Cardiovascular malformations and oesophageal atresia

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In a retrospective study of 345 patients with oesophageal atresia, cardiovascular malformations were present in 96 patients (27.8%) and were the commonest associated malformations: 83 (86.5%) of these patients died, compared with 40 out of 156 patients (25.6%) who had oesophageal atresia with no other malformations. Persistent ductus arteriosus was the commonest lesion, followed by ventricular septal defect, secundum atrial septal defect, right-sided aortic arch, dextrocardia, anomalous right subclavian artery, and defects of the atrioventricular valves.

Patients with cardiovascular malformations had a lower birthweight, a shorter gestation, and were more likely to have an abnormally low fetal growth rate.

A right-sided aortic arch or an anomalous right subclavian artery in patients with oesophageal atresia should suggest the possibility of thymic or parathyroid hypoplasia or agenesis.

Now that oesophageal atresia itself can be corrected, the associated cardiovascular malformations are of increasing importance.

Early diagnosis, more sophisticated preoperative preparation, safer anaesthesia, improved surgical techniques, and control of infection have led to a greatly increased survival rate after operations to repair and correct oesophageal atresia, and this has been heralded as 'the epitome of modern surgery' (Myers, 1973). It is now possible to salvage over 90 per cent of infants with oesophageal atresia who weigh more than 1.5 kg at birth and who do not have other malformations incompatible with life (Belsey, 1972). In patients with oesophageal atresia, attention is increasingly being drawn to other malformations that have a bearing on the prognosis, treatment, and decision to operate.

A retrospective survey has been performed on 345 patients with oesophageal atresia born in the south west of England, and because cardiovascular malformations are the commonest associated malformations in this series this association merits special attention.

Patients and methods

Using diagnostic indices provided by thoracic surgeons, paediatricians, pathologists, and hospital medical records departments, records of patients with oesophageal atresia, with or without a tracheo-oesophageal fistula, were traced. Wherever possible antenatal details were obtained from hospital antenatal records and from the

general practitioner. There were 324 liveborn and 21 stillborn cases. Necropsies had been performed in 153 out of the 172 cases who had died.

Results

1) Incidence of cardiovascular malformations
Of the 345 patients with oesophageal atresia, 156 (45.2%) had no other malformations. The commonest associated malformations were cardiovascular, present in 96 patients (27.8%), followed by other gastrointestinal malformations in 78 patients (22.6%), genitourinary malformations in 64 patients (18.6%), and skeletal malformations in 61 patients (17.7%).

Of the 21 stillborn cases, 6 had cardiovascular malformations, and since this incidence is not significantly different from the incidence in live-born cases, the stillborn cases will not be considered separately.

2) Sex

There were 186 male patients and 159 female patients. Of the 96 with cardiovascular malformations, 48 were male and 48 female.

3) Type of cardiovascular defect

These are set out in Table 1. No case is included under more than one heading.

4) Survival

The extremely poor survival rate for patients with oesophageal atresia and cardiovascular malformations is shown in Table 2.

5) Gestation

The results for patients in whom the gestation was recorded, and excluding those in whom labour was surgically induced, are shown in Table 3. Patients with oesophageal atresia and cardiovascular malformations had a significantly shorter gestation than patients with oesophageal atresia and no other malformations, but this effect was not specific for those with cardiovascular malformations since the pre-

sence of non-cardiovascular malformations was also associated with a shorter gestation.

6) Birthweight

The results, for patients in whom the birthweight was recorded, are shown in Table 4. Patients with oesophageal atresia and cardiovascular malformations had a significantly lower birthweight than patients with oesophageal atresia and no other malformations. The cases with cardiovascular malformations were associated with a lower birthweight than were those with non-cardiovascular malformations, though the difference was not quite significant.

