The left ventricle in congenital isolated pulmonary valve stenosis

A morphological study

ERIC HARINCK,† ANTON E. BECKER,
ADRIE C. GITTENBERGER-DE GROOT, ARENTJE OPPENHEIMER-DEKKER,
AND ADRIAN VERSPRILLE‡

From the Anatomical and Embryological Laboratory of the University of Leiden; and the Department of Pathology, University of Amsterdam, Wilhelmina Gasthuis, Amsterdam, The Netherlands

The wall thickness of the left ventricle was measured in the hearts of 16 children and 2 adults who died of congenital pulmonary valve stenosis. A right-to-left shunt through a patent foramen ovale had existed in 12 cases and was excluded in the other 6. The thickness of the left ventricular wall and the interventricular septum was increased in the majority of hearts, especially in the older patients. There was a good correlation between wall thickness and histological appearance of the left ventricular myocardium; in 2 cases there was also evidence of left ventricular myocardial fibrosis. The coronary arteries appeared normal in all cases. A direct interaction between the ventricles was thought to be a possible mechanism.

Congenital pulmonary valve stenosis with intact ventricular septum is usually regarded as a lesion affecting only the right side of the heart. However, haemodynamic studies with isolated heart preparations of animals have shown that augmentation of the right ventricular load has an unfavourable influence on the performance of the left ventricle (Henderson and Prince, 1914; Bucher and Von Capeller, 1954; Ullrich et al., 1954; Moulopoulos et al., 1965; Urschel et al., 1971; Elzinga, 1972; Elzinga et al., 1974; Harinck, 1974; Versprille et al., 1974). Moreover, sustained augmentation of the right ventricular load by banding of the main pulmonary artery in dogs will ultimately lead to hypertrophy of the left ventricle (Laks et al., 1969, 1972).

It is surprising, therefore, that little is known about the left ventricle in patients with isolated congenital pulmonary valve stenosis. As this information is of clinical importance, a morphological study of human hearts with isolated pulmonary valve stenosis, with particular emphasis on the occurrence of pathological changes in the left ventricle, was undertaken.

Subjects and methods

The hearts from 18 patients, aged 3 days to 26 years, were examined. All had congenital pulmonary valve stenosis, with or without an open foramen ovale but with no cardiac or other lesion that could have interfered with the function of the left ventricle.

Four patients died without an operation; in the other 14 pulmonary valvotomy had been carried out, and death had followed shortly afterwards in all but one patient who died 4 years later. In 12 cases a right-to-left shunt through an open foramen ovale had been present before death, in the other 6 the presence of a shunt had been excluded. The hearts were fixed in 80 per cent alcohol to which some glycerin had been added.

Macroscopical examination

Wall thickness was measured as described by Lev et al. (1961) and Rowlatt et al. (1963), in the right ventricle 0.5 to 1.0 cm below the pulmonary orifice (RV-P), and in the left ventricle at its maximum thickness (LV-M). The maximal thickness of the interventricular septum (IVS-M) was measured from a cut perpendicular to the axis of the heart. Trabeculae were excluded in all measurements.

Because values for ventricular wall thickness of
normal hearts fixed as described above were not available, the values for normal hearts fixed in formaldehyde (Rowlatt et al., 1963) were used. Before a comparison was made between the values obtained from our own study and these reference values, the influence of the different fixation fluids on ventricular wall thickness was investigated with transverse sections of pig hearts. The thickness of the lateral wall of the left ventricle and of the interventricular septum were measured before and after fixation in 80 per cent alcohol or formaldehyde. After a fixation period of 3 months there was no significant difference between these two methods of fixation. If we accept that human hearts do not differ in this respect from pig hearts, the values for wall thickness in our study may be compared with the normal values of Rowlatt et al. (1963).

**MICROSCOPICAL EXAMINATION**

In 16 of the 18 hearts a microscopical study could be performed. The sections were taken from the sites used for the measurements of wall thickness. The diameter of the myocardial cells was measured using an ocular micrometer. A total number of 50 measurements was taken in each case, for both right and left ventricular myocardium. An average fibre diameter was then calculated.

Fibrosis was defined as an increase of connective tissue. The presence of fibrosis was graded in a semiquantitative manner, as follows: a slight increase was graded as + (Fig. 1A) and a greater increase as ++ (Fig. 1B).

Particular attention was also given to myocardial fibre arrangement and to the intramural coronary arteries.

**Results**

**MACROSCOPICAL APPEARANCES**

On inspection of the specimens right ventricular...
hypertrophy was a constant feature in all cases. Moreover, gross inspection, particularly in the older hearts, also showed that there was an increase in wall thickness of the left ventricle in the majority of those hearts studied (Fig. 2 and 3). The results of measurement of the ventricular wall thickness are compared with the normal values in the paediatric age group in Fig. 4. The values for right ventricular wall thickness (RV-P) are plotted against age from birth, and those for maximal thickness of the left ventricular wall (LV-M) are plotted against age from conception; this method was that used by Rowlatt et al. (1963). The values for right ventricular wall thickness are all above the 95th centile of the reference values. The values for maximal left ventricular wall thickness in the older children are mostly on or above the 95th centile.

