Cardiovascular malformation in infant deaths

10-year clinical and epidemiological study

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The infant mortality from cardiovascular malformations in a region with a population of 2 million inhabitants during a 10-year period has been studied. The study involved validation of the diagnoses and judgement whether the cardiovascular malformation was the dominating or a contributing cause of death. It is shown that the incidence of fatal cardiovascular malformations is probably overestimated in the official death statistics. Evaluation of the clinical findings and necropsy reports are important aids in obtaining more reliable figures of the incidence.

The rate of referral of infants with cardiovascular malformations has increased during the period of this study, so that the number of operable lesions not referred has decreased. The infant mortality rate, found in this study, of 1.33 per 1000 liveborn babies constitutes about 20 per cent of all liveborn infants with cardiovascular malformations. The most common lesions found in those who died belonged to the group constituting the hypoplastic left heart syndrome. The proportion of this type of malformation, about 20 per cent of all those dying, is higher than in other similar studies. This difference can probably be explained by variations in selection and classification.

Infant mortality in congenital heart disease has been studied on a number of occasions. Since the classical work of Abbot in 1936 a number of reviews and studies of cases less selected than Abbot's have greatly increased our knowledge of the incidence and mortality (McMahon, McKeown, and Record, 1953; Carlgren, 1959; Hay, 1966; Carlgren, 1969; Landtman, 1971; Mitchell, Korones, and Berendes, 1971; Feldt *et al.*, 1971; Campbell, 1973). By using various approaches to trace the cases we believe that the following study might give even more accurate figures of the incidence of fatal cardiovascular malformations. This presentation includes an evaluation of the validity of the official statistics. Aspects related to practical medical care have been investigated. Thus, the study includes estimation of the severity of the heart lesions, the apparent cause of death, and the occurrence of extracardiac malformations and other diseases. The rate of referral of the patients from other hospitals to the heart centre has also been studied.

Subjects and methods

The section of paediatric cardiology at the Department of Paediatrics in Uppsala serves the regions of Uppsala and Umeå which have a population of about 2 million. Through the Central Bureau of Statistics death certificates were obtained relating to liveborn infants in these regions for the period from 1961 to 1970 who died during their first year of life, with the diagnosis of cardiovascular malformation given as the main or complicating cause of death. With the aid of these death certificates, hospital records and necropsy reports were requested from the hospitals in these regions and, in a few cases, from the institutes of forensic medicine. The files of the paediatric heart centre in Uppsala were also studied to trace cases that might have escaped the death registration at the Central Bureau of Statistics. A pilot study was also made using a computerized list of diagnoses on all discharged in-patients (including those who died) for all hospitals in the region of Uppsala. This pilot record study included cases from the years 1964 and 1965 only, and the material was checked against the death certificates already received.

With the information thus obtained, the cases were studied with respect to the diagnoses of cardiovascular malformation and other diseases. Data from each individual included personal identification number, sex, birthweight, year of death, age at death, and place at

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death (in hospital, at home or other place). From information on the death certificate the type of the heart diagnosis was obtained, i.e. whether it was the underlying or a complicating cause of death and whether the diagnosis was based on findings at necropsy or not. In addition a note was made as to whether the case had been admitted and investigated at the heart centre or not.

All the available information about each case was considered in order to obtain a final diagnosis and to determine if the lesion was a dominating, contributing, or insignificant cause of death, or if there was no heart disease present at all. The ways in which the final diagnosis was arrived at were recorded, and it was noted whether it was based upon cardiac catheterization and angiocardiology, findings at heart operation, necropsy, or from clinical examination only.

The definition of cardiovascular malformation used was that of Mitchell *et al.* (1971), i.e. a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance. Extracardiac diagnoses were coded as well and divided into diseases dominating or contributing as causes of death. Because of the varying quality of necropsy data an evaluation was made of the reliability of the necropsy findings.

Results and comments

From the primary data of the official death statistics, which was our main source of information, 485 infants with a diagnosis of congenital heart disease were traced.

Another 10 cases were retrieved through the files of the heart centre and another 4 cases from the pilot record study. The death certificates of these 14 infants were specially searched for at the Central Bureau of Statistics but only 10 were found. These cases had other severe diseases as well, and probably the physician had thought that it was sufficient to note these causes of death.

The evaluation of whether the cardiovascular malformation was the dominating or the contributing cause of death, or if it was insignificant, is difficult and involves subjective judgements. Examples of these difficulties include a mongoloid infant with endocardial cushion defect and bronchopneumonia, and a premature infant with respiratory distress syndrome and ventricular septal defect. The presence or absence of cardiac failure before the final days of life has been used as an aid in making this judgement.

