Hypertrophic cardiomyopathy in infants of poorly-controlled diabetic mothers

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SUMMARY Twelve newborn infants of poorly-controlled diabetic mothers were transferred from outlying maternity hospitals for neonatal intensive care. Respiratory distress and cardiomegaly were the presenting signs. Ten infants were large for dates (macrosomic) and had echocardiographic evidence of myocardial hypertrophy, reduced ejection time, and systolic anterior movement of the mitral valve (in 6 infants). These findings are similar to those of adults with idiopathic hypertrophic subaortic stenosis. Two infants died. In survivors the myocardial hypertrophy persisted for at least 2 weeks but the evidence of functional subaortic stenosis had disappeared by 4-7 days. The 2 infants who were appropriately grown had cardiomegaly as a result of ventricular dilatation. This was associated with hypoglycaemia and acidosis, and disappeared when these metabolic disturbances were corrected.

Hypertrophic cardiomyopathy is a condition characterised by stiff, hypertrophied ventricular muscle, predominant thickening of the ventricular septum, impaired relaxation, and powerful but incoordinate contraction.¹ The condition in adults is familial, and probably represents an autosomal dominant trait. There is functional subaortic obstruction in severe cases and this is referred to as idiopathic hypertrophic subaortic stenosis (IHSS). Previous reports have suggested that IHSS may occur transiently in infants of diabetic mothers.²⁻⁴ This paper reports echocardiographic findings in 12 infants of diabetic mothers who were admitted to hospital for newborn intensive care. Ten of these infants appeared to have many echocardiographic features characteristic of IHSS; and in 2 infants the findings suggested ventricular dilatation rather than hypertrophy.

Patients

From February 1978 to September 1979, 12 infants of diabetic mothers were admitted to newborn intensive care units in San Francisco and Belfast. Eight infants were in San Francisco and 4 were in Belfast. The infants had been born in outlying hospitals where the antenatal care of their mothers had been supervised. Transfer was arranged within 4 hours of birth in each case. Poor control of maternal diabetes had been a major feature in each pregnancy; 5 mothers had episodes of ketoacidosis

associated with infections, 6 had severe polyhydramnios, and in addition 5 were hypertensive. Three mothers had class A diabetes, 1 class B, 3 class C, 4 class D, and 1 class F (White's classification).⁵ Delivery was by caesarean section in 7 mothers and per vaginam in 5. Ten infants had asphyxia with Apgar scores <7 at one minute. There were 9 boys and 3 girls. Mean gestational age was 37 weeks and mean birthweight 3640 g. Fig. 1 shows a growth chart of birthweight against gesta-

Fig. 1 Growth chart of gestational age against birthweight for UK infants.⁶ The mean, 5th, and 95th centiles are shown. Ten infants are on the 90th centile or above and are large for dates (group 1) and the 2 smaller infants, shown as open circles, form group 2.

tional age for babies in the UK;⁶ 9 of the 12 infants studied were on or above the 95th centile of weight for age, one was on the 90th centile, one on the 25th centile, and one < the 5th centile. The 10 infants on or above the 90th centile were considered to be large for dates (group 1), and the 2 smaller infants were considered separately (group 2). Two infants in group 1 died about 48 hours after birth. There was no clinical evidence of congenital anomaly of cardiovascular or other system in any infant.

Methods

M-mode echocardiography (Ekoline 20A in San Francisco, and Teknika Echomatic in Belfast) was

used to assess myocardial thickness and left ventricular contractility in all 12 infants within 24 hours of birth, and in the 10 surviving infants at both 4–7 days and 11–13 days. Septal wall thickness (SWT) and left ventricular posterior wall thickness (LVPWT) were measured as described by Hagan *et al.*⁷ and Solinger *et al.*⁸

Left ventricular contractility was assessed by two different methods; firstly, the percentage shortening of the internal dimension of the left ventricle (% SID)⁹ and, secondly, the left ventricular pre-ejection period to ejection time ratio (LPEP/LVET ratio).¹⁰ Percentage SID was calculated by the formula⁹

$$\% \text{SID} = \frac{\text{LVEDD} - \text{LVESD}}{\text{LVEDD}}$$

where LVEDD = left ventricular end-diastolic dimension

and LVESD = left ventricular end-systolic dimension

LPEP/LVET ratio was measured from echograms of aortic valve recorded at paper speeds of 100 mm/second (Fig. 2).¹⁰

Results

Group 1. Eight of these 10 infants had presented with respiratory problems after birth which were believed to be due to respiratory distress syndrome. Murmurs were present in 4 of them. On chest x-ray films all 10 infants had cardiomegaly (mean cardiothoracic ratio 0.72). Nine infants had abnormal electrocardiographs with either flat T-waves over the anterior chest beats (4 babies), right ventricular hypertrophy of moderate degree (6 babies), or ventricular ectopic beats (1 baby) (Fig. 3).

