Cardiol Young 2002; 12: 436–444

ISSN 1047-9511

Original Article

Coronary arterial abnormalities in pulmonary atresia with intact ventricular septum diagnosed during fetal life

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Abstract *Objectives*: To establish the prevalence of coronary arterial abnormalities in mid-trimester fetuses with pulmonary atresia with intact ventricular septum, and whether their presence correlates with right ventricular morphology. *Background:* The presence of coronary arterial fistulas significantly alters the surgical options and prognosis for patients with pulmonary atresia with intact ventricular septum. The lesion can reliably be diagnosed using fetal echocardiography, and further definition of the prognosis is important for counselling parents. *Methods:* We examined the hearts of 39 pathological specimens diagnosed during fetal life, 3 of whom died postnatally. Coronary arterial abnormalities were defined as non-connection of the left or right coronary arteries to the aorta, ostial stenosis, marked tortuosity, dilation, thickening or abnormal myocardial branching. Mild tortuosity, or myocardial bridging, were considered normal. We measured the dimensions of the tricuspid valve along with the inlet and outlet portions of the ventricles. Ebstein's malformation, tricuspid valvar dysplasia, and the presence or absence of the infundibulum, were especially noted. We examined also 12 normal hearts as controls. *Results:* Coronary arterial abnormalities were found in 14/39 (36%). The dimensions of the right ventricle and tricuspid valves, and the gestational ages of the fetuses, were compared for these 14 with the 25 having no abnormalities using independent t-tests. The gestational ages were similar, 21.9 vs 21.1 weeks. The mean dimensions of the tricuspid valve, median z-scores, and right ventricle were smaller, 2.9 vs 7.2 mm; $p < 0.002$; -4.46 vs 0.23; $p < 0.03$; and 6.9 vs 13.7 mm; $p < 0.002$, for those with coronary arterial abnormalities. Ebstein's malformation, or dysplasia of the tricuspid valve, was present in 4 of 14 with, vs 15 of 25 without, coronary arterial abnormalities. A patent infundibulum was noted in 34 of 39 specimens. *Conclusions:* Mid-trimester fetuses with pulmonary atresia with intact ventricular septum already exhibit coronary arterial abnormalities, with a prevalence of 36%. The presence of a patent infundibulum confirms that atresia of the pulmonary valve is an acquired process. Coronary arterial abnormalities are seen in 50% of those with hypoplastic right ventricles, but less frequently in the presence of well developed ventricles. This is important information for those involved in counselling parents.

Keywords: Fetal echocardiography; Ebstein's malformation; fistulous communications; tricuspid valvar dysplasia

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Supported by a grant from The British Heart Foundation.

Accepted for publication 21 June 2002

THE CARDIAC MALFORMATION CONSISTING OF pulmonary atresia with an intact ventricular septum encompasses varying degrees of tricuspid valvar abnormalities,[1–10] right ventricular hypoplasia, and abnormalities of the coronary arteries. The

surgical algorithm for successful management of this lesion depends on the severity of each of these associated lesions.[5,11–19] Fetal diagnosis is now well established,[20–26] and it has been suggested that the pulmonary valve may become atretic during fetal life.[25–27] The specific factors responsible for the onset, extent, and severity of coronary arterial abnormalities are not known, although there are hypotheses with regard to their embryological origin. In this respect, fetal investigation offers the potential to chart the evolution of the changes. There are case reports of fetuses with coronary arterial fistulas, and two recent larger studies.[22–25] The purpose of our study was to document the frequency and extent of coronary arterial abnormalities in cases of pulmonary atresia with intact ventricular septum seen in fetal life and coming to autopsy. We sought to correlate their association with hypoplasia of the right ventricle and tricuspid valve in order to increase the understanding of this condition.

Methods

We examined 39 hearts obtained at autopsy from fetuses diagnosed with pulmonary atresia with intact ventricular septum at the Guy's Fetal Cardiology Unit from 1984 to 1996. During that period, 85 fetuses had been diagnosed with this entity. All autopsied examples were available for study. Gestational ages ranged between 16 and 40 weeks, although only 6 fetuses were later than 24 weeks gestation. Three of the specimens were from babies diagnosed during fetal life who had undergone either surgical intervention or radiofrequency ablation of the pulmonary valve postnatally. Our examination included measurements of the tricuspid valvar orifice at the annulus, right ventricular inflow dimension from the atrioventricular valvar hinge-point to the apex, inspection of the right ventricular endocardial surface for evidence of endocardial fibroelastosis, the tricuspid valve for dysplasia, stenosis, and Ebstein's malformation, and evaluation of the right ventricular outflow tract. We also looked carefully for ventriculo-coronary fistulous connections, examined the coronary arterial orifices, and noted abnormalities of branching, tortuosity, thickening or dilation on the external surface of the heart. The right ventricular cavity was also inspected for the presence of obvious fistulas between the coronary arteries and the ventricular cavities. These features were compared with findings on hearts obtained from 12 fetuses with normal cardiac anatomy.

