

## Left ventricular function in $\beta$ thalassaemia major

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**SUMMARY** The left ventricular dimension and posterior wall dynamics were studied by computer assisted analysis of M mode echocardiography in 25 normal children (group 1) and 32 transfusion dependent children with  $\beta$  thalassaemia major who had no evidence of heart failure (group 2). Twenty seven of those in group 2 remained well but five died of cardiac decompensation within 12 months. Compared with group 1, the left ventricular fractional shortening and ejection fraction were normal in those in group 2 who survived but diminished in those who died. Evaluation of left ventricular dimension and posterior wall dynamics during systole (peak shortening rate, peak velocity of circumferential fibre shortening, and peak posterior wall thickening rate) showed similar findings in that only the group who died had abnormal values. The left ventricular dimension and posterior wall diastolic dynamics (peak relaxation rate, normalised peak relaxation, peak wall thinning, and normalised peak wall thinning rate), however, showed progressively slower rates in all the children in group 2. The findings suggest that left ventricular diastolic dysfunction occurs early in myocardial impairment in patients with  $\beta$  thalassaemia major. When there are abnormalities in both diastole and systole, the myocardial impairment is advanced and the prognosis is poor.

Iron overloading is inevitable in children with  $\beta$  thalassaemia major because of repeated blood transfusions and enhanced gastrointestinal absorption. When cardiac impairment from iron deposition is severe enough to be clinically obvious, the disease is advanced and the subsequent survival is brief.<sup>1 2</sup> Henry *et al* used conventional M mode echocardiography to study these patients and found that most had normal resting left ventricular ejection fractions; some who had low values, however, died within six months.<sup>3</sup> Leon *et al* used radionuclide cineangiography to measure the left ventricular ejection fraction during exercise and found that the index in the thalassaemic patients did not increase as in normal subjects but either dropped or remained unchanged.<sup>4</sup> Normally, however, the ejection fraction does not change appreciably during submaximal exercise, and it is often difficult to exercise young children enough. Computer assisted analysis of M mode echocardiography, developed by Gibson and Brown,<sup>5</sup> has been used to evaluate left ventricular function in various kinds of myocardial diseases,<sup>6-14</sup> but its use in children with  $\beta$  thalassaemia major has not been reported. We report our experience with computer assisted analysis of M mode echocardiography to evaluate the left ventricular function in these patients.

### Patients and methods

The subjects were divided into two groups. Group 1 comprised 25 normal schoolchildren to serve as controls. Group 2 comprised 32 children with homozygous  $\beta$  thalassaemia who needed regular blood transfusion; none had clinical evidence of heart failure and at the time of study none was on iron chelation treatment. In the follow up period, 27 in group 2 remained well but five developed overt congestive heart failure and died within 12 months of the initial echocardiographic study. The two groups were comparable for age, sex, weight, and height (table 1).

The echocardiographic study was performed by one of us (KCL) when the subjects were at rest, and in group 2 one week after a blood transfusion when their haemoglobin concentration was more than 110 g/l. If the Hg concentration was less than this, the echocardiographic study was not carried out. Electrocardiogram, phonocardiogram, and cross-sectional echocardiograms were carried out with an Advanced Technology Laboratory MK 600 sector scanning system. Firstly, a subjective assessment of left ventricular regional contraction was obtained by using the left ventricular long axis, short axis and apical four chambered views. To obtain the M mode

Table 1 Comparability of the groups

	Group 1		Group 2	
			Survived (n=27)	Died (n=5)
Mean (range) age (years)	9.5 (7-13)		10.5 (6-14)	12.8 (11-16)
Sex:				
Male	13		15	2
Female	12		12	3
Weight (kg)	19.5-35		18.4-34.5	22-34
Height (cm)	115-140		108-134	120-139

