-five (19%) of the patients died, including seven who were stillborn. Of the remaining 48 deaths, 26 (54%) occurred between birth and 3 months of age, eight (17%) between 3 months and 1 year, and 14 (29%) over the age of 1 year. Six of the deaths in this last group followed operation. In 24 patients the cause of death was not related to the presence of the ventricular septal defect (Table 4). Nineteen of these deaths occurred during the first month of life and were associated with

either the complications of premature birth or major malformations outside the cardiovascular system. In 10 of these patients the presence of a ventricular septal defect was not suspected during life. Four of the 24 unrelated deaths occurred after the first month of life, usually after operation for major non-cardiac malformations, and one death, in a haemophiliac, occurred at the age of 7 years.

There were 15 deaths in which the presence of a ventricular septal defect appeared to be a major contributing factor. Nine infants, one of whom had Down's syndrome, died with congestive cardiac failure. A 12-year-old child with Down's syndrome died with pulmonary vascular disease and five other children with Down's syndrome died within the first year of life with acute respiratory infections. Four of these children had been symptom free before the acute illness and the contribution to the death made by the ventricular septal defect in these cases is difficult to assess. Eight deaths followed surgery of the ventricular septal defect and there was one late death in a postoperative patient, 12 years after surgery.

Twenty-four deaths (8% of the liveborn patients) can, therefore, be attributed to the presence of a ventricular septal defect.

SURGICAL TREATMENT

Thirty-five patients underwent open heart surgery for closure of the ventricular septal defect at ages ranging from 5 years to 11 years. An associated intracardiac anomaly was present in 12 of these cases and was a major factor in the decision to operate in 10. In 28 patients, open heart surgery was performed as a primary procedure, while in a further seven patients, banding of the pulmonary artery had been carried out in infancy. Banding alone was carried out in two. Thus, nine children underwent banding of the pulmonary artery and of these two died. After open heart surgery there were six hospital deaths and one late death in a 17-year-old patient with pulmonary vascular disease. Ligation of a persistent ductus arteriosus was carried out in four infants, with subsequent surgical closure of the ventricular septal defect in two of these cases. The ventricular septal defect in the remaining two cases was small and both children are symptom free at 13 and 14 years of age, respectively.

Of the 37 patients receiving surgical treatment for a ventricular septal defect, 26 were from the group of patients with symptoms, 39% of that group. There were no symptoms before operation in the remaining 11 (5% of the asymptomatic group).

The preoperative haemodynamic data were reviewed in all 37 patients who underwent operation. In eight with a normal pulmonary artery pressure and a pulmonary to systemic flow ratio of 2:1 or less, the defect found at operation was small. The patients were

symptom free at the time and it is probable that surgical treatment would not now be recommended.

BACTERIAL ENDOCARDITIS

Only one episode of bacterial endocarditis was recorded during the period of follow up totalling 2253 patient years with an open ventricular septal defect, or approximately 0.5 case per 1000 patient years. The patient was a child of 8 years who had undergone pulmonary artery banding in infancy. The episode was treated successfully and the ventricular septal defect was repaired four months later.

AORTIC REGURGITATION

Aortic regurgitation developed in five (1.7%) patients and was confirmed by cardiac catheterisation in all cases. Three of the patients underwent operation, for closure of the ventricular septal defect in two cases, and for aortic valve replacement and closure of the ventricular septal defect in the third. Of the remaining two patients, one is symptom free at 16 years of age with physical signs of a small ventricular septal defect and mild aortic regurgitation. The remaining child has Down's syndrome and developed signs of aortic regurgitation at 11 years of age. Congestive cardiac failure developed at that time but has been controlled successfully with digoxin and diuretics.