Serial histological sectioning was performed on four abnormal fetuses of 18, 20, 22 and 29 weeks gestation. We did not perform serial sectioning on all of the specimens as they would be lost to further education and research. After careful examination, measurement and photography, the entire heart was dehydrated through graded alcohol and embedded in paraffin wax following the technique usually used in our laboratory to study the conduction system. The hearts were then serially sectioned along the short axis of the ventricular mass, cutting sections at a thickness of 10 microns. All the sections were retained and, initially, one section in every 25 cut was mounted for three small hearts and 1 in 50 for the other, larger heart. The sections were stained using the Masson's trichrome techniques. When necessary, intermediate sections were mounted and stained in areas of particular interest along the coronary arterial pathway.[28] The echocardiograms of some of the fetuses were reviewed to determine whether coronary arterial abnormalities were visible. Autopsy angiography was attempted in four cases.

Criterions for abnormal coronary arteries

The coronary arteries were considered abnormal when they showed any of the following features: non-connection with aorta; orificial stenosis; abnormal patterns of branching; abnormal tortuosity; thickening or dilation; and visible fistulous communications with the right ventricular cavity. The presence of intertrabecular spaces, mild myocardial bridging, or mild tortuosity of the coronary arteries as noted on external inspection were considered as normal variations.

Specimens were then divided into groups with and without gross evidence of coronary arterial abnormalities. The two groups were evaluated for the presence of Ebstein's malformation or tricuspid valvar dysplasia. Independent t-tests and chi squared tests were used to compare the data from the two groups.

Results

Of the 39 specimens, 14 exhibited abnormalities of the coronary arteries. These abnormalities are listed in Table 1. Four specimens had abnormalities of both

Table 1. Coronary arterial abnormalities found in the selected specimens.

Number of specimens	Type of coronary abnormality
1	Non-connection of both right and left coronaries
1	Atresia of orifice of right coronary artery
1	Stenosis of orifice of right coronary artery
2	Visible fistulas within right ventricular cavity
8	Right coronary arterial dilation, thickening and/or tortuosity
7	Left coronary arterial dilation, thickening and/or tortuosity
1	Circumflex arterial dilation, thickening and/or tortuosity

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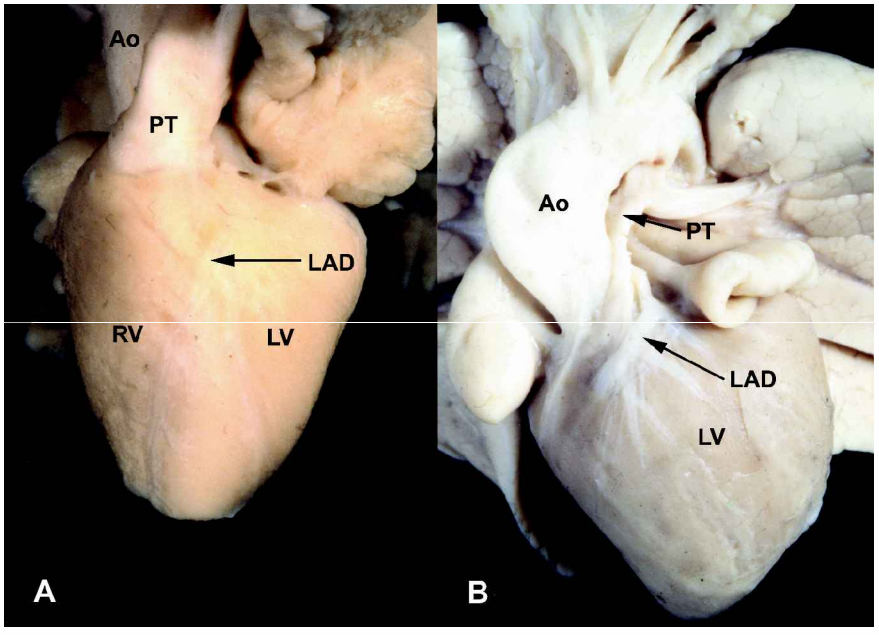

Figure 1.
(A) Appearance of normal left anterior descending coronary artery; (B) dilated proximal segment of the left anterior artery. Ao: aorta; LV: left ventricle; PT: pulmonary trunk; RV: right ventricle.