Each infant in group 1 had echographic evidence of thickening of interventricular septum and left ventricular posterior wall (Fig. 4). This hypertrophy persisted for at least 2 weeks and was initially

LPEP=left ventricular pre-ejection period, LVET=left ventricular ejection time.

Fig. 2 Aortic valve echogram recorded at 100 mm/second in an infant of a diabetic mother. In this infant LPEP/LVET ratio was 0.44 which is above the normal mean for newborn infants (0.35) and suggests disordered left ventricular contractility.

Fig. 3 Lead II of an electrocardiogram from an infant of a diabetic mother taken at half standardisation. Some ventricular ectopic beats are shown.

Fig. 4 Echocardiograms of normal infant and of infant of diabetic mother taken to show right ventricle (RV), interventricular septum (IVS), and left ventricle (LV). The mitral valve is marked (MV). There is marked thickening of IVS (0.6 cm) compared with normal (0.3 cm). Left ventricular posterior wall (PLVW) is also thickened (0.5 to 0.3 cm). Slight systolic anterior movement of mitral valve can be seen arrowed.

associated with alterations in % SID and LPEP/LVET ratio (Fig. 5). SWT was 0.56 at 24 hours and LVPWT was 0.48 cm, both considerably greater than normal (0.3 cm).^{7 8} SWT/LVPWT ratio was 1.2 which is above the normal range of 0.9 to 1.0. Mild systolic anterior movement of the mitral valve was present in 6 infants (Fig. 4). LPEP/LVET ratio was increased at 24 hours due to a reduction in LVET since LPEP values were in the normal range¹¹ (Table 1). Although the myocardial hypertrophy persisted for 2 weeks, % SID and LPEP/LVET ratio decreased with time and were both normal by 4-7 days. Indeed, paradoxically there was a direct correlation between LPEP/LVET ratio and % SID (Fig. 6) which was contrary to what would be expected in the failing heart.

These changes in left ventricular contractility were

not significantly related to the degree of myocardial thickening or to biochemical disturbances (hypoglycaemia, hypocalcaemia, hypokalaemia or hyperkalaemia, and acidaemia) (all $r < 0.3$).

Two of the infants in group 1 died within 48 hours of birth from cardiorespiratory failure. One had been given a beta-blocker (propranolol) when close to death without apparent change in clinical condition, and the other had been treated with digoxin, also

Fig. 5 Plots of mean $\pm$ 1 SD for myocardial thickness, % SID, and LPEP/LVET ratio with postnatal age of the 10 large for dates infants. The shaded areas represent the normal range for term infants.^{7 8 11} Septal wall thickness (SWT) and left ventricular posterior wall thickness (LVPWT) remain increased for up to 2 weeks postnatally. The septum is hypertrophied to a greater extent than the LVPW with SWT/LVPWT ratios of 1.2, 1.2, and 0.9 where normal is 0.9 to 1.0. % SID = percentage shortening of internal dimension of left ventricle, LPEP = left ventricle pre-ejection period, and LVET = left ventricular ejection time.

Table 1 Comparison of systolic time intervals (mean $\pm$ 1 SD) in infants of diabetic mothers and normal newborn infants at 24 hours

	Normal*	Infants of diabetic mothers
LPEP (msecond)	70 $\pm$ 10	69 $\pm$ 8
LVET (msecond)	196 $\pm$ 17	161 $\pm$ 19
LPEP/LVET ratio	0.36 $\pm$ 0.05	0.43 $\pm$ 0.06

LPEP = left ventricular pre-ejection period, LVET = left ventricular ejection time.

*Halliday *et al.*¹¹

Fig. 6 Correlation of LPEP/LVET ratio and % SID in initial echocardiograms. Group 2 infants are shown as open circles. The relationship is significant ($r = 0.62$, $P < 0.02$).

Table 2 Mean organ sizes of infants of diabetic mothers

Size	Weight as % of normal*	
	IHSS (n = 2)	Infants of diabetic mothers† (n = 21)
Body weight	113	141
Body length	109	112
Heart weight	200	174
Liver weight	139	179
Brain weight	83	97
Spleen weight	147	127
Lung weight	113	127

*Schulz *et al.*¹² †Naeye¹³

IHSS = idiopathic hypertrophic subaortic stenosis.

without apparent alteration in clinical course. At necropsy both had hearts that were about twice the normal weight¹² (Table 2). Shown in the table for comparison are the findings in 21 large for date infants of diabetic mothers studied by Naeye.¹³ In both of our infants SWT was 0.6 cm which corresponded precisely to that found by echocardiography during life. There was no evidence of anatomical subvalvular aortic stenosis at necropsy. On histological examination the heart showed some vacuolar and hydropic changes (Fig. 7) but these were non-specific and did not amount to any clear cardiomyopathy. There was no disorganisation of myocardial fibres or inflammatory cell infiltrate, and special staining failed to show excessive deposition of glycogen within the cellular cytoplasm.