The validity of the diagnoses has been estimated, and the material has been divided into four categories from this point of view. The first group comprises cases examined at necropsy by a heart pathologist and with a detailed necropsy, or cases examined by one of us after death (M.M.). The second group are cases examined by another experienced pathologist and/or diagnosed with the

TABLE 1 *Reported cardiovascular malformations by method of diagnosis*

<i>Method of diagnosis</i>	<i>No. of infants</i>
Necropsy by heart specialist	202
Necropsy by experienced pathologist and/or angiocardiology	164
Necropsy by other pathologist or clinical examination only	103
Insufficient information	30
Total	499

aid of heart catheterization and angiocardiology. The third group are necropsy cases examined by less experienced pathologists or clinicians. The last group are cases where the diagnosis is more or less guesswork because of insufficient or contradictory information. The number of cases in each group is shown in Table 1.

Of the 499 infants with the diagnosis of cardiovascular malformation, 51 were found not to have any cardiovascular malformation according to our criteria. One explanation for this discrepancy is that anatomically patent foramen ovale and persistent ductus arteriosus before the age of 14 days has been reported as a malformation. Another explanation is that a number of cases were thought to have a cardiovascular malformation at the time of filling out the death certificate before necropsy had been performed. When the necropsy disclosed other primary diseases instead, such as pulmonary disease or intracranial haemorrhage, the attending physicians failed to correct the certificate.

There were 448 cases remaining who had died

TABLE 2 *Rate of infant deaths with cardiovascular malformation as dominating or contributing cause of death*

<i>Year</i>	<i>No. of infant deaths - per 1000 liveborn infants - with cardiovascular malformation</i>		
	<i>As dominating cause of death</i>	<i>As contributing or insignificant cause of death</i>	<i>Total</i>
1961	1.4	0.1	1.5
1962	0.9	0.3	1.2
1963	1.3	0.4	1.7
1964	1.1	0.3	1.4
1965	1.4	0.4	1.8
1966	1.4	0.2	1.6
1967	1.0	0.3	1.3
1968	1.6	0.3	1.9
1969	1.8	0.4	2.2
1970	1.5	0.1	1.6
Total	1.33	0.27	1.60

during the first year of life with a cardiovascular malformation. From the pilot record study covering only two years and only in the Uppsala region we have tried to estimate the 'loss' of cases during the period of study. This figure is calculated to be 4 per cent. Another 'loss' which is not determinable is cases with cardiovascular malformation which were overlooked at necropsy or hidden within the infant group not being brought to necropsy. The necropsy rate for all liveborn infants dying during the first year of life was 74 per cent during 1969 to 1970 in the whole of Sweden; for those with cardiovascular malformations the necropsy rate was 84 per cent (A. M. Bolander, 1974, personal communication).

Of the 448 cases, there were 76 where the cardiovascular malformation was classified as a contributing or an insignificant cause of death. Using these figures yearly incidences per 1000 liveborn infants have been calculated and are presented in Table 2.

During the 10-year period 279 601 infants were born alive in the regions studied. The number of cardiovascular malformations differs considerably from year to year, but this number is small, and conclusions regarding any special trend could hardly be drawn from this material. An infant mortality rate of 1.60 per 1000 live births is in good agreement with other studies (Gardiner and Keith, 1951; Carlgren, 1959; Kerrebijn, 1966; Feldt *et al.*, 1971). The mortality rate of 1.33 (cardiovascular malformations as dominating cause of death) is definitely lower than these reports, but there are, on the other hand, no other directly comparable figures obtainable from the published reports. After the year 1965 the surgical intervention in infancy increased considerably. There is hardly any change to be seen in the mortality figures after this year but when the specific causes of mortality are studied, differences are apparent, as, for instance, in transposition of the great arteries.

In Table 3, the material is presented as cases referred and not referred to the heart centre. In 1965 a circular letter was sent to the paediatricians in these regions. In this letter published reports were presented giving favourable surgical results in infants with cardiovascular malformations. The number of cases referred subsequently increased.

Most of the non-referred cases had associated severe malformations, or other conditions, such as immaturity, reducing the relative importance of the heart lesion. The number of infants with a birth-weight of 2500 g or less was 98 in this material (22%). It is of interest to note that this figure is similar to that of Landtman (1971) who found 24 per cent with low birthweight in his series of 777 infants and children with cardiovascular malformation who were examined at necropsy.