INFUNDIBULAR STENOSIS

Infundibular pulmonary stenosis with a pressure gradient of more than 20 mmHg at cardiac catheterisation was found in 13 patients. All had a left-to-right shunt. Some evidence of right ventricular outflow obstruction (an atypical murmur for an isolated ventricular septal defect, or right ventricular hypertrophy on the electrocardiogram) had been present from early infancy in all but one patient. Seven patients were treated for congestive cardiac failure, but this was related to the presence of an additional lesion (large persistent ductus, aortic regurgitation) in two cases. No child had a clinical course suggesting evolution from a large left-to-right shunt with pulmonary hypertension to the situation of acyanotic Fallot's tetralogy. Eleven of the patients with infundibular stenosis underwent operation, the presence of this being a major indication in six, all of whom had ventricular defects of small size at the time.

SPONTANEOUS CLOSURE

Spontaneous closure of the ventricular septal defect was recorded in 90 patients (31%). In 87 of these the diagnosis was made on clinical grounds alone. With a total observation period of 2253 patient years with the ventricular septal defect open, the spontaneous closure rate is therefore 40 per 1000 patient years. Spontaneous closure was noted more frequently in the

asymptomatic patients, 36.5% of this group having closed spontaneously up to the time of review. Among patients with symptoms, only 21% closed spontaneously. Patients with Down's syndrome are excluded from these calculations and are considered separately (Table 5). An actuarial analysis of the rate of spontaneous closure for the first 10 years of follow up is shown in Fig. 2. The number of spontaneous closures noted during each year is expressed as a percentage of the number of patients known to be alive and under follow up with an open ventricular septal defect at the beginning of that year. Though spontaneous closure was noted in patients up to the age of 16 years the analysis has not been continued to this age because of the relatively small number of patients remaining under follow up beyond 12 years (Fig. 1). There was a relatively uniform rate of spontaneous closure during the first 10 years of life, averaging 3% per annum.

Table 5 Fate of 287 liveborn patients with ventricular septal defect: those patients with Down's syndrome, whether symptomatic or asymptomatic, are treated separately

	Symptomatic (66 patients)	Asymptomatic (202 patients)	Down's syndrome (19 patients)
Spontaneous closure	14 (21%)	74 (37%)	2 (11%)
Alive, small open VSD	10 (15%)	79 (39%)	6 (32%)
Operation	26 (39%)	11 (5%)	0
Death unrelated to VSD	4 (6%)	18 (9%)	2 (11%)
Death without operation, related to VSD	8 (12%)	0	7 (37%)
Lost to follow up	4 (6%)	20 (10%)	2 (11%)

DOWN'S SYNDROME

The 20 patients with Down's syndrome merit separate consideration. One child with Down's syndrome was stillborn. Two were lost to follow up and in a further two spontaneous closure of the defect was observed. Six are alive with the defect open and in all the physical signs suggest that it is small. Two patients with small defects died of an unrelated cause, one of severe gastroenteritis and one after an operation for Hirschsprung's disease. In seven patients (37%) the presence of a ventricular septal defect probably contributed to the death of the patient. One died in infancy with congestive cardiac failure. A 12-year-old child died with pulmonary vascular disease and five others died within the first year of life with respiratory infections.

PROGNOSIS

The fate of the 287 liveborn patients is shown in Table 5. Children with Down's syndrome are assessed separately. In the 202 patients who were asymptomatic there were no deaths related to the presence of the ventricular septal defect. Spontaneous closure was noted in 37% of this group compared with only 21% of

Fig. 2 An actuarial analysis of spontaneous closure of ventricular septal defect among 287 liveborn patients during the first 10 years of life. The number of spontaneous closures noted during each year is expressed as a percentage of the number of patients alive under follow up with an open ventricular septal defect at the beginning of that year.

the symptomatic group. Twenty-six (39%) of the symptomatic group underwent operation and a further eight (12%) died very probably as a direct consequence of the presence of a ventricular septal defect.

