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Surgery for Congenital Heart Disease

Disease of the left ventricle in pulmonary atresia
with intact ventricular septum

The limiting factor for long-lasting successful surgical intervention?

Eight hearts with pulmonary atresia with intact ventricular septum were studied grossly and microscopically. The right ventricle was composed of inlet, infundibular, and trabecular portions in two hearts, without trabecular portions in three hearts, and consisted of an inlet part only in another three hearts. Pulmonary atresia was classified as membranous in two hearts; the other six hearts had muscular atresia. The left ventricle showed a range of abnormalities, albeit mostly discrete. A mitral valve with short tendinous chords was present in four hearts; one of these had a cleft mitral valve. All hearts (except the heart of a 1-day-old neonate) had a prominent subaortic septal bulge. All hearts had left ventricular hypertrophy, which exceeded twice the standard deviation of normal in two patients. None of the hearts had histologic features of hypertrophic cardiomyopathy. The density of intramyocardial coronary arteries was normal in each patient, but medial thickening (20 to 100 μ m diameter arteries) had occurred in four patients. Signs of acute myocardial ischemia (hydropic cell swelling) were present in all; one heart (the oldest case of 6 months) contained areas of replacement fibrosis and calcifications indicative of previous infarction. Quantification of the volume density of endomysial (interfiber) collagen (Picrosirius red microspectrophotometry) showed high levels in all, within the range of normal in five patients, but exceeding twice the standard deviation of normal in three patients. In all cases the values obtained in the subendocardial layers were higher than those obtained subepicardially. The observations show that the left ventricle in hearts with pulmonary atresia with intact ventricular septum contains abnormalities that may render the left ventricle less capable to cope with a volume

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load. The high values of endomysial (interfiber) collagen suggest chronic ischemia in relation to left ventricular hypertrophy as the main mechanism involved. Therefore, as a late consequence, the left ventricle could be the limiting factor for long-lasting successful surgical intervention. (J THORAC CARDIOVASC SURG 1994;108:1-8)

The anatomic status of the right ventricle (RV) is the keystone for surgical treatment in patients with pulmonary atresia with intact ventricular septum¹⁻³—a point illustrated by the analysis of hearts of patients who died after operation⁴ and by the observation that tailoring treatment to RV anatomy results in a lower overall mortality.⁵ A retrospective clinical study showed that the determinants of outcome of surgical procedures were dominated largely by anatomic variables, such as a tricuspid/mitral ratio of less than 0.6, an obliterated RV apex, and RV fistulous communications.⁶ A recent report of a large prospective multi-institutional study of the outcome of surgical procedures in neonates showed that a small diameter of the tricuspid valve and severe RV coronary dependency were the anatomic risk factors for time-related death.⁷ However, some patients have a depressed left ventricular (LV) ejection fraction, which may be associated with a diminished myocardial mass.⁸⁻¹¹ The preoperative evaluation of 15 patients with pulmonary atresia with intact ventricular septum showed seven patients with impaired LV compliance.⁹ Six of these seven patients received an initial palliative systemic-to-pulmonary shunt (a Waterston shunt), a 1-day-old baby underwent a pulmonary valvotomy only, but none survived infancy. A more recent analysis of nine neonates who died as a result of surgical procedures (shunt, valvotomy, or both) showed at preoperative evaluation a depressed LV ejection fraction and a decrease in LV contractility.¹² Morphologic analysis in these cases showed an overall increase in LV fibrous tissue in all and foci of LV myocardial infarction in two.¹²

In light of the previously mentioned scenario, we have looked specifically into the disease, both grossly and microscopically, of the LV in hearts with pulmonary atresia with intact ventricular septum.