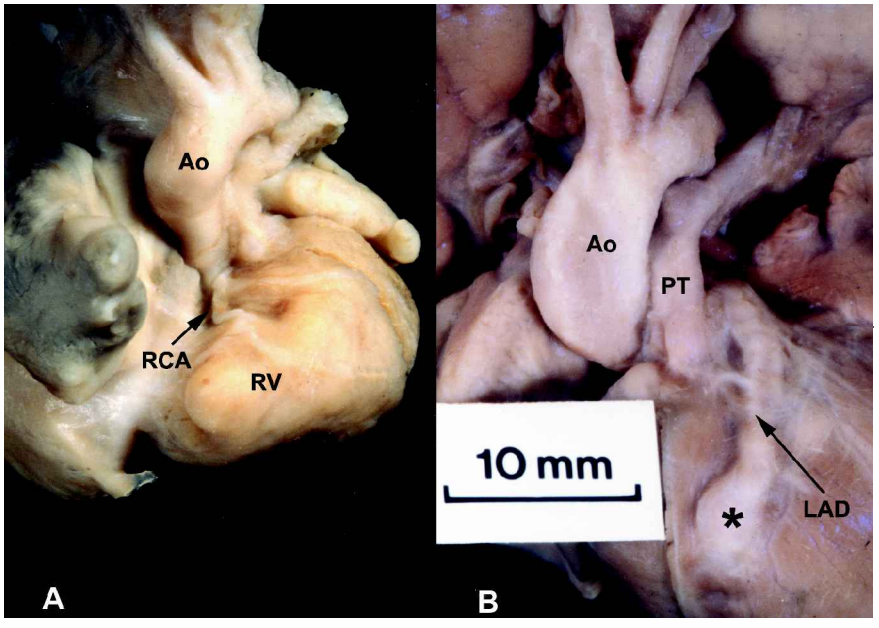

Figure 2.
(A) Tortuous right coronary artery (RCA) with prominent right ventricular free wall branches; (B) markedly dilated, irregular left anterior descending coronary artery (LAD) with further dilation (*) indicating site of fistula. Ao: aorta; RV: right ventricle; PT: pulmonary trunk.

the left anterior descending and right coronary arteries. One specimen with orificial atresia of the right coronary artery had additional abnormalities of the left anterior descending and circumflex arteries. The specimen with stenosis of the orifice of the right coronary artery showed a normal left system. Examples are shown in Figures 1–3. Of the hearts studied histologically, right dominant coronary arterial patterns were seen in two specimens, from fetuses of 20 and 29 weeks gestation, whereas the other two specimens, from fetuses of 18 and 22 weeks, did not have a well-defined inferior (posterior) descending coronary artery. Serial sectioning confirmed our observations of fistulous ventriculo-coronary connections in all four specimens. Multiple fistulous connections between the right ventricular cavity and the inferior and/or anterior descending coronary arteries were found in three specimens, from fetuses of 18, 20, and 29 weeks gestation, respectively (Fig. 4a). These three hearts had hypoplastic right ventricles. The cavity was lined with endocardial fibroelastosis which was particularly noticeable in the outflow tract. Only one fistula between the anterior descending artery and the right ventricular cavity was found

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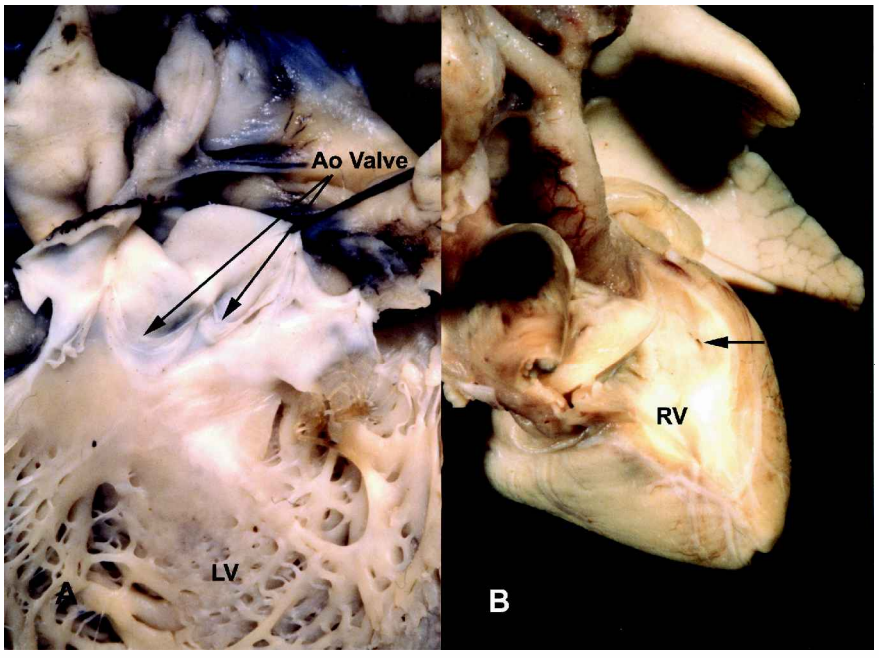