TABLE 3 *Rate of referral for cardiac investigation of infants with a reported diagnosis of cardiovascular malformation*

Year	No. of infants referred	No. of infants not referred	Total
1961	5	38	43
1962	11	26	37
1963	15	40	55
1964	11	34	45
1965	16	41	57
1966	28	29	57
1967	16	27	43
1968	22	44	66
1969	28	28	56
1970	29	11	40
Total	181 (36%)	318 (64%)	499
1961-1965	58 (24%)	179 (76%)	237
1966-1970	123 (47%)	139 (53%)	272

Other similarities with the study of Landtman and with other series are evident when the associated diseases and malformations are analysed (Table 4). The results in this table confirm the observations made by others that infants dying with a diagnosis of cardiovascular malformation constitute a heterogeneous group in which other malformations are often the dominating causes of death. In 254 cases the cardiovascular malformation was judged to be the dominant cause of death *without* any other significant disease or malformation being present. Thus, there are 194 cases with other significant diseases.

TABLE 4 *Diseases and malformations associated with cardiovascular malformations*

Disease category	No. with disease	
	As single complicating lesion	Together with other complicating lesions
Anomalies of central nervous system	7	8
Anomalies of digestive system	14	37
Anomalies of respiratory system	3	11
Cleft palate and cleft lip	4	10
Anomalies of genitourinary system	2	23
Anomalies of musculoskeletal system	5	21
Down's syndrome	17	36
Other anomalies	20	28
Birth injuries	7	9
Asphyxia	31	16
Diabetic embryopathy	2	1
Rubella embryopathy	2	1
Bronchopneumonia	32	59
Other diseases	12	21

TABLE 5 Age at death of infants with cardiovascular malformation

Age of death	No. of infants	Per cent distribution
0-6 days	140	31
7-28 days	85	19
1-2 months	83	19
3-5 months	70	16
6-11 months	70	16
Total	448	100

There were 76 cases where the cardiovascular malformation was only of contributing or even insignificant importance. In the remaining group of 118 cases there is a considerable number of infants as earlier mentioned where the decision has been difficult as to whether the heart malformation or other disease should be classified as the dominant cause of death.

The age of death is given in Table 5. The age distribution confirms observations in other comparable series that death in early infancy is most common (Carlgrén, 1959; Hay, 1966; Mitchell *et al.*, 1971; Feldt *et al.*, 1971). Of the 225 cases dying during the first month of life, 184 (82%) were not referred for cardiac investigation. No less than 62 cases of those not referred died before reaching the age of 2 days. Very few, approximately 10, of these 62 cases had cardiovascular malformations which

were correctable. Even though the referral rate improved during the last 5 years of the study, there were still a considerable number of cases where the cardiovascular malformation could have been treated.

The list of specified cardiovascular lesions originally included 38 diagnoses. The number of diagnoses has been reduced to 20 by merging similar malformations. We have done this to give a better survey and to make the material more easily comparable with other studies. We have roughly followed the list of diagnoses given in the paper of Mitchell *et al.* (1971). Various combinations of malformations is a common finding. As seen from Table 6 we have grouped a few of them together, for instance mitral and aortic atresia. Under this heading we have included mitral valve stenosis/atresia with rudimentary left ventricle (73 cases), interrupted aortic arch (10 cases), hypoplasia of left ventricle (6 cases), aortic atresia with normal mitral valve (3 cases), pulmonary vein atresia/cor triatriatum (2 cases), hypoplasia of ascending aorta/aortic arch (2 cases), and finally mitral valve atresia with ventricular septal defects (1 case).

When various combinations of cardiovascular malformations are present, it is often difficult to state which malformation is the dominating one, as exemplified by ventricular septal defect associated with an obstructive lesion of the aortic arch and a persistent ductus arteriosus. Within the miscellan-

TABLE 6 Frequency of specific lesions as dominating or contributing cause of death

Diagnosis	Dominating as cause of death	Contributing as cause of death	Total	
			No.	Per cent distribution
Mitral and/or aortic valve atresia	97	0	97	21.7
Ventricular septal defect	26	37	63	14.1
Transposition of great arteries, isolated	40	0	40	8.9
Endocardial cushion defect, partial/complete	34	1	35	7.8
Fallot/pulmonary valve atresia and ventricular septal defect	24	0	24	5.4
Transposition of great arteries, complicated	24	0	24	5.4
Tricuspid valve atresia	18	1	19	4.2
Persistent ductus arteriosus	5	11	16	3.6
Truncus arteriosus communis	16	0	16	3.6
Atrial septal defect of secundum type	1	14	15	3.3
Aortic valve stenosis	10	5	15	3.3
Coarctation of aorta, preductal	14	0	14	3.1
Pulmonary valve atresia with intact ventricular septum	13	0	13	2.9
Total anomalous pulmonary venous drainage	12	0	12	2.7
Endocardial fibroelastosis	6	1	7	1.6
Anomalous origin of coronary artery	5	0	5	1.1
Coarctation of aorta, postductal	1	2	3	0.7
Single/common ventricle	3	0	3	0.7
Miscellaneous	9	4	13	2.9
Diagnosis not specified	14	0	14	3.1
Total	372	76	448	100