Patients and methods

The study is based on eight heart specimens with pulmonary atresia and intact ventricular septum. Six hearts were from neonates, 1 to 7 days of age; five of these patients died before operation, whereas the sixth patient died at the time of a shunt procedure. One heart was from a neonate who died 3 weeks after birth without surgical intervention. The remaining heart was from an infant 6 months of age. This patient died after a modified Blalock-Taussig shunt. Twenty-four normal hearts were selected as controls. These specimens were age-matched as fol-

Fig. 1. Opened LV of a heart with pulmonary atresia with intact ventricular septum and a distinct subaortic septal bulge.

lows: 14 hearts were obtained from neonates of 1 to 7 days of age, three hearts were from babies 3 to 4 weeks of age, and seven hearts were obtained from babies 4 to 8 months of age.

Gross observations. The RV was analyzed on the basis of the tripartite concept.¹ The size of the RV cavity, its component make-up, as well as the structure of the tricuspid valve and that of the atretic pulmonary orifice were observed together with other features, such as the presence or absence of endocardial fibroelastosis and ventricular-coronary artery fistulas. Cross sections at 1 mm intervals were made along the epicardial course of the main coronary arteries.

The LV was studied grossly by focusing primarily on wall thickness and the structure of the mitral valve. The thickness of the LV free wall was measured at the base of the heart, closely underneath the mitral valve, and at the apex. Trabeculae were excluded.

Table I. The relevant morphologic findings in hearts with pulmonary atresia with intact ventricular septum

Case	Age at death	Tripartite RV structure			Ebstein's anomaly of TV	Distorted LV geometry (septal bulge)	Short chords of MV	Ventricular–coronary artery fistulas
		Inlet	Infundibular	Trabecular				
1*	1 day	+	+	+	—	—	—	—
2	1 day	+	+	—	—	+	—	+
3	2 days	+	+	—	—	+	+	—
4	2 days	+	—	—	—	+	—	—
5*	3 days	+	+	+	—	+	+	—
6	7 days	+	—	—	+	+	+	—
7	3 weeks	+	—	—	+	+	—	—
8	6 months	+	+	—	+	+	+	—

TV, Tricuspid valve; MV, mitral valve.

*Hearts with valvar atresia; all remaining specimens had muscular atresia.

Table II. LV wall thickness in hearts with pulmonary atresia with intact ventricular septum compared with mean values and standard deviation in age-matched normal hearts

Case	LV wall thickness (mm)					
	Basal part			Apical part		
	Age group			Age group		
	0-7 days	3-4 weeks	5-7 months	0-7 days	3-4 weeks	5-7 months
PA-IVS						
1	3			2		
2	5			4		
3	4			3		
4	8*			7*		
5	5			4		
6	5			4		
7		6			5	
8			10*			7
Normal hearts	4.6 ± 0.6	6.3 ± 0.5	7.7 ± 0.7	3.5 ± 0.7	5.7 ± 0.5	6.8 ± 0.7

Values are expressed as mean ± standard deviation. PA-IVS, Hearts with pulmonary atresia with intact ventricular septum.

*These exceed the value of 2× the standard deviation in normal hearts.

The results were compared with those obtained from similar measurements in the age-matched normal hearts.

Microscopic observations. The LV myocardium was studied in each of the eight hearts with pulmonary atresia and intact ventricular septum, and the results were compared with those obtained from the study of 12 of the 24 normal hearts. The latter were age-matched as follows: six hearts from patients between 0 and 7 days of age, three hearts from patients 3 to 4 weeks of age, and three hearts from patients between 5 and 7 months of age. A block of tissue was taken from the LV wall at the site used for the measurements of wall thickness. The tissue was fixed in 4% buffered formalin and embedded in paraplast. Sections were cut at 7 μm thickness and stained with hematoxylin and eosin, an elastic tissue stain and with Picrosirius red F3BA stain, which stains selectively for collagen.¹³

Analysis of intramyocardial coronary arteries. Two hundred microscopic fields were screened at a magnification of ×230. A distinction was made among arteries less than 20 μm in external diameter, those between 20 and 100 μm, and those

greater than 100 μm in external diameter. The measurements were taken with an ocular micrometer. The total surface area studied was calculated and the density of coronary arteries was then expressed per square millimeter. The mean medial thickness of the intramyocardial coronary arteries was expressed as a percentage of the external diameter. To be included in this morphometric study, the vessels had to be either round or oval on cross section and had to show a distinct media; for the vessels that met the latter criterion reason, vessels less than 20 μm in diameter were excluded from the study of medial thickness because they lacked a distinct media.

