Endocardial fibroelastosis and hypoplasia of the left ventricle in neonates without significant aortic stenosis

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SUMMARY Endocardial fibroelastosis in neonates with hypoplasia of the left ventricle is usually associated with severe aortic stenosis or atresia. In this study three hearts were examined, in which severe hypoplasia of the left ventricular cavity with myocardial hypertrophy and endocardial fibroelastosis were associated with small but non-stenotic subaortic outflow tracts and aortic valves. These features were contrasted with those of neonatal left heart hypoplasia in aortic stenosis and atresia. The index cases were examples of the very rare contracted form of endocardial fibroelastosis.

Endocardial fibroelastosis—thickening of the endocardial layer by abundant collagen and elastic tissue—is uncommon and usually identified in association with malformations of the left ventricle. When cardiac malformations are present the endocardial fibroelastosis is often considered to be secondary to the malformation, although this is by no means proved. Endocardial fibroelastosis lining a hypoplastic ventricular cavity is, however, usually associated with aortic atresia or severe aortic stenosis. The primary form of endocardial fibroelastosis is that which occurs as a seemingly isolated phenomenon in anatomically normal hearts. Although its aetiology and pathogenesis are obscure, primary endocardial fibroelastosis has been related to various factors.[1][2] Infective[3][4] and metabolic[5][6] agents have been implicated as well as the effects of hypoxia[7] or lymphatic obstruction.[8] Other workers have focused on a non-specific response to raised intramyocardial tension.[9] Familial incidence is reported in humans and animals,[10][11] but genetic mechanisms remain unclear. Irrespective of its cause this form of endocardial fibroelastosis, usually associated with a dilated left ventricle, can in most cases be classified as a congestive (dilated) cardiomyopathy of childhood.

Nevertheless, there is another very rare form of primary endocardial fibroelastosis, the so called restrictive or contracted form.[12] In this type the endocardial fibroelastosis lines a small left ventricular cavity, but there is no associated mitral valve disease or significant outflow tract obstruction. Apart from its initial description,[12] we are unaware of any subsequent detailed account of this entity, although Keith *et al* have reviewed it in general terms.[13] To date we have seen three cases of this rare contracted form of primary endocardial fibroelastosis. In this study, we analysed the clinicopathological features with special reference to left ventricular morphology and aortic root size and compared them with those of cases of hypoplastic left heart syndrome associated with aortic atresia or aortic stenosis.

Materials and methods

The first case (case 1) of neonatal fibroelastosis without significant left ventricular outflow tract obstruction was seen recently at the Brompton Hospital, London. To ascertain if similar cases in infants less than 1 month old existed with this contracted form of endocardial fibroelastosis we reviewed the cardiac pathology records at the Brompton Hospital, the Hospital for Sick Children, London, the Academisch Medisch Centrum, Amsterdam, and the Cardiac Research Centre, Killingbeck Hospital, Leeds. Two similar cases (cases 2 and 3) were found in the Leeds records. We also discovered 46 cases of neonatal

Table *Summary of cases*

Case No	Age at death (days)	Clinical findings	Necropsy findings				
			Mitral valve	LV wall	Endocardial thickness (mm)	Size of aorta (mm)	Aortic valve
1	1	Pale and cyanosed, poor pulses	Small, short chordae	Hypertrophied (+++)	3	3·5	Bileaflet, non-stenotic
2	2	Pale and cyanosed, poor pulses	Small, short chordae	Hypertrophied (+++)	1	6	Trileaflet, minimal stenosis
3	3	Pale and cyanosed, poor pulses	Almost normal	Hypertrophied (++)	1·5	6	Trileaflet, non-stenotic

++, moderately; +++, severely; LV, left ventricular.

fibroelastosis in the presence of significant congenital malformations of the left side of the heart. From these we selected two cases for comparison with the index case. All the hearts had been fixed in 10% buffered formaldehyde. After the heart in case 1 had been photographed and sectioned in four chamber long axis planes (right angles to the inlet part of the ventricular septum) a block of tissue incorporating the left atrium and left ventricle was removed and prepared for histological study using standard methods. In addition to haemotoxylin and eosin, sections were stained with Masson's trichrome and elastic van Gieson's stains.