TABLE I *Type of cardiovascular defect*

<i>Cardiovascular defect</i>	<i>No. of cases</i>
a) <i>Ventricular septal defect</i>	
Alone	7
With persistent ductus arteriosus	5
With persistent ductus and secundum ASD	2
With common atrium	1
With secundum ASD and azygos continuation of inferior cava	1
With secundum atrial septal defect and right-sided aortic arch	1
With right-sided aortic arch	1
b) <i>Persistent ductus arteriosus</i>	
Alone	14
(Those with other malformations are included with the other malformation)	
c) <i>Atrial septal defect</i>	
Secundum ASD alone	3
Secundum ASD with persistent ductus arteriosus	3
Two secundum ASDs	1
Secundum ASD with partial anomalous pulmonary venous drainage	1
Secundum ASD with persistent ductus arteriosus and dextrocardia	1
Secundum ASD with persistent ductus arteriosus and anomalous right subclavian artery	1
Secundum ASD with mild mitral regurgitation and anomalous left iliac vein draining into left renal vein	1
d) <i>Aortic arch defects</i>	
Right-sided aortic arch only	5
With persistent ductus arteriosus and other undiagnosed cardiac lesions	1
Anomalous right subclavian artery only	1
Anomalous right subclavian artery with persistent ductus arteriosus	2
Anomalous right subclavian artery with persistent ductus arteriosus and right-sided aortic arch	1
e) <i>Atrioventricular valve defects</i>	
Tricuspid atresia	2
Bicuspid right atrioventricular valve	1
Mitral valve atresia, single ventricle, four pulmonary veins uniting to form single trunk draining into left atrium	2
Mitral valve atresia, hypoplastic left ventricle, VSD, secundum ASD, persistent ductus arteriosus, coarctation of aorta, right-sided aortic arch	(twins)
AV canal	1
AV canal, persistent ductus arteriosus, bicuspid pulmonary and aortic valves, coarctation of aorta, common atrium	1
AV canal, hypoplastic left ventricle, hypoplastic segment of aorta, right-sided aortic arch, anomalous right subclavian artery	1

TABLE I (Cont'd)

Cardiovascular defect	No. of cases
f) <i>Dextrocardia</i>	
Dextrocardia only	4
With other undiagnosed cardiac lesions	1
With persistent ductus arteriosus	1
(There were no cases of situs inversus)	
g) <i>Aortic valve defects</i>	
Bicuspid aortic valve, persistent ductus arteriosus	1
Aortic valve stenosis, VSD, persistent ductus arteriosus	1
Aortic valve stenosis, secundum ASD, persistent ductus arteriosus	1
h) <i>Coarctation of aorta</i>	
Alone	1
With persistent ductus arteriosus, VSD, and secundum ASD	1
i) <i>Venous anomalies</i>	
Left adrenal draining into inferior vena cava	1
Azygos continuation of inferior vena cava	1
j) <i>Fallot's tetralogy</i>	
Alone	1
With persistent ductus arteriosus and right-sided aortic arch	1
With dextrocardia	1
k) <i>Undiagnosed cardiac lesions</i>	
Congenital heart disease where precise anatomical diagnosis not known	6
l) <i>Others</i>	
VSD, persistent ductus arteriosus, common atrium, total anomalous pulmonary venous drainage, hypoplastic right ventricle	1
Double outlet right ventricle, VSD	1
Double outlet right ventricle, VSD, persistent ductus arteriosus, secundum ASD, coarctation of aorta	1
Truncus arteriosus, VSD	1
Transposition of great arteries, VSD	1
Pulmonary atresia, common atrium, hypoplastic right ventricle	1
Pulmonary atresia, VSD, persistent ductus arteriosus	1
Single coronary artery, persistent ductus arteriosus	1
Fibroelastosis of left ventricle	1
Cor biloculare, truncus arteriosus	1
Aortic arch atresia beyond left carotid artery, with anomalous left and right subclavian arteries arising from descending aorta	1
Hypoplastic left ventricle, secundum ASD	1
Total	96

7) Fetal growth

Assessing fetal growth with the percentile charts of Thomson, Billewicz, and Hytten (1968), for patients in whom information on gestation and birthweight was available, the results are shown in Table 5. These show that patients with oesophageal atresia and cardiovascular malformations are more likely to have fetal growth retardation than those with oesophageal atresia only, but this effect is not specific for cardiovascular malformations as it is shown to the same degree in patients with oesophageal atresia and non-cardiovascular malformations.