Quantification of myocardial fibrosis. The volume density of collagen in the LV myocardium was quantified with microdensitophotometry on sections stained with picro Sirius red F3BA.^{13,14}

Statistical analysis. Data of normal hearts were expressed as the mean ± standard deviation. Data obtained in hearts with pulmonary atresia with intact ventricular septum outside a range of the mean value of normal ± 2 standard deviation were regarded abnormal.

Fig. 2. The opened left side of a heart with pulmonary atresia with intact ventricular septum (case 8). **A**, Small coronary sinus type atrial septal defect caused by a partially unroofed coronary sinus. The anterior leaflet of the mitral valve shows a small central cleft. The tendinous chords of the mitral valve are short and irregularly thickened with an abnormal branching pattern (see **B**). The LV wall shows marked hypertrophy at the basal part, exceeding twice the standard deviation of the mean value of age-matched normal hearts. **B**, Detail of the almost dysplastic tendinous chords arising from the posteromedial papillary muscle and insertion into the corresponding mitral valve leaflets.

Table III. Density and medial thickness of intramyocardial coronary arteries in hearts with pulmonary atresia with intact ventricular septum compared with mean values and standard deviation in normal hearts

Case	Density (mm ²)			Medial thickness (%)	
	<20 μ m	20-100 μ m	>100 μ m	20-100 μ m	>100 μ m
PA-IVS					
1	0.16	0.71	0.04	12*	—
2	0.24	0.67	0.04	16*	18
3	0.24	1.41	0.20	10	9
4	0.47	1.65	0.04	14*	10
5	0.24	0.98	0.04	8	7
6	0.35	1.68	—	7	6
7	0.35	1.10	0.04	9	8
8	0.39	1.06	—	13*	10
Normal hearts	0.36 $\pm$ 0.10	1.24 $\pm$ 0.35	0.09 $\pm$ 0.06	9 $\pm$ 1	8 $\pm$ 3

Values are expressed as mean $\pm$ standard deviation. PA-IVS, Hearts with pulmonary atresia with intact ventricular septum.

*These exceed the value of 2 $\times$ the standard deviation in normal hearts.

Results

Gross observations. All eight hearts with pulmonary atresia and intact ventricular septum were of the hypertrophic type. The relevant morphologic findings are summarized in Table I.

Each of the eight hearts, none of them with a decompressed RV, had a dilated LV cavity. In seven of the eight hearts, the geometry of the LV cavity was compromised by a distinct subaortic septal bulge (Fig. 1). In the heart

of the oldest infant (6 months), this area showed distinct endocardial thickening, which correlated with the facing anterior leaflet of the mitral valve. The septal convexity towards the left corresponded with marked RV hypertrophy.

Four hearts showed short and almost dysplastic tendinous chords of the mitral valve (Fig. 2). One of these hearts had a small central cleft of the anterior mitral valve leaflet and a small coronary sinus–type atrial septal defect

Table IV. Picrosirius red values of the myocardium in hearts with pulmonary atresia with intact ventricular septum compared with mean values and standard deviation in normal hearts

Case	Picrosirius red value	
	Subendocardium	Subepicardium
PA-IVS		
1	41	37
2	44	42
3	50*	46*
4	53*	49*
5	43	40
6	38	33
7	41	38
8	54*	37
Normal hearts	39 ± 3†	36 ± 3†

*These exceed the value of 2× the standard deviation in normal hearts.

†Values are mean ± standard deviation.

as a result of a partially unroofed coronary sinus (Fig. 2; case 8). No abnormalities of the aortic valve were seen. Fibroelastosis of the LV endocardium was not encountered.

