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

PHILIP C URSELL,* CATHERINE A NEILL, ROBERT H ANDERSON, SIEW Y HO, ANTON E BECKER, LEON M GERLIS

From the Department of Paediatrics, Cardiothoracic Institute, Brompton Hospital, London; the Department of Pathology, Academisch Medisch Centrum, University of Amsterdam and Interuniversity Institute, the Netherlands; and the Cardiac Research Unit, Killingbeck Hospital, Leeds

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. Infection and metabolic agents have been implicated as well as the effects of hypoxia or lymphatic obstruction. Other workers have focused on a non-specific response to raised intramyocardial tension. Familial incidence is reported in humans and animals 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. 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, we are unaware of any subsequent detailed account of this entity, although Keith et al have reviewed it in general terms. To date we have seen three cases of this rare contracted form of primary endocardial fibroelastosis. In this study, we analyzed 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...
Endocardial fibroelastosis and left heart hypoplasia

Table  Summary of cases

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age at death (days)</th>
<th>Clinical findings</th>
<th>Necropsy findings</th>
<th>Endocardial thickness (mm)</th>
<th>Size of aorta (mm)</th>
<th>Aortic valve</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Pale and cyanosed, poor pulses</td>
<td>Small, short chordae</td>
<td>Hypertrophied (++)</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Pale and cyanosed, poor pulses</td>
<td>Small, short chordae</td>
<td>Hypertrophied (+++)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Pale and cyanosed, poor pulses</td>
<td>Almost normal chordae</td>
<td>Hypertrophied (+)</td>
<td>1.5</td>
<td>6</td>
</tr>
</tbody>
</table>

++, 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.

Discussion

In 1960 Edwards classified endocardial fibroelastosis as occurring in a "dilated" and a "contracted" form based upon the size of the left ventricle. Since this classification was introduced it has been used by pathologist and cardiologist alike. 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 and some cases of critical neonatal aortic stenosis. The contracted form of endocardial fibroelastosis without significant left ventricular outflow tract obstruction or other major cardiac malformations is rarely reported. 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. 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. 1). 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.
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. 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. 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. 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: neonates with critical aortic stenosis, hypoplasia of the ascending aorta, and endocardial fibroelastosis with sinusoids have a poor prognosis with or without surgery.

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.
Endocardial fibroelastosis and left heart hypoplasia

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.

At the time of the study CAN was a visiting professor from the Department of Paediatrics, Johns Hopkins University, Maryland, USA. RHA and SYH are supported by the Joseph Levy Foundation and the British Heart Foundation. LMG is supported by the National Heart Research Fund.

References