Figure 3.
(A) Absence of a coronary orifice with the aortic valvar sinuses is shown in an opened specimen; (B) right ventricular view showing the orifice of a coronary cameral fistula (arrow). Ao Valve: aortic valve; RV: right ventricle.

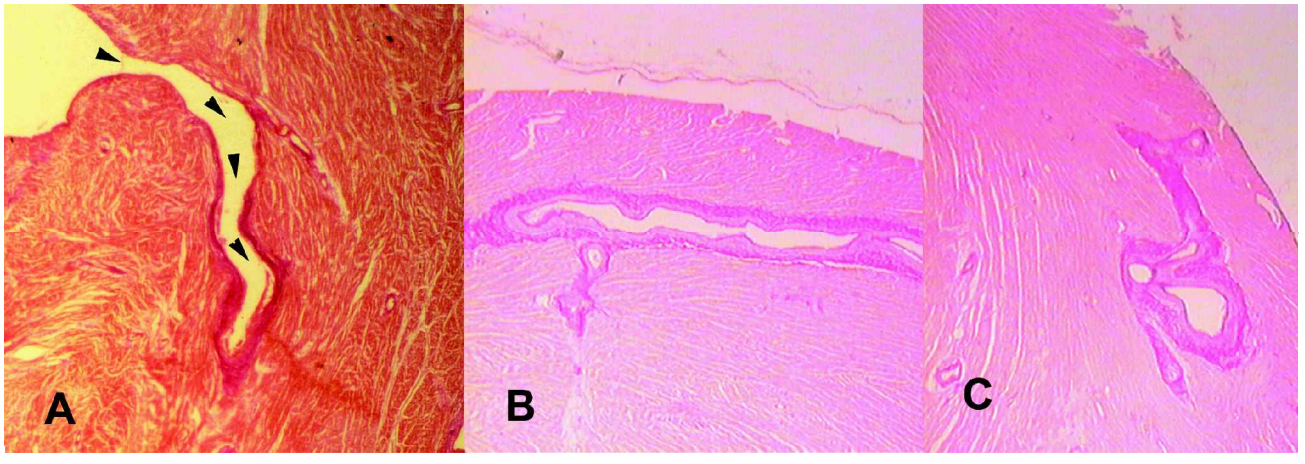

Figure 4.
(A) Fistulous communication (arrow heads) between the right ventricular cavity and a septal artery; (B) intra-myocardial course of the left anterior descending coronary artery; and (C) tortuous left anterior descending coronary artery.

in the fourth specimen, from a fetus of 22 weeks gestation. The ventricular cavity was also hypoplastic in this heart, but it was not lined with endocardial fibroelastosis.

The orifices of the coronary arteries originated from the appropriate aortic sinuses in all four hearts. A flap of aortic wall was found at the orifice of the left coronary artery in one heart from a fetus of 22 weeks (Fig. 5a). This feature had not been noticed on gross examination. In this heart, a patch of fibrous tissue was seen in the mid-portion of the ventricular septum, and the papillary muscles of the mitral valve were also affected by patches of fibrous tissue and calcification (Fig. 5b).

In general, the epicardial and intramural coronary arteries were prominent owing to thickening of their adventitial layers. The anterior descending coronary artery was tortuous and intramyocardial for much of its course in two specimens of 18 and 22 weeks gestation (Fig. 4b, c). Stenotic lesions were not seen in the arterial lumens except in two specimens. Intimal proliferation was seen in the anterior descending coronary artery close to the site of a fistula in the youngest specimen, which was from a fetus of 18 weeks gestation. The oldest specimen, of 29 weeks gestation, showed localized areas of medial hypertrophy in the anterior and inferior descending coronary arteries. These were not located close to fistulas.