Results

The clinical presentation, investigations, and necropsy findings are shown in the Table.

ANATOMICAL FEATURES

All three hearts were normally structured and connected, and the salient features were in the left ventricle and its outflow tract. They were remarkably similar in the three cases and can be illustrated by reference to those in case 1. The mitral orifice was smaller than normal, but the mitral valve leaflets were unremarkable. The tendinous chords of the mitral valve, however, were short and thick (Fig. 1a). The hypertrophied slit-like left ventricle was completely lined by a dense white layer of fibrous tissue measuring up to 0·3 cm in thickness (Fig. 1b). A thick white cord of fibrous tissue traversed the ventricular cavity from the septum to the anterolateral free wall. The aortic valve was bicuspid but otherwise normal (Fig. 1c), and the aortic annulus measured 0·5 cm in diameter. The calibre of the ascending aorta appeared small but measured at least 0·35 cm in diameter at all points (Fig. 1b). Discrete coarctation of the aorta was not present. The duct was closed with a surgical clip.

HISTOLOGICAL FEATURES

Histologically, the thickened endocardium was composed of numerous spindle shaped fibroblast-like cells amidst abundant collagenous tissue and elastic fibres

lying parallel with the ventricular cavity (Fig. 2). Several slit-like crevices (sinusoids) lined by endocardial fibroelastosis extended from the left ventricular cavity through the inner one third of the myocardial wall. In addition, there was perivascular fibrosis of the intramyocardial vessels. Two small infarcts composed of calcified dense fibrous tissue were identified in the myocardium. The thick cord identified on gross examination contained a central core of cardiac muscle cells around which there were concentric layers of fibroelastotic tissue. Except for contraction bands in subendocardial muscle cells, the remainder of the myocardium was histologically normal.

Discussion

In 1960 Edwards classified endocardial fibroelastosis as occurring in a "dilated" and a "contracted" form based upon the size of the left ventricle.[12] Since this classification was introduced it has been used by pathologist and cardiologist alike.[14 15] Of the many cases of the contracted form of endocardial fibroelastosis, the overwhelming majority are associated with significant left ventricular outflow tract obstruction. They comprise the so called hypoplastic left heart syndrome[16 17] and some cases of critical neonatal aortic stenosis.[18 19] The contracted form of endocardial fibroelastosis without significant left ventricular outflow tract obstruction or other major cardiac malformations is rarely reported.[13] In neonates it is a very rare condition.