When the relation between left ventricular wall thickness and body weight is plotted (Fig. 5) the values for maximal thickness of the left ventricle exceed the 95th centile in all children of 10 kg or more. The LV-M value of the 13-year-old boy is not shown as his body weight just before death is unknown. In the majority of patients the body weights were in accordance with their ages and heights; 2 cases were even robust.

The results of the macroscopical investigation of the two adults are shown in Table 1. The wall thickness of both right and left ventricle of the 25-year-old man was above normal. The wall thickness of the right ventricle in the 26-year-old women was considerably increased, and though the left ventricle appeared large its wall thickness was within normal limits; however, the microscopical appearance (see Table 2) indicated left ventricular hypertrophy. Fig. 6 shows that there is a positive

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**Fig. 2** View of opened sinus part and outflow tract of the right ventricle (above), with distinct hypertrophy of the wall. The opened left ventricle (below), with the septum on the left, shows no increase in wall thickness. A right-to-left shunt had existed through an open foramen ovale in this patient, age 14 months (23 from conception), bodyweight 8.4 kg.

**Fig. 3** View of opened right ventricle (above), to show pronounced right ventricular hypertrophy. The opened left ventricle (below) also shows considerable hypertrophy of its wall. In this patient no right-to-left shunt had existed; age 9½ years (10 from conception), bodyweight 22.6 kg.
correlation between the maximal thickness of the left ventricular wall (LV-M) and the maximal thickness of the interventricular septum (IVS-M).

MICROSCOPICAL APPEARANCES
The histological findings are summarised in Table 2. The assessment of whether or not there was hypertrophy was based mainly upon personal experience.

Under 1 year of age an average fibre diameter of less than 5 μ is considered normal. In the age group from 1 to 10 years a diameter of less than 10 μ is considered normal. These figures apply to myocardium of both right and left ventricles. In the age group from 10 to 20 years an average fibre diameter of less than 10 μ is considered normal for the right ventricle, and of less than 15 μ for the left ventricle. When these figures are taken into account it is seen that 15 of the 16 hearts examined histologically showed evidence of right ventricular hypertrophy; the only heart without histological evidence of right ventricular myocardial hypertrophy was that of the 14-day-old infant.

Evidence for left ventricular hypertrophy was found in 10 of the 16 hearts studied; there was a definite tendency for this to be seen in the older patients.

Fibrosis of the right ventricular myocardium appeared in 8 cases and always accompanied an increase in right ventricular wall thickness. The left ventricular myocardium showed fibrosis of moderate degree in 3 cases, each with pronounced left ventricular hypertrophy. Apart from the hypertrophic changes, no other abnormalities of the myocardium

<p>| Table 1 Macroscopical findings in 2 adults |
|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (y)</th>
<th>RV-P</th>
<th>LV-M</th>
<th>IVS-M</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>25</td>
<td>9</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>F</td>
<td>26</td>
<td>16</td>
<td>12</td>
<td>12</td>
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Measurements are given in millimetres.
RV-P, right ventricular wall thickness; LV-M, maximal wall thickness of the left ventricle; IVS-M, maximal thickness of the interventricular septum.
Table 2  Microscopical features of myocardium of right and left ventricles

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Right ventricle</th>
<th>Left ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Myocardial fibre diameter ((\mu))</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>3d</td>
<td>M</td>
<td>2-5 (-)</td>
<td>-</td>
</tr>
<tr>
<td>14d</td>
<td>F</td>
<td>7-5 (+)</td>
<td>-</td>
</tr>
<tr>
<td>3m</td>
<td>F</td>
<td>7-5 (+)</td>
<td>-</td>
</tr>
<tr>
<td>4m</td>
<td>M</td>
<td>7-5 (+)</td>
<td>-</td>
</tr>
<tr>
<td>5m</td>
<td>M</td>
<td>12-5 (+)</td>
<td>+</td>
</tr>
<tr>
<td>14m</td>
<td>F</td>
<td>12-5 (+)</td>
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<td>5y</td>
<td>F</td>
<td>12-5 (+)</td>
<td>+</td>
</tr>
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<td>6y</td>
<td>F</td>
<td>15 (+)</td>
<td>-</td>
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<tr>
<td>26y</td>
<td>F</td>
<td>20 (+)</td>
<td>+</td>
</tr>
</tbody>
</table>

The interpretation of the average fibre diameter is shown in brackets: (+), hypertrophy; (-), no hypertrophy. Fibrosis is indicated by —, absent; +, mild; ++, severe.

Discussion

This study has shown that left ventricular hypertrophy may be present in patients with isolated pulmonary valve stenosis. However, it should be noted that ventricular wall thickness as a guide to the presence of hypertrophy has the disadvantage that false negative results may occur because of dilatation. It follows that cases with increased ventricular wall thickness may have been missed, but even so half the cases presented had LV-M values above the 95 per cent confidence limits when LV-M was plotted against age (Fig. 4). Moreover, we feel confident that left ventricular hypertrophy does occur, since 10 of the 16 hearts studied histologically showed evidence of left ventricular hypertrophy. This finding suggests that the condition of congenital pulmonary valve stenosis is one that affects not only the right side of the heart. The mechanisms that underlie the appearance of left ventricular hypertrophy are still a matter of dispute. The phenomenon cannot simply be attributed to the degree of hypertrophy of the right ventricle since no positive correlation between the LV-M and RV-P values was found. Experimental studies with animals have shown that an increase in the afterload of the right ventricle, produced by banding the main
pulmonary artery, results in right ventricular hypertrophy within a few days (Spann et al., 1967; Archie et al., 1974), though hypertrophy of the left ventricle does not become manifest until some months later (Laks et al., 1969, 1972; Harinck, 1974). Apparently a time factor is of importance, since hearts of younger infants in our series showed less left ventricular hypertrophy than those of older children, or none at all. Keith and coworkers (1967) have stated that hypertrophy of the left ventricle is seen only in patients with severe pulmonary stenosis. On the other hand, Herbert and Yellin (1969) were unable to confirm this, finding abnormally high left ventricular end-diastolic pressures in patients with even a mild to moderate pulmonary stenosis.

Although histological examination of the hearts in our series showed only hypertrophy with normal looking coronary arteries, Beçu et al. (1976) have reported a bizarre arrangement of left ventricular muscle fibres and involvement of coronary vessels.

It has been suggested that myocardial hypoxia is a factor in the development of left ventricular hypertension, particularly in patients with a right-to-left shunt through a patent foramen ovale. Increased blood viscosity from concomitant polycythemia, secondary to this shunt, may be an additional factor. However, left ventricular hypertension was not confined to cases in our series with a right-to-left shunt, but occurred also in patients without a shunt; furthermore, the left ventricular hypertrophy was not more pronounced in the hearts with a right-to-left shunt than in those without.

In acute haemodynamic studies in animals it was shown that coronary blood flow diminished when the afterload of the right ventricle was raised (Elzinga, 1972; Harinck, 1974). This phenomenon may be an additional possible cause of myocardial hypoxia. However, it has also been shown that coronary blood flow adapts to a sustained increase in right ventricular afterload (Archie et al., 1974).

Anatomical continuity of the musculature between right and left ventricles has been suggested as a possible cause for the development of left ventricular hypertrophy in patients with chronic lung disease (Rao et al., 1968). Sustained stress to the right ventricle may then lead to abnormalities in the left ventricle. However, if this were true, one might also expect the reverse to take place, with sustained stress to the left ventricle directly influencing the right; such an effect, as far as we know, has never been described. Nevertheless, the possibility of a direct interaction between the ventricles cannot be ruled out.

It is suggested that changes occurring on the right side of the heart result in altered left ventricular geometry. Increase in afterload of the right ventricle results in an increase in right ventricular end-diastolic volume, which may flatten the globular or egg-shaped left ventricle (Harinck, 1974; Versprille et al., 1974) which then has a less favourable shape for the development of pressure. In fact, changes in geometry of the left ventricle induced by alterations in right ventricular load have been reported by Urschel et al. (1971) and by Bemis et al. (1974). These investigators showed that an acute constriction of the main pulmonary artery in dogs causes an increase in the anteroposterior diameter of the left ventricle and a reduction of the septum to free wall diameter. Thus, the radius of the lateral wall of the left ventricle is enlarged. According to the modified Laplace equation, this part of the left ventricle has to produce more tension (and thus work) to maintain a given stroke volume at a given aortic pressure. Sustained increased tension may lead eventually to hypertrophy. In our opinion, this mechanism could be of prime importance in the pathogenesis of the left ventricular hypertrophy.

It is also interesting to note that prolonged and pronounced hypertrophy of myocardium subsequently leads to fibrosis, a feature well known from other pathological conditions.

Indeed, right ventricular fibrosis was a frequent feature in our series. Three of the older children, with pronounced left ventricular hypertrophy, also presented features of fibrosis in the left ventricular myocardium. Obviously such alterations will affect myocardial function, though a considerable lapse of time is needed. These anatomical findings further endorse the impression that problems may arise from the left ventricular myocardium in patients with isolated valve pulmonary stenosis, primarily a malformation confined to the right heart.

References


Elzinga, G., van Grondelle, R., Westerhof, N., and van den
The left ventricle in congenital isolated pulmonary valve stenosis

Requests for reprints to Dr. Eric Harinck, Wilhelmina Kinderziekenhuis, Nieuwe Gracht 137, Utrecht, The Netherlands.