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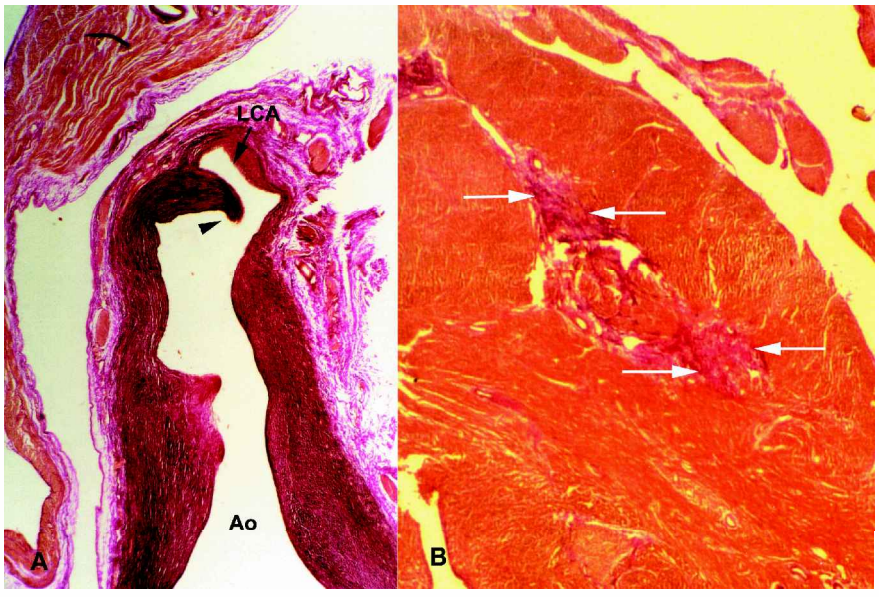

Figure 5.
(A) A flap (arrow head) of aortic wall guards the orifice of the left coronary artery; with (B) a transverse section through the ventricular septum showing a fibrotic area (arrows). Ao: aorta; LCA: left coronary artery.

Table 2. A comparison of gestational ages, valvar, and right ventricular function among patients with normal and abnormal coronary arteries.

Group	Gestation (weeks) (mean ± sd)	TV (mm) (mean ± sd)	TV z-score (med & range)	RV (mm) (mean ± sd)	Ebstein's or TV abnormality	
					Present	Absent
Normal coronary arteries	21.9 ± 6.3	7.2 ± 4.6	0.23 (−16.6–20.1)	13.7 ± 7.4	15 (38.5%)	10 (25.6%)
Abnormal coronary arteries	21.1 ± 2.9	2.8 ± 1.6	−4.46 (−5.6–7.3)	6.9 ± 3.2	4 (10.3%)	10 (25.6%)
	NS	p = 0.002	p = 0.03	p = 0.002		

Of the specimens, 34 had a persistent infundibulum which could be traced to the pulmonary valve. Two specimens without a patent infundibulum had severe Ebstein's malformation, and the other three had severely hypoplastic right ventricles. Marked endocardial fibroelastosis of the right ventricle was visible in three specimens, with one further specimen showing involvement of the papillary muscle. One of the specimens with endocardial fibroelastosis had a stenotic right coronary orifice and hypoplasia of the right coronary artery with mild tortuosity of the left anterior descending coronary artery.

Review of some of the echocardiograms had not proved helpful in recognizing fetuses with coronary arterial abnormalities except in the fetus already reported. Autopsy angiography was unsuccessful.

A comparison of gestational ages, tricuspid valvar annular size and median z-scores, right ventricular dimension, presence or absence of Ebstein's malformation, and tricuspid valvar dysplasia for the two groups is shown in Table 2. As the gestational ages were not significantly different between the two groups, the absolute tricuspid valvar and right ventricular sizes were compared. These were greater in the fetuses without coronary arterial abnormalities. The median tricuspid valve z-score for those with coronary abnormalities was significantly lower than those with normal coronary arteries ($p < 0.03$); the range of z-scores was narrower but, of note, the specimen with the smallest tricuspid z-score (−16.6) had normal coronary arteries. Tricuspid valvar dysplasia, and Ebstein's malformation, were seen more commonly in fetuses without coronary arterial abnormalities. In those specimens without tricuspid valvar abnormalities, there were equal numbers in the two groups. The prevalence without valvar abnormalities was higher in the groups with coronary arterial abnormalities since the total number in this group was smaller. Of interest, all three specimens with absent infundibulums, low tricuspid valve z-scores, and normal tricuspid valves had normal coronary arteries. One of the two specimens with Ebstein malformation and absent infundibulum had normal coronary arteries.