8) Family history

In 2 patients with oesophageal atresia and cardio-

vascular malformations there was a first degree relative with cardiovascular malformations. One patient with oesophageal atresia, a ventricular septal defect, and a persistent ductus arteriosus, had an elder brother with a ventricular septal defect. The other patient with oesophageal atresia had the left adrenal vein draining into the inferior vena cava; he had a brother who died with aortic atresia and a hypoplastic left ventricle.

9) Clustering

Searching for time-clustering, using estimated dates of conception, and Knox's (1959) time interval analysis method, revealed no evidence of clustering of cases with oesophageal atresia and cardiovascular malformations.

TABLE 2 *Survival of patients with oesophageal atresia according to presence of additional malformations*

	Dead	Alive	
Oesophageal atresia, no other malformations	40 (25.6%)	116 (74.4%)	$\chi^2_{(1)}$ with Yates' correction = 85.6, P < 0.001
Oesophageal atresia + cardiovascular malformations	83 (86.5%)	13 (13.5%)	
Oesophageal atresia + non-cardiovascular malformations	49 (52.7%)	44 (47.3%)	$\chi^2_{(1)}$ with Yates' correction = 24.0, P < 0.001

TABLE 3 *Gestation of patients with oesophageal atresia according to presence of additional malformations*

	< 34 weeks	34 to 37 weeks	38 weeks or over	
Oesophageal atresia, no other malformations	12 (8.9%)	26 (19.3%)	97 (71.9%)	$\chi^2_{(2)} = 11.8$, P < 0.005
Oesophageal atresia + cardiovascular malformations	10 (12.8%)	30 (38.5%)	38 (48.7%)	
Oesophageal atresia + non-cardiovascular malformations	9 (11.1%)	25 (30.9%)	47 (58.0%)	$\chi^2_{(2)} = 1.4$, not significant

TABLE 4 *Birthweight of patients with oesophageal atresia according to presence of additional malformations*

	< 1.5 kg	1.5 to 2.49 kg	2.5 kg and over	
Oesophageal atresia, no other malformations	10 (6.7%)	39 (26.2%)	100 (67.1%)	$\chi^2_{(2)} = 30.8$, P < 0.001
Oesophageal atresia + cardiovascular malformations	9 (9.9%)	54 (59.3%)	28 (30.8%)	
Oesophageal atresia + non-cardiovascular malformations	8 (9.4%)	36 (42.4%)	41 (48.2%)	$\chi^2_{(2)} = 5.9$, not significant

TABLE 5 *Fetal growth rate of patients with oesophageal atresia according to presence of additional malformations*

	< 5th centile	5-95th centile	
Oesophageal atresia, no other malformations	33 (23.2%)	109 (76.8%)	$\chi^2_{(1)}$ with Yates' correction = 19.8, P < 0.001
Oesophageal atresia + cardiovascular malformations	47 (52.8%)	42 (47.2%)	
Oesophageal atresia + non-cardiovascular malformations	40 (48.2%)	43 (51.8%)	$\chi^2_{(1)}$ with Yates' correction = 0.2, not significant

Discussion

Cardiovascular malformations were the commonest associated malformations in a series of 345 patients with oesophageal atresia, as has been found previously in smaller series (Baker *et al.*, 1972; Henrikson and Petterson, 1970; Holder and Ashcraft, 1966; Holder *et al.*, 1964; Martin, 1965; Waterston, Bonham Carter, and Aberdeen, 1962; Wayson *et al.*, 1965).