Since the left ventricular outflow tract was not obstructed in any of our cases, they are examples of primary endocardial fibroelastosis or at least primary cardiomyopathy with reactive endocardial fibroelastosis. The concept of endocardial fibroelastosis representing reactive tissue which increases in thickness with time has been emphasised by others.[4 11 20] In our cases much of the thickness of the left ventricular wall was fibroelastotic tissue. Even without the endocardial fibroelastosis, however, the myocardial hypertrophy was severe (Fig. 1b). The relatively inelastic and poorly compliant fibroelastotic tissue undoubtedly further constrained the distensibility and compliance
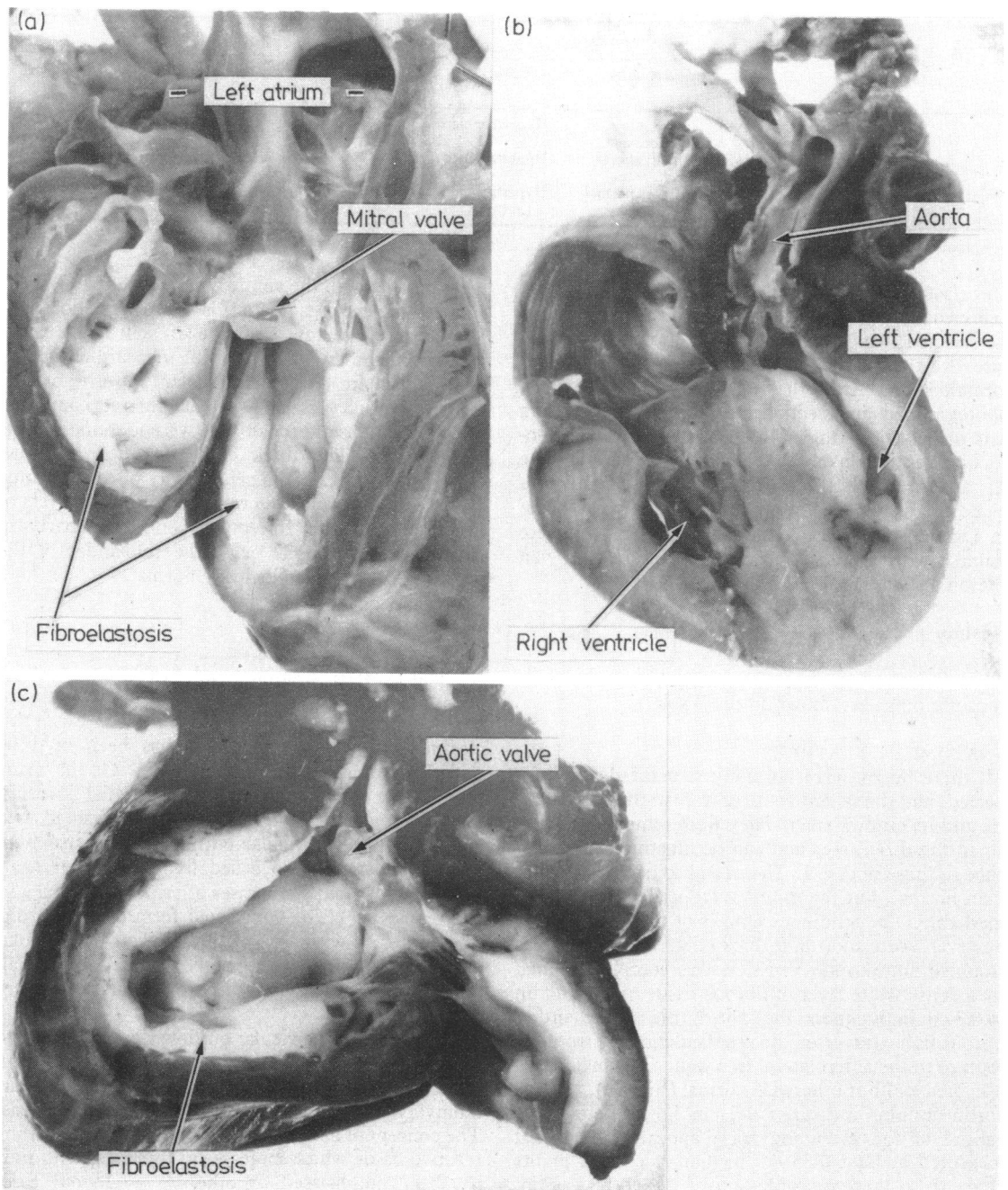
Fig. 1 *Morphological appearance of (a) left atrium and left ventricle showing thick endocardial fibroelastosis and thickened tendinous chords of the mitral valve; (b) long axis section showing a tiny left ventricular cavity, thick endocardial fibroelastosis, and non-stenotic aortic annulus; and (c) left ventricular view showing non-obstructive aortic outlet.*
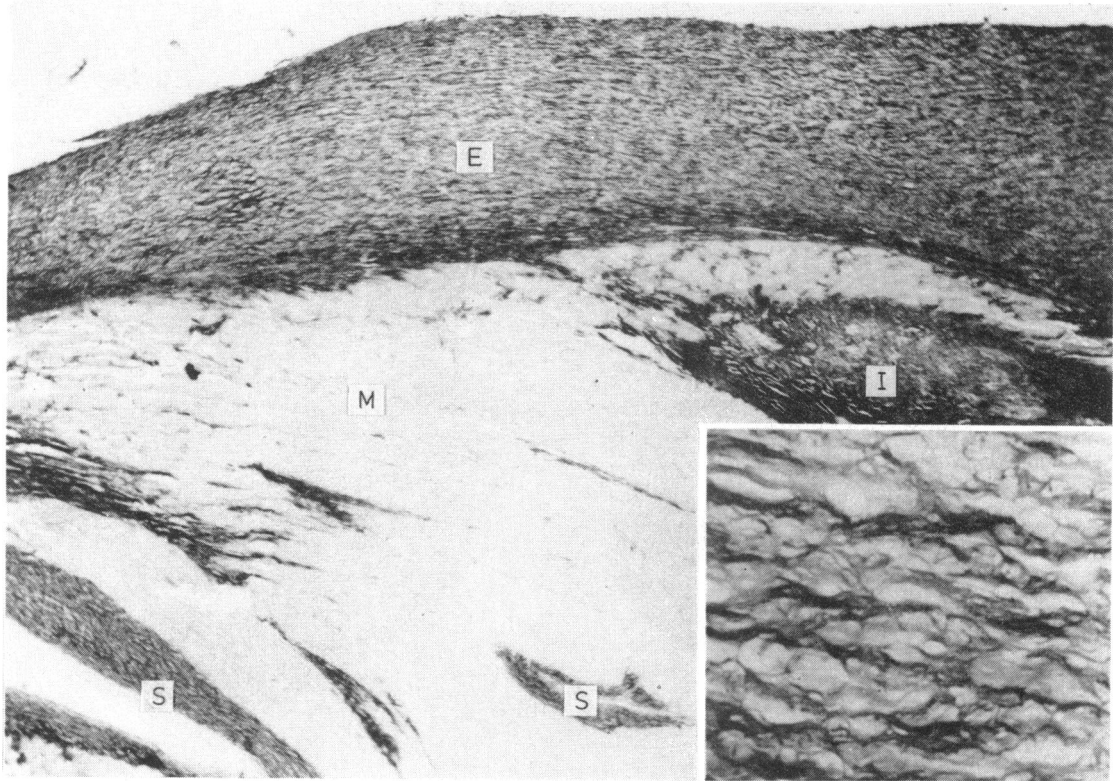
Fig. 2 *Histological section of the left ventricle showing the abnormally thick endocardium (E) overlying myocardium (M). Slit-like crevices (sinusoids (S)) are lined by thickened endocardium. A healed myocardial infarct (I) consisting of calcified dense fibrous tissue is present within the subendocardial region. At higher magnification (inset) the endocardial tissue is seen to contain wavy dark staining elastic fibres lying parallel.*