Discussion

The difficulties attending the complete identification of congenital heart disease within a population have been reviewed in detail by Hoffman.² Congenital heart defects are not always identifiable at birth and the highest incidence of them is seen in those studies which intensively follow the progress of all children within a cohort of births over a number of years.^{12 13} Studies which rely on referral of cases to a centre or registry may underestimate the true incidence, particularly in the case of asymptomatic infants who may never come to medical attention. The incidence of ventricular septal defect in our study is similar to that reported by Bound and Logan¹⁴ in an adjacent area of North-West England and to that of Carlgren¹⁵ in Gothenburg, Sweden. Comparison with the intensive studies of Mitchell *et al.*¹² and Hoffman and Christianson,¹³ however, suggests that some cases have been missed by us. It is unlikely that new cases of ventricular septal defect born within the registry area were referred to paediatric cardiac centres outside Liverpool, nor is the likely number of cases lost before they could be identified owing to movement of population out of the registry area during the period of study sufficient to account for this.

There are two other possible explanations. First, in studies of stillborn infants with a high necropsy rate, the incidence of ventricular septal defect varied from 110 per 10 000 stillbirths (Hoffman and Christianson¹³) to 150 per 10 000 (Bound and Logan¹⁴). These figures

suggest that between 30 and 50 cases of ventricular septal defect might have been expected in our group of 3212 stillborn infants, as compared with the seven defects actually identified.

Second, during the period under review it was not the policy of this unit to subject all children and infants with a ventricular septal defect to cardiac catheterisation. As a result, in 65% of cases the diagnosis was made on clinical grounds alone. In the comparable study of Bound and Logan,¹⁴ 52% of ventricular septal defects were similarly diagnosed. Studies in which a considerably higher proportion of cases were catheterised,^{4, 5} are not comparable with our study because case selection was biased towards the larger and haemodynamically more significant defects and away from those which close spontaneously during early infancy.

The accuracy of the clinical diagnosis of ventricular septal defect by experienced observers has been shown to be good.^{10, 11} There is no reason therefore to believe that we have significantly overestimated the incidence of ventricular septal defect in the population studied and indeed it is probable that our strict criteria for inclusion in the study (together with the structure of the registry) have resulted in some patients being missed, particularly those who were asymptomatic with small defects. Though the study may therefore be weighted very slightly towards the larger defects, it is, we hope, representative of the full spectrum of the condition both epidemiologically and as it presents to hospital practice.

In the past decade, there has been a change in the choice and timing of surgical procedures in ventricular septal defect, with a tendency for early intracardiac repair to be preferred to a two-stage procedure involving early banding of the pulmonary artery followed by later total correction.¹⁶ The main indications for surgical treatment, however, namely intractable congestive cardiac failure in infancy, and the prevention of pulmonary vascular disease at a later age, remain unchanged. Our study, therefore, allows the proportion of patients with a ventricular septal defect who will require operation to be assessed. Thirty-seven patients in this series underwent operation but we consider that this would now be considered appropriate in only 29. A further 15 children, seven of whom had Down's syndrome, died with symptoms which suggested that the ventricular septal defect was a major contributory cause of death. If it is assumed that these 15 children would now receive surgical treatment, then 44 children, or 15% of the liveborn patients, can be regarded as potential surgical candidates. The precise number of patients undergoing surgery today would depend to some extent on the attitude of the individual units to the surgical treatment of children with Down's syndrome and to success in the management of other major non-cardiac malformations. There is no evidence,

however, to suggest that the proportion of patients with larger defects was greater in the infants who died from unrelated causes than in the group as a whole. It is, therefore, unlikely that more than 15% of the original group of patients would require surgical treatment according to our present criteria for closure. We estimate that of these, 40% would require operation on a semi-emergency basis within the first year of life, a further 35% with an isolated ventricular septal defect would undergo elective operation probably at about 12 months of age, while the remaining 25% would have an additional intracardiac defect which would be the major indication for operation at a time determined by the nature and severity of that additional lesion.