When we compared dimensions against gestational ages in patients with and without coronary arterial abnormalities, 11 of 18 fetal hearts with right ventricular inflow lengths below 2 standard deviations from the norm had coronary arterial abnormalities.

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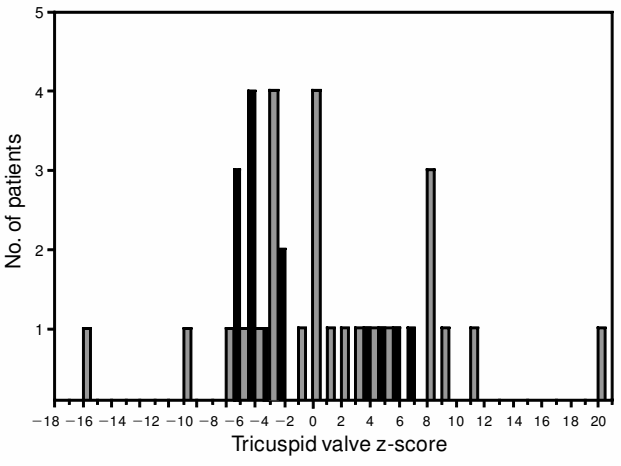

Figure 6.
Standardized tricuspid valvar diameters for patients with (■) and without (▣) coronary arterial abnormalities.

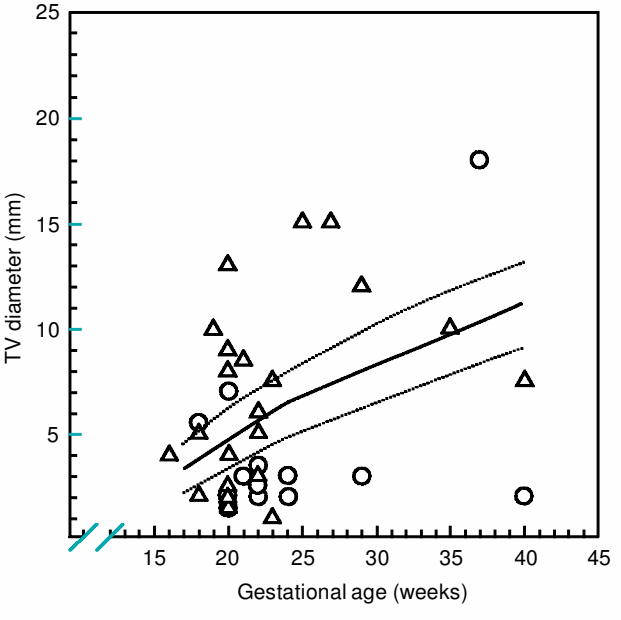

Figure 7.
The relationship between tricuspid valvar diameter and gestational age in fetal hearts with pulmonary atresia and intact ventricular septum and either normal (△) or abnormal (○) coronary arteries.[43] *TV: tricuspid valve.*

Of 19 fetal hearts with a tricuspid valvar diameter below 2 standard deviations, 11 had coronary arterial abnormalities, the proportion corresponding closely with the results for the length of the right ventricular inflow. Figure 6 shows the distribution of specimens with and without coronary arterial abnormalities and their corresponding tricuspid valve z-scores. A plot of the tricuspid valve diameter of all specimens with normal mean and 95% confidence intervals is shown in Figure 7.

Discussion

Our findings show that coronary arterial abnormalities develop early in fetuses with pulmonary atresia and intact ventricular septum, being present already by the second trimester. Thus, the potential for further deterioration is present throughout the second and third trimesters. This has obvious possible consequences in terms of myocardial ischemia and endocardial fibroelastosis due to the deleterious effects on myocardial perfusion of aortic run-off into the right ventricle or coronary arterial stenosis in a pressure-loaded ventricle. Despite these concerns, fetuses with pulmonary atresia and intact ventricular septum seem to survive to term. In general, tricuspid regurgitation due to severe Ebstein's malformation or tricuspid valvar dysplasia is more likely to cause fetal death.[29,30] Survival may be due to the fact that, as the oxygen saturation does not differ significantly between the aorta and right ventricle, and the pressure is equal in both arterial trunks, hypoxic coronary arterial perfusion does not occur. In addition, diastolic coronary arterial run-off into the right ventricle may be limited by the smaller right ventricular size, with its higher systolic pressure maintaining myocardial perfusion distal to the coronary stenosis.