echocardiographic tracings, the M mode ultrasonic beam was directed along the centre of the left ventricular short axis at the level of the tip of the mitral valve. The M mode echocardiographic tracings were recorded with maximal expansion together with the phonocardiograms and electrocardiograms at a paper speed of 100 mm/s. Only those high quality tracings with uninterrupted endocardial and epicardial surfaces were chosen. The echocardiograms were digitised by the method of Gibson and Brown<sup>5</sup> with a Hewlett Packard 9874A digitiser (resolution 0.0025 cm, relative accuracy 0.0125 cm) and processed by a Hewlett Packard 9836A computer. End diastole and end systole were taken to occur at the onset of Q wave of the electrocardiogram and A2 of the phonocardiogram, respectively. The left ventricular posterior septal endocardial and posterior wall endocardial and epicardial surfaces were digitised continuously. The digitised data were plotted with a Hewlett Packard 2671G graphic printer (figure). If the plot was satisfactory and free from artefacts, the left ventricular dimension, posterior wall thickness, and their respective rates of change with time were determined; otherwise, the digitisation was repeated. At least three consecutive cardiac cycles were digitised and the mean value calculated. The following indices of left ventricular dimension and posterior wall were obtained:

(A) Conventional left ventricular M mode echocardiographic indices—(1) end diastolic dimension, (2) end systolic dimension, (3) fractional shortening (1-end systolic dimension/end diastolic dimension), (4) ejection fraction (calculated from the formula of Teichholtz *et al*<sup>15</sup>), (5) end diastolic wall thickness, (6) end systolic wall thickness, and (7) wall fractional thickening (end systolic wall thickness/end diastolic wall thickness)—1.

(B) Left ventricular dimension dynamic indices—(1) Systole (a) peak dimension shortening rate (peak systolic rate of left ventricular dimension change), and (b) peak velocity of circumferential fibre

shortening (peak systolic rate of left ventricular dimension change/end diastolic dimension). (2) Diastole (a) peak dimension relaxation rate (peak diastolic rate of left ventricular dimension change), and (b) normalised peak dimension relaxation rate (peak diastolic rate of left ventricular dimension change/end diastolic dimension).

(C) Left ventricular posterior wall dynamic indices—(1) Systole (a) peak wall thickening rate (peak systolic wall thinning rate), and (b) normalised peak wall thickening rate (peak systolic wall thickening rate/end diastolic wall thickness). (2) Diastole (a) peak wall thinning rate (peak diastolic wall thinning rate), and (b) normalised peak wall thinning rate (peak diastolic wall thinning rate/end diastolic wall thickness).

In 10 patients the echocardiographic examination and digitisation were repeated by the same worker (KCL) and the results of the two studies were compared.

The results for both groups were expressed as the mean (1 SD), and the *t* test (Bonferroni<sup>16</sup>) was used for comparison. The differences were taken to be significant when the *p* value was <0.05.

## Results

The mean heart rates in the two groups were similar.

### CONVENTIONAL M MODE ECHOCARDIOGRAPHIC INDICES (TABLE 2)

The mean end diastolic dimension and end systolic dimension of those in group 2 who survived were significantly larger than those in group 1 (*p*<0.05). Likewise the corresponding values among those in group 2 who died were also significantly larger than in both group 1 and group 2 who survived. The fractional shortening and ejection fraction of group 2 who survived were not significantly different from those in group 1, but those of group 2 who died were significantly diminished (*p*<0.001).

Although the mean end diastolic wall thickness of group 2 (particularly those who died) was significantly greater than group 1, the mean end systolic wall thickness of the three groups was not significantly different. Thus the left ventricular wall fractional thickening was significantly reduced in group 2 survivors (*p*<0.01) and even more reduced in group 2 patients who died (*p*<0.001).