Persistent ductus arteriosus was the commonest lesion. However, it was usually accompanied either by major cardiac defects or by severe neonatal respiratory problems, and only one patient with a ductus survived the neonatal period to require ligation of the ductus. The high proportion of patients with a ventricular septal defect is similar to previous series (Henrikson and Petterson, 1970; Mellins and Blumenthal, 1964; Waterston *et al.*, 1962; Wayson *et al.*, 1965). A secundum atrial septal defect, a right-sided aortic arch, an anomalous right subclavian artery, dextrocardia, and defects of the atrioventricular valves were also common. In the largest published series of cases with oesophageal atresia and cardiovascular malformations, 5 out of 48 cases had a right-sided aortic arch, 9 had an aberrant right subclavian artery, and 1 had dextrocardia. Our own figure of 7 patients with an anomalous right subclavian artery is probably erroneously low. It is clear that this defect was only documented in years gone by, when operation notes were recorded in much greater detail than is the practice now. This defect tends to be overlooked at necropsy unless its presence is specifically sought, so that its true incidence will only be known if a systematic record is made at the time of surgery or necropsy.

Abnormalities of the right subclavian artery are of special interest in oesophageal atresia, and this association of defects has attracted both discussion and speculation (Fluss and Poppen, 1951; Lister, 1964). It appears that anomalies of the fourth arch and its remnants are definitely associated with oesophageal atresia, and one suggestion is that pressure from an anomalous right subclavian artery crossing behind the oesophagus could interfere with normal oesophageal development. However, it is unlikely that oesophageal atresia could be produced by pressure from an aberrant vessel, since the oesophageal defect is present before the vascular tree has developed (Smith, 1957; Warkany, 1971). It is more probable that an absent segment of the oesophagus would allow a vessel to persist instead of disappearing during development. Another suggestion is that the aberrant vessel could lead to a deficient blood supply to the oesophagus, and thus to oesophageal atresia, in the same way that ischaemia

can lead to atresia of the small intestine (Earlam, 1972; Louw, 1959; Tsujimoto, Sherman, and Ravitch, 1972). However, this theory fails to explain the tracheo-oesophageal fistula which is nearly always present in patients with oesophageal atresia.

Although it appears that patients with oesophageal atresia and cardiovascular malformations have a particularly poor survival rate, the cardiovascular malformations are not necessarily causative in this respect because non-lethal defects, only discovered at necropsy, have been included. However, defects apparently non-lethal, such as a right-sided aortic arch, or an anomalous right subclavian artery, may have rather sinister implications in an infant with oesophageal atresia, in view of the known association between aortic arch, right subclavian artery, and third and fourth pharyngeal pouch anomalies (Freedom, Rosen, and Nadas, 1972). These patients can have a fairly wide spectrum of defects, the severest form being complete aplasia of both the thymus and parathyroid glands leading to profound hypocalcaemia and defective thymic-mediated cellular immune function (Freedom *et al.*, 1972). In a series of 23 cases with this syndrome of cardiovascular anomalies and anomalies of the third and fourth pharyngeal pouches, two cases also had oesophageal atresia (Freedom *et al.*, 1972). Since one assumes that cases of this syndrome who also have oesophageal atresia are more likely to die neonatally, before diagnosis of their immunological or metabolic deficit, it is hardly surprising that this association has not been noted in the present series. Presumably the diagnosis is always missed unless a physician thinks of it before the patient succumbs. It is worth noting that an association between a right-sided aortic arch and oesophageal anomalies has been noted in 12 German shepherd dogs and 12 dogs of other breeds, all of whom had other cardiac lesions (Mulvihill and Priester, 1973).