It is not possible to use our findings to define the true prevalence or severity of coronary arterial involvement. This is because the data came from a highly-selected population of fetuses, mostly from the early second trimester, diagnosed antenatally, usually from an abnormality noted on a four-chamber view used for screening. This has a reported rate of success between 20 and 70%. Our method of selection of coronary arterial abnormalities by inspection could also be an underestimate of the true incidence, as coronary arterial and right ventricular angiography are usually used post-natally to detect and define such abnormalities.[1,7,11,13] The use of colour mapping and Doppler may help determine a more accurate incidence in fetal cases.[23,25] Further, the number of coronary artery abnormalities seen in one specimen may be less relevant, clinically, than the presence of orificial atresia as the sole lesion in another specimen. Postnatal autopsy series also describe coronary arterial abnormalities,[5–8,10] but these reports are also likely to represent the severest end of the spectrum. They do not detect lesser involvement, and it is known that coronary arterial abnormalities involute following relief of obstruction of the right ventricular outflow tract. The suggested frequency for coronary arterial abnormalities in population-based series is of the order of 40–46% of cases.[31,32] Coronary arterial abnormalities, nonetheless, occur more frequently, and are more severe, in the patients with greater degrees of hypoplasia of the right ventricle.[2,5,7,10,13,14,18,19] It is likely,

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therefore, that our own autopsy series represents the more severe end of the spectrum.

With this in mind, it is noteworthy that specimens having hypoplastic right ventricles, or hypoplastic tricuspid valves, were seen almost as frequently in our material without as with coronary arterial abnormalities. In consequence, the findings of right ventricular hypoplasia during fetal life cannot be considered predictive for coronary arterial abnormalities. It is not clear why the specimens without infundibulums did not have any coronary artery abnormalities, a finding not confirmed by post-natal angiography. Perhaps the smaller number in this series which were diagnosed so early in fetal life did not allow for progressive obliteration of the infundibulum in others with coronary arterial abnormalities. On the other hand, if the right ventricular cavity is of good size, especially if there is Ebstein's malformation, the fetus is likely to have normal coronary arteries. This is also suggested from experience in postnatal life.[2,5,7,10,13,14,18,19] These findings are of potential importance in counselling parents, and also for possible intervention when this become feasible. Although we found that echocardiography was of limited value in visualizing coronary artery abnormalities, colour mapping and Doppler were either not available or in their early stages for most of our time-frame. In more recent cases, the presence of coronary arterial abnormalities has been better documented during fetal echocardiography.[23–25] As noted by Maeno et al.[23] extensive interrogation using these modalities increased the diagnostic accuracy of the test, and provided additional information relating to the potential severity of the lesion. It is not clear whether it is possible to define right ventricular "coronary arterial dependence" from fetal echocardiography.

As anticipated, serial histological sectioning confirmed the presence of coronary fistulous connections to the right ventricular cavity. Three of the four specimens sectioned showed right ventricular endocardial fibroelastosis. The unusual shelf observed at the orifice of one coronary artery may be due to incomplete coronary ingrowth, or may be secondary to abnormal retrograde and antegrade pressure or flow.

Limitations

We have already made reference to several of the limitations of our study. These include the highly selective nature of the study, and the selection of specimens from the more severe end of the spectrum of pulmonary atresia and intact ventricular septum. Another limitation is the fact that not all specimens were examined serially to confirm whether the external coronary arterial abnormalities did, in fact, represent fistulous connections in all cases. This would have lost the specimens from any further education and research. We do not know how many connections were present in fetuses in whom the external appearances of the coronary arteries appeared normal. Unfortunately, autopsy angiography was not successful.

Developmental implications

In the early embryonic stages of formation of the heart, the right ventricular myocardium initially obtains oxygen directly from the cavity. The embryonic development of coronary arteries has been reviewed recently and is briefly summarized.[33–36] Pro-epithelial tissue lies between the sinus horns and hepatic primordium and provides angioblasts, fibroblasts and blood cells that form the epicardium. A progenitor population of coronary smooth muscle, perivascular connective tissue and endothelial cells migrate from the pro-epicardium to the tubular heart along with precursers of the epicardial mantle. Sinusoids and discontinuous channels form initially in the subepicardium and fuse into networks of capillaries which grow into the myocardium. Further migration into the channels occurs, this time of smooth muscle progenitors, and differentiation produces more recognisable blood vessels. Ingrowth of two of these vessels into the aorta connects the lumen of the aorta and the coronary arterial tree.[33,34]

The vascular growth factors, vascular endothelial growth factor and basic fibroblastic growth factor, are almost certainly involved in this process. The stimulus for their expression is not fully known, but haemodynamic factors are involved.