The number of patients with haemodynamic data in our study is small and we are, therefore, unable to distinguish differing haemodynamic categories as others have done.^{3, 5} It is clear, however, that the proportion of cases with smaller defects was considerably higher than that reported previously by Campbell.³ At the time of review, the defect had closed spontaneously in 90 patients and was clinically small in a further 95 asymptomatic patients. Together they represent 64% of the liveborn patients, and 69% of the patients surviving the first month of life.

The incidence of bacterial endocarditis in our series is relatively low at 0.5 per 1000 patient years of follow up. This contrasts with the figures of 4.7, 2.1, and 1.5 per 1000 patient year found by Griffiths *et al.*,¹⁷ Shah *et al.*,¹⁸ and Gersony and Hayes,¹⁹ respectively. Our study contains, however, a high proportion of years of patient follow up from the first two years of life with relatively few years of follow up from the second decade of life. The low incidence of bacterial endocarditis in children under 2 years of age has been clearly documented²⁰ and our figure may well represent more accurately the true incidence of this complication during the first decade of childhood than the higher incidence reported from series which contain a greater number of patients from later childhood and adult life. This conclusion is supported by the figure of 0.7 incidents of endocarditis per 1000 patient years of follow up calculated from the data of Corone *et al.*⁵ for the first 10 years of life.

As might be expected, the incidence of spontaneous closure of ventricular septal defect varies considerably in reported series according to the selection of cases, the length of follow up, and the age distribution of the population studied. Thus, Evans *et al.*¹⁰ documented spontaneous closure in 37 of 120 patients (31%), most of whom had small left to right shunts initially. Alpert *et al.*²¹ followed a group of 55 infants with small ventricular septal defects for five years, during which time 58% closed spontaneously. More recently, Keith¹⁶ has shown an overall spontaneous closure rate of 16.5% in a group of 630 children followed to an average age of 7 years. The incidence of spontaneous closure was

highest (26%) in those children considered to have small defects. By contrast, though spontaneous closure is well documented in adult life,¹ it is thought to be less frequent. In our study spontaneous closure was noted in 90 patients, representing 32% of the patients surviving beyond the neonatal period. Since many children remaining under review with a small defect are under 15 years of age, further spontaneous closures may be anticipated.

Conclusions

The criteria used for diagnosis of a ventricular septal defect are of considerable importance in the study of the natural history of this lesion. Since most patients with a ventricular septal defect are symptom free and some defects will close spontaneously even in infancy, haemodynamic or angiographic confirmation of the diagnosis cannot be insisted upon. For this reason it is likely that any such study will have to rely to a considerable extent on clinical information alone. We tried to minimise diagnostic error by a long duration of follow up and by strict diagnostic criteria but may, thereby, have missed some cases. Nevertheless, conclusions can be drawn from our study. The mortality of this group of patients was 17% among liveborn patients, with 71% of the deaths occurring within the first year of life. These figures may be expected to fall with the more aggressive modern approach to the surgical treatment of symptomatic infants together with lower operative mortalities. It should be noted, however, that almost 50% of the total number of deaths were unrelated to the presence of the ventricular septal defect, most occurring at an age at which even a large defect would not be expected to produce symptoms. For this reason the early mortality among infants with a ventricular septal defect is likely to remain substantial.

About 25% of children with a ventricular septal defect develop symptoms, usually during infancy. The remainder will be symptom free throughout childhood. Even among the former, the possibility of a relative reduction in size or of spontaneous closure of the defect is appreciable, and overall about 65 to 70% of patients will have defects which are small, or become small during early childhood. By our present criteria only about 15% of cases will require operation. If, as has been suggested recently,²² it is considered justifiable to close small ventricular septal defects in adolescence in order to reduce the risk of bacterial endocarditis, this figure would be increased considerably.

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Requests for reprints to Dr J L Wilkinson, Royal Liverpool Children's Hospital, Myrtle Street, Liverpool L7 7DG.