Abnormal communications between the RV cavity and the coronary arteries were found in one case. Both the right and the left coronary artery had a fistulous connection with the RV cavity. No interruption or stenosis of coronary arteries was found.

LV wall thickness is shown in Table II. Two hearts (cases 4 and 8) showed marked hypertrophy of the LV wall, which exceeded twice the standard deviation of the mean value of the age-matched normal hearts (Fig. 2). In one instance (case 4, 2 days of age), the increased LV wall thickness was present both at the basal part of the heart and at the apex; in the second case (case 8, 6 months of age), the increased wall thickness was present only at the basal part of the LV.

Microscopic observations. No sign of myocardial disorganization was found in any of these hearts, including the two cases with excessive LV wall thickness, other than the usual degrees of fiber disarray.¹⁵

In each case, the LV myocardium showed hydropic cell swelling of myocytes in the subendocardial zone. Coagulation necrosis was not encountered. However, one heart (case 8) contained areas with extensive myocardial replacement fibrosis of the LV (Fig. 3) with patchy calcifications in the subendocardial layers.

The density of the intramyocardial coronary arteries in the LV of hearts with pulmonary atresia and intact ventricular septum was similar to that seen in the normal control hearts (Table III). However, four hearts had a marked increase in mean medial thickness of arteries with

Fig. 3. Micrograph of the LV myocardium with extensive patchy replacement fibrosis. Picrosirius red stain, magnification ×35.

an external diameter between 20 and 100 μm, compared with normal hearts (Table III). Intimal thickening of intramyocardial coronary arteries was not encountered.

The quantification of the total myocardial collagen content showed values within the normal range in most hearts, albeit high values compared with those of normal hearts (Table IV). The normal values did not differ among the three age groups. In three hearts (cases 3, 4, and 8) the subendocardial zone of myocardium showed a volume density of collagen twice the standard deviation of the mean value of normal hearts (Fig. 4). Two of these hearts (cases 3 and 4) showed similar high values in the subepicardial area.

Discussion

In patients with pulmonary atresia with intact ventricular septum, the LV is of crucial significance because it functions basically as the sole pumping chamber. Surgical procedures, such as a systemic-to-pulmonary shunt, also carry the potential risk of additional volume loading

Fig. 4. Micrographs of the LV myocardium stained with Picrosirius red for total collagen (case 8). **A**, Low-power magnification of myocardium shows fibrous tissue in perivascular location but no conspicuous increase of interstitial fibrous tissue (magnification $\times 35$). **B**, Higher magnification of the same section shows a distinct endomysial (inter-fiber) collagen network. Microdensitophotometry showed a volume density of collagen twice the standard deviation of the mean value of age-matched normal hearts (magnification $\times 175$).

of the LV. This volume loading creates the paradoxical situation that LV function may become a main factor, whereas the major pathologic condition appears confined to the RV.

The significance of this point is illustrated by the preoperative observation that patients with pulmonary atresia with intact ventricular septum may have increased LV volumes, which, in some, is associated with a decrease in LV ejection fraction and with severe depression in LV contractility.⁸⁻¹²

Our present observations may be relevant in light of these previously mentioned considerations.

Mitral valve. The mitral valve in four of the eight heart specimens had short tendinous chords to the extent that, at sites, the valve leaflets were almost continuous with the apexes of the papillary muscle groups. The clinical significance of this observation remains unclear, although a previous morphologic study had shown one patient who, after RV outflow tract reconstruction, had mitral regurgitation considered to be caused by short chordal attachments.⁴