Although earlier studies have cited the presence of cameral-capillary connections,[7] Hutchins et al.,[37] could find none in their study of serial sections of human embryonic hearts. They concluded that, in the absence of these connections, their development in fetuses with pulmonary outflow tract obstruction must be due to an abnormal process of proliferation and growth of the capillary and coronary arterial network at this developmentally sensitive time. Recently, Manner[38] reported a study of quail-chick chimeras, in which he found embryonic ventriculo-coronary communications which disappeared during normal development. Further work to establish how the abnormal haemodynamics are responsible for the signalling and production of the abnormal growth of these vessels would be most interesting.

Another hypothesis based on examination of pathologic specimens suggests there are two forms of this disease: one with endocardial fibroelastosis, myocardial sinusoids, but no coronary cameral fistulas; and the other form with coronary cameral fistulas and no endocardial fibroelastosis.[39] The presence of coronary cameral fistulas indicates a separate disease entity.

To support this, it has been demonstrated that inhibition of epicardial cell growth in an embryonic quail-chick chimera model may result in failure of the coronary ostia to develop and in the production of coronary cameral fistulas in hearts with major abnormalities in septation and other malformations.[40] It is possible that the quail-chick chimera model used by Manner et al.[38] represents the rescue phase of the experiment conducted by Gittenberger-de Groot et al.[40] Endocardial fibroelastosis was found in our specimens with and without coronary artery fistulas. We believe that it is difficult to develop a hypothesis to explain different forms of this condition based on limited fetal echocardiography studies or evaluation of small numbers of pathological specimens without taking the larger clinical experience into consideration.

Information from fetal echocardiographic and postnatal observations may add more information to explain the pathogenic mechanisms of pulmonary atresia with intact ventricular septum. Lougheed et al.[41] reported that 7% of twin-to-twin pregnancies are complicated by the recipient twin developing varying degrees of right ventricular hypertrophy, outflow tract and valvar obstruction which may progress to atresia. The interesting observation they made was that progression of outflow tract obstruction may occur after the hemodynamic stimulus has been corrected. This may be in-utero or even post-natally. These findings suggest that the fetal right ventricle may develop progressive hypertrophy and outflow obstruction as a generalized response to different hemodynamic loads. It sheds doubt on the initiating pathogenetic event causing pulmonary atresia with intact ventricular septum which has been previously thought to be an abnormality of the pulmonary valve. It may, therefore, be a hemodynamic abnormality, an abnormality of the pulmonary valve, the result of a malfunction of a gene at a specific time in embryogenesis, or a combination of these events.

Our findings, therefore, are consistent with an earlier theory[42] that the presence of coronary arterial abnormalities depends on the relative timing and degree of right ventricular obstruction, coupled with the degree of the "safety valve" effect of tricuspid valvar incompetence at the time of normal development of the capillaries and the coronary arterial system. These coronary cameral connections are likely an abnormal process rather than persistence of normal capillary connections. Thus, severe degrees of right ventricular hypoplasia are likely due to early obstruction and decreased right ventricular flow, and hence, are associated with a higher prevalence of coronary arterial abnormalities. In cases with Ebstein's malformation, in which the potential increase in right ventricular pressure is relieved by tricuspid incompetence, there is a low prevalence of coronary arterial abnormalities. Those fetuses with hypoplastic right ventricles without coronary arterial abnormalities may have experienced a gradual build-up of right ventricular obstruction occurring after this sensitive period of embryogenesis. This would be consistent with both the high frequency of infundibular patency in this series, and with the fetal echocardiographic observations of acquired pulmonary atresia. What remains unclear is the nature of the initiating event in its pathogenesis.

Conclusions

Our study of 39 fetal heart specimens with pulmonary atresia intact ventricular septum has, already at midtrimester, demonstrated coronary arterial abnormalities in one-third of cases, which is similar to the postnatal incidence. Half the cases with hypoplastic right ventricles, however, had coronary arterial abnormalities. This is of importance in understanding the natural history of this complication, for counselling after fetal diagnosis and, perhaps, for those contemplating future fetal intervention.

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