of the left ventricle before and after birth.

The small calibre of the ascending aorta was presumably a consequence of diminished blood flow through the ascending aorta secondary to left ventricular dysfunction in utero. Aortic size has been correlated with left ventricular volume in animal fetuses.[21] In case 1 the diameter of the ascending aorta corresponded to that of a 26 week human fetus and in cases 2 and 3 to that of one of 28 weeks.[22] This almost certainly indicates that the left ventricular disease antedated the twenty eighth week of gestation.

We compared the cases of endocardial fibroelastosis without significant outflow tract obstruction with a case of endocardial fibroelastosis associated with moderately severe aortic stenosis and a case of endocardial fibroelastosis associated with aortic atresia. The left ventricles of the two latter hearts were small teardrop shaped cavities with appreciably hypertrophied ventricular walls (Fig. 3). There was a gradation in the amount of fibroelastotic tissue from less than 0·5 mm thickness in the case of aortic atresia to 3 mm in the

left ventricle of the Brompton case without significant outflow tract obstruction. The mitral valves of all the hearts were somewhat hypoplastic but otherwise normal. Patency of the mitral orifice appeared to be a prerequisite for the development of endocardial fibroelastosis in the left ventricle.[13] Clearly, the left ventricular cavity is grossly distorted when the "contracted" form of endocardial fibroelastosis is present. We believe that this is the major adverse factor accounting for the usually poor outcome of these patients[23]: neonates with critical aortic stenosis, hypoplasia of the ascending aorta, and endocardial fibroelastosis with sinusoids have a poor prognosis with or without surgery.[18 19]