LV geometry. All heart specimens—except for the heart of a 1-day-old infant—showed distortion of the LV geometry caused by a subaortic septal bulge, which corresponded to the hypertrophic RV. Zuberbuhler and Anderson¹⁶ found such convex bulging of the LV septal surface in 11 of 37 hearts with pulmonary atresia with intact ventricular septum. Razzouk and associates¹⁷

described a 3-year-old patient with pulmonary atresia with intact ventricular septum who had subaortic stenosis 4 days after a Fontan procedure. The authors consider it likely that the obstruction was caused by the septal bulge, which developed either *de novo* or was unmasked by the procedure. The prevalence of the septal bulge in this condition suggests that the potential for subaortic stenosis is present in most patients. A similar geometric disturbance in hearts of patients with congenital isolated pulmonary valve stenosis has previously been considered as a potential mechanism for LV hypertrophy because of less effective LV pump function.¹⁸

LV hypertrophy. As expected LV myocardial hypertrophy is a uniform finding in these hearts. The fact that measurements of LV wall thickness show values within a normal range, compared with age-matched normal hearts, should not be wrongly interpreted. In fact, because all these hearts had LV chamber dilation, the observation of “normal” values for LV wall thickness actually indicate an increase in myocardial mass; this is not to deny that the ratio of LV mass to end-diastolic volume may be inadequate, as demonstrated by Daliento and associates.¹² Their observation emphasizes that the LV in some patients with pulmonary atresia and intact ventricular septum apparently cannot cope well with an increased volume load.

The present series included two hearts with excessive wall thickness, exceeding twice the standard deviation of

the mean value of normal hearts. The question arose as to whether these hearts could represent hypertrophic cardiomyopathy. Our histologic studies, however, did not show myocardial fiber disorganization in the sense of excessive myocardial whorls with intercellular bridgings and crossings occupying vast areas of the LV wall, which are considered characteristic for this condition.¹⁹ In our opinion, the observation of type I fiber disarray²⁰ in hearts with pulmonary atresia with intact ventricular septum¹² also supports a concept of hypertrophy rather than disease. Indeed, myocardial hypertrophy may accentuate features of disarray, which basically fits within a spectrum of normal myocardial architecture.¹⁵ It is our conviction that LV myocardial hypertrophy is the mere consequence of the hemodynamic situation in pulmonary atresia with intact ventricular septum.

Myocardial fibrosis. Previous studies of hearts with pulmonary atresia with intact ventricular septum have shown a range of ischemic changes, unrelated to the presence of coronary arterial fistulas, culminating in frank coagulation necrosis and scar formation and also affecting the LV myocardium.^{12, 21, 22} The present series also contained one heart (case 8, 6 months of age) in which extensive subendocardial areas of replacement fibrosis with calcific deposits were encountered, thus indicating previous myocardial infarction.

However, the present study also includes high levels of endomysial (interfiber) collagen, diffusely present throughout the LV myocardium. The method used is highly accurate and based on the Picosirius red stain, which stains selectively all collagen types, and the quantification of the volume density of collagen with a microdensitophotometer. This technique allows for the detection of subtle changes that certainly cannot be detected by light microscopy and the naked eye. Thus, in three of the eight cases, the overall values of collagen exceeded twice the standard deviation of the mean value in normal hearts. The one heart with a coronary arterial fistula (case 2, 1-day-old) showed levels that were high but not in excess of twice the standard deviation. Two of the three hearts with an excessive increase in fibrous tissue had excessive LV thickness also. These observations suggest that the volume of myocardial fibrous tissue relates to myocardial wall thickness. The mechanisms involved remain speculative, but the overall high values of collagen may be considered in the light of chronic ischemia. One of the specimens in the present series showed excessive fibrosis (twice the standard deviation of normal) only in the subendocardial zone, compared with the subepicardial layers (not statistically significant). This observation is pertinent with regard to a heart with a dilated LV chamber, increased ventricular wall thickness and hence potential impair-

ment of transmural coronary perfusion despite the observation that the density of the intramyocardial coronary arteries is not different from that in normal hearts. Indeed, the combined effects of myocardial hypertrophy and chronic ischemia may set into pace a process of progressive deterioration of the LV. Thus, it seems to us that the changes in the LV need consideration in planning surgical strategies for these patients.

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