### LEFT VENTRICULAR DIMENSION DYNAMIC CHANGES (TABLE 3)

The systolic dynamic changes (peak dimension shortening rate and velocity of circumferential fibre shortening) of group 2 survivors were not significantly different from group 1, but only group 2

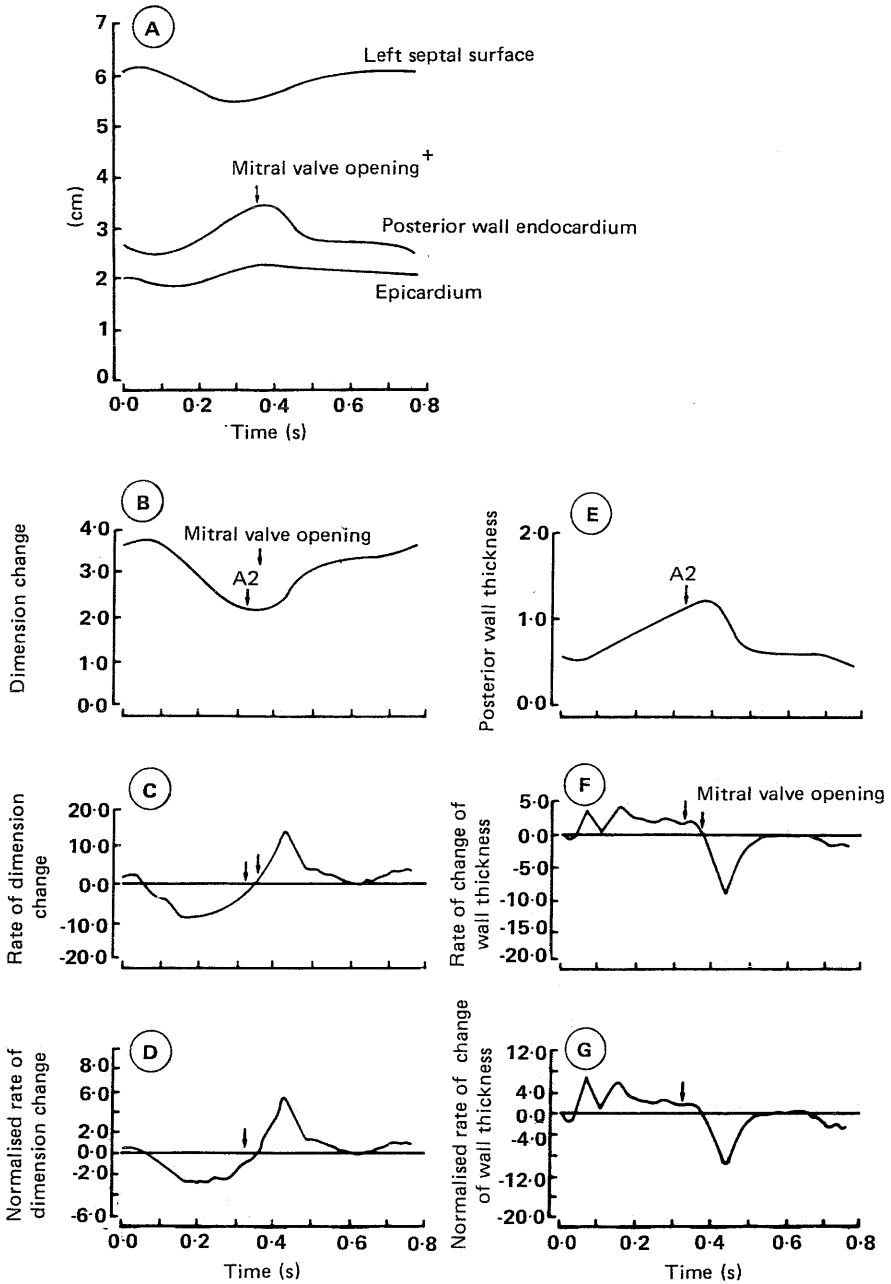


Figure After digitisation the computer plots out the echogram (A). If the plot is satisfactory it will then plot the dimension change (B); the rate of dimension change (C); the normalised rate of dimension change (D); the posterior wall thickness (E); the rate of change of wall thickness (F); and the normalised rate of change of wall thickness (G).

patients who died showed significantly abnormal values ( $p < 0.05$  and  $p \geq 0.01$ , respectively). The diastolic dynamic changes, however (peak dimension relaxation rate and normalised peak dimension relaxation rate) of group 2 survivors were already depressed ( $p < 0.01$  and  $