By limiting our study of endocardial fibroelastosis to necropsy findings in neonates of less than 1 month old we minimised complicating factors such as time and treatment. Primary endocardial fibroelastosis in older children may well be a process similar to that occurring in infants, but the onset of the disease is less well defined. In our cases the disorder was unequivoc-
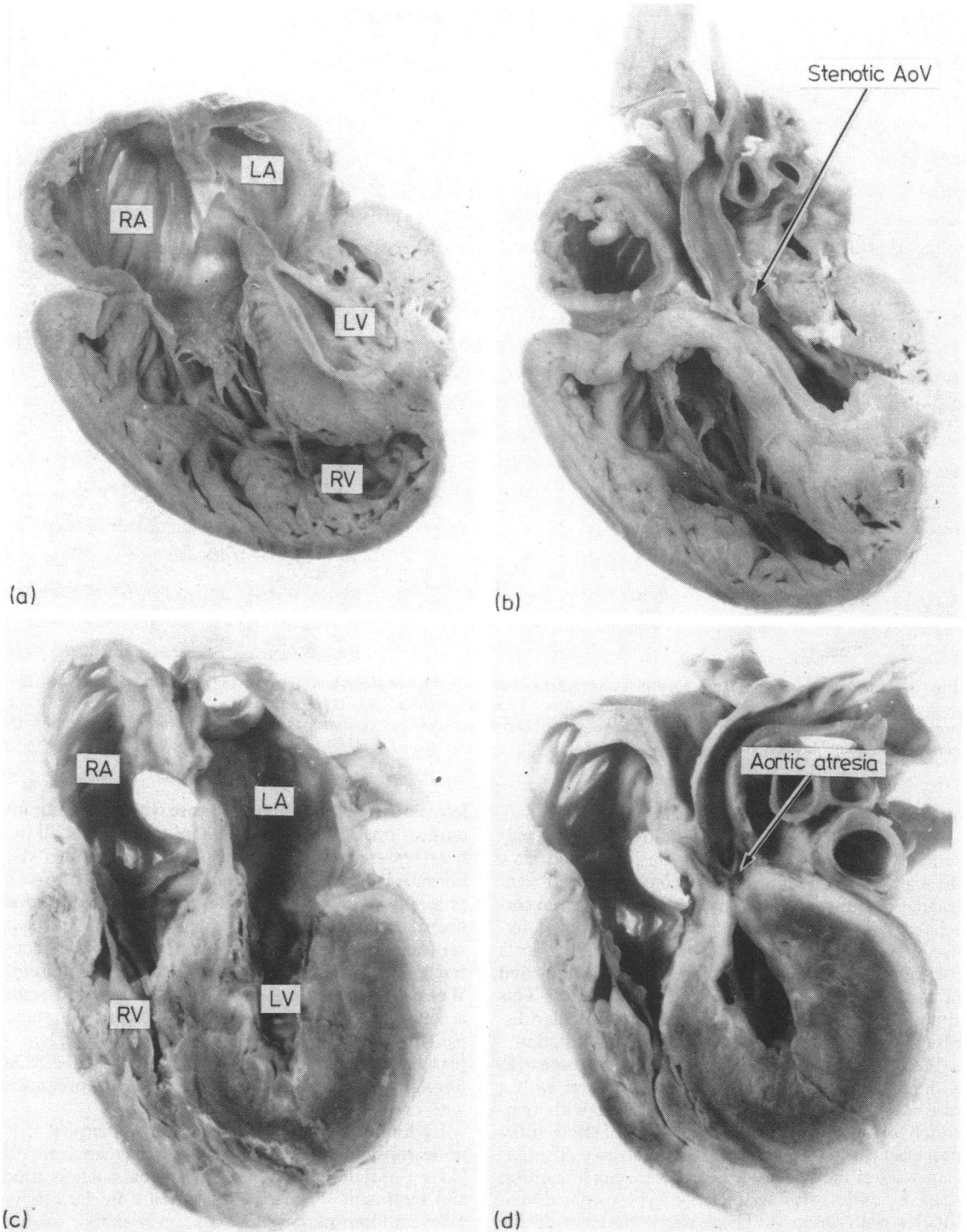
Fig. 3 *Long axis four chamber sections through a heart with aortic stenosis ((a) and (b)) compared with a heart with aortic atresia ((c) and (d)). Note moderate endocardial fibroelastotic lining of the left ventricle in the heart with a stenotic aortic valve (AoV). RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium.*

ally of intrauterine onset. The course of the disease process was therefore less than 10 months and probably less than four months since organogenesis was complete and the aortic root sizes were equal to or less than those of a 28 week fetus. By focusing on cases of primary endocardial fibroelastosis which had developed over a relatively short and well defined period of time, the aetiology and pathogenesis of this disease process may be clarified. Certain other scientific tools, such as electron microscopy and immunohistochemistry, may be of use in this regard.

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