eous group are cases where it was not possible to judge which lesion was the dominating one. The frequency of occurrence of various combinations of malformations is described in detail by Fontana and Edwards (1962). Our results in this respect are similar and will, therefore, not be presented here.

It can be seen that mitral and/or aortic atresia, commonly grouped under the heading of hypoplastic left heart syndrome, is by far the most common heart lesion. When the frequency of these lesions is compared to that reported in other series a striking difference is noted. Mitchell *et al.* (1971) present data giving a relative frequency of 9.8 per cent of mitral and/or aortic atresia among infants dying before the age of 1 year. A corresponding figure from the study of Landtman (1971) is 10.8 per cent as compared to our figure of 21.7 per cent. In other necropsy series, the incidence in infants less than 1 month of age can be obtained. Rowe and Cleary (1960) give the highest figure, 27 per cent, Mehrizi, Hirsch, and Taussig (1964) have 13 per cent, and Lambert, Canent, and Hohn (1966) have 22 per cent in their series. The corresponding figure in the material presented here is 32.0 per cent. There are probably several explanations for this difference, especially when the mortality figures from the whole first year of life are compared. One reason could be that the lesions have been grouped among other heart diagnoses. Another explanation is that the cases are selected differently, so that the cases dying during the first days of life have not been referred to the place where the necropsy material has been collected. A third explanation, which seems to be less probable, could be geographical or ethnic differences in the true occurrence of these lesions.

The material presented includes a great number of correctable or at least operable lesions. There are 33 postoperative deaths included in the material. The number of postoperative deaths has increased during the last years of the study, and this is explained by the increased referral rate with increased numbers of operations in infancy. Examples of postoperative deaths include 1 with postductal coarctation (the only death where this was a dominating cause of death), 9 with transposition of the great arteries, 3 with Fallot's tetralogy, 2 with ventricular septal defect, and 3 with persistent ductus arteriosus. It is evident that the study presented here cannot give a true picture of the natural and 'unnatural' history of many heart lesions especially as the situation is continually changing. There are, for instance, 14 cases with isolated transposition of the great arteries surviving from the last years of the study.

Discussion

The experience from this study shows that the use of death certificates alone does not give a reliable figure for the incidence of cardiovascular malformations as a whole or of the various types of lesions. An appeal to the attending physicians to correct the death certificate after necropsy would be one way towards improvement. Increasing the rate of necropsy and improving the knowledge of the pathologists are other desirable but more difficult ways to obtain a true picture. A systematized necropsy form could possibly help to improve diagnosis as well. It is possible that the rules for reporting and coding of the causes of death could be improved in such a way that difficulties in interpretation as to whether the cardiovascular malformation is the underlying or contributing cause, could be overcome. Until such improvements have been achieved it seems to be necessary to collect information not only from the death certificate but also from additional sources. It seems to be important also to describe the ways in which the primary data have been collected if one is to make the results from different published series more comparable.

The rate of referral for cardiac investigation and treatment has improved during the period of study, as seen from Table 3. The increased referral rate has resulted in an increased number of operations and an increase in survival, as seen for instance in transposition of the great arteries. It is our experience that during the last years of the study very few cases with correctable lesions have not been referred for investigation.

The rate of referral could be further increased but we are approaching the point where such a great part of the total resources for medical care would be required for these cases that cost-benefit aspects have to be considered. Such considerations are relevant not only to the question of the distribution of resources for medical care. For instance, increased rate of referral would include a greater number of infants with associated severe incurable lesions. Palliative procedures in such cases which lead to prolonged suffering for the infant and the family are questionable.

A figure of interest in this connexion is the total number of infants and children with recorded cardiovascular malformation. The pilot record study of children born in 1966 and 1967 in these regions showed that the incidence of living and dead infants and children with cardiovascular malformation is 6.5 per 1000 live born (the relatively common cases of symptom-free neonates with high frequency early-midsystolic murmur along the left sternal border have not been included). Thus the infant mortality rate of 1.33 per 1000 live-born observed in this study con-

stitutes about 20 per cent of all liveborn infants with cardiovascular malformations.

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