Many of the cardiovascular malformations were serious or lethal, the largest group of these being defects of the atrioventricular valves. Tricuspid atresia was present in 2 patients, and though the association of oesophageal atresia and tricuspid atresia has apparently only been specifically documented three times (Silver *et al.*, 1972), this is because the association of cardiovascular malformations and oesophageal atresia has so far attracted little systematic study. A common atrioventricular canal was present in 3 patients. Though both oesophageal atresia and endocardial cushion defects are associated with Down's syndrome, none of these 3 patients had Down's syndrome. However, it is interesting that one of them, who in addition had congenital cataracts (also associated with Down's syndrome), had a twin sib with Down's syndrome,

cataracts, and a normal heart and oesophagus. Mitral valve atresia, with a single ventricle and the 4 pulmonary veins uniting to form a single trunk before draining into the left atrium, was found in 2 patients with oesophageal atresia who were dizygotic female twins.

There was not a single case of isolated pulmonary stenosis, but otherwise most commonly encountered cardiovascular malformations were represented in this series. However, no particular lesion, other than defects of the fourth arch, seems to be associated with oesophageal atresia, and no other particular malformation pattern has emerged. Nora and Nora (1973) have suggested that there is a syndrome called the 'VACTEL' association, the essential features of which are vertebral, anal, cardiac, tracheal, oesophageal, and limb defects, and they reported on 10 such patients. Not one patient with this conglomeration of defects has appeared in the present survey, and there must be reservations about the validity of the 'VACTEL', 'VATER' (Quan and Smith, 1972), 'VACTERL' (Kaufman, 1973), 'VERTAL' (Balci *et al.*, 1973), or 'VATERR' (Quan and Smith, 1973) concepts and their almost never-ending possible variations.

The birthweight and intrauterine growth rate of patients with oesophageal atresia and cardiovascular malformations was lower than those with oesophageal atresia only, though not lower than those with oesophageal atresia and non-cardiovascular malformations. It is impossible to say whether the cardiovascular malformations retarded the fetal growth, or whether both share a common cause, but clearly the effect is not specific for cardiovascular defects as it was also found in those with non-cardiovascular malformations. In addition, patients with oesophageal atresia and cardiovascular malformations had a statistically significantly shorter gestation than patients with oesophageal atresia only, though the reasons for this are not clear. However, the shorter gestation is likely to be one contributory factor to the poor survival rate of patients with oesophageal atresia and cardiovascular malformations, as are their low birthweight and abnormally low fetal growth rate. Maternal age, paternal age, parity, marital status, and social class were not significantly different in cases of oesophageal atresia with cardiovascular malformations from those without cardiovascular malformations. No seasonal effect could be detected in the cases with cardiovascular malformations.

Apart from thalidomide, as a rare cause of oesophageal atresia, the aetiology of this malformation is unknown. Thus, the finding in 1959 by Knox of clustering in dates of birth of cases of oesophageal atresia, regardless of what other malformations they

had, was of some importance. He showed that within 2, and possibly 4 weeks of a case there was an increased risk of another, but that this was not evident after 4 weeks. In this study the same method of time interval analysis was used, but instead of taking the dates of birth the estimated dates of conception were taken. The results showed no clustering of cases of oesophageal atresia with cardiovascular malformations.

With changes in management of patients with oesophageal atresia, there is an increasing tendency to assess patients with cardiovascular malformations carefully, sometimes with the aid of cardiac catheterization, before surgical repair of the defect. In this way, patients who have cardiovascular lesions incompatible with life have been spared lengthy and futile thoracic surgery when a fatal outcome is inevitable. The present series of 96 patients is large enough to give a general impression of what kind of cardiovascular malformations are to be expected in patients with oesophageal atresia. Some of the defects, such as a right-sided aortic arch, and anomalous right subclavian artery, are worth bearing in mind, partly because of their importance to the surgeon during mediastinal dissection, and also because when discovered they should alert the medical team to the possibility of hypocalcaemia or immunological problems caused by parathyroid or thymic hypoplasia or agenesis.

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