Group 2. These two smaller infants had cardiomegaly due to ventricular dilatation and myocardial thickness was normal.^{7,8} They also showed disordered contractility (Fig. 6) but this was related to hypoglycaemia and acidaemia and improved when these metabolic disturbances had been corrected. Both infants survived and their condition was normal at follow-up.

Discussion

Pathognomonic echographic findings of IHSS are asymmetrical septal hypertrophy¹⁴ and systolic anterior movement of the mitral valve.¹⁵ Additional findings are narrow left ventricular outflow tract,

Fig. 7 Histological section of the heart from an infant of a diabetic mother showing hydropic changes but no evidence of disorganisation of myocardial cells.

high ejection fraction, and altered left ventricular ejection time (LVET).^{16 17} When outflow obstruction is severe LVET may be lengthened but in patients without outflow obstruction the myocardial hypertrophy tends to be less, systolic anterior movement of the mitral valve absent,^{15 16} and LVET shortened.¹⁸

There have been reports of hypertrophic cardiomyopathy in infancy^{2-4 19-21} and either a positive family history of IHSS²¹ or the presence of maternal diabetes^{2-4 21} seems to be a common association.

In our infants there was no family history of IHSS although we did not perform echographic studies on their 1st-degree relatives. Each mother had either gestational diabetes mellitus or was a known diabetic requiring insulin before her pregnancy. In each case the diabetes had been poorly controlled during pregnancy. Episodes of ketoacidosis and marked polyhydramnios were common antecedents. All the infants had cardiomegaly on radiographic and echographic examination. In the 10 infants (group 1) the cardiomegaly was due to hypertrophy especially of the interventricular septum and left ventricular posterior wall, but in the 2 smaller infants there was dilatation of the heart in association with hypoglycaemia and acidaemia. Hypoglycaemia has been associated with cardiac enlargement and heart failure in the newborn^{22 23} and I believe that the infants in group 2 belonged in this category.

The 10 large infants (group 1) however, demonstrated many of the echocardiographic findings of IHSS:¹⁷ myocardial hypertrophy with asymmetrical septal hypertrophy, vigorous contraction, and increased ejection fraction or %SID, reduced LVET, and mild systolic anterior movement of the mitral valve. These findings were not related to hypoglycaemia, hypocalcaemia, potassium disturbances, or to acidosis. The hypertrophy remained for at least 2 weeks but evidence of left ventricular outflow obstruction (increased %SID, reduced LVET, and mild systolic anterior movement of the mitral valve) had disappeared by 4-7 days in the 8 surviving infants. At necropsy in 2 infants there was no evidence of anatomical subvalvular stenosis although the hypertrophy suggested by echocardiography was confirmed. These infants had pathological evidence of hyaline membrane disease.

Whether the presence of hypertrophic cardiomyopathy could explain the respiratory difficulty of these infants and the death of 2 of them is debatable. Eight of the 10 infants had clinical findings that were compatible with respiratory distress syndrome, and the presence of hyaline membranes at necropsy in 2 of them tends to support this diagnosis as tenable. The absence of anatomical subaortic stenosis at necropsy does not however, exclude the presence of functional outflow obstruction.

Beta-blockade with propranolol has been shown to be effective in one infant with IHSS¹⁹ but this treatment was used in only one of our infants. Propranolol was given late in the clinical illness of this infant without any apparent amelioration in his condition. In another infant the hypertrophic cardiomyopathy was associated with a potentially serious arrhythmia—namely frequent ventricular ectopic beats. This infant survived after treatment designed to suppress the arrhythmia, but if this disturbance of rhythm had occurred *in utero* then fetal death may well have occurred. Sudden, unexplained death of the fetus near term is a well-known feature of the diabetic pregnancy. One could speculate that cardiac arrhythmia might be a cause of this phenomenon in the poorly-controlled diabetic pregnancy.

The aetiology of the left ventricular outflow obstruction in these infants is uncertain. It is possible that the septal hypertrophy was a part of the generalised increase in organ size of the large for dates infant of the diabetic mother.¹³ In favour of this hypothesis is the tendency for the hypertrophy to resolve during the first year of life in those infants studied by Gutgesell *et al.*⁴ We feel that our infants did not have any structural congenital heart disease that could account for the myocardial hypertrophy. It has been reported that left ventricular outflow obstruction occurs in 18% of infants of diabetic mothers whether or not symptoms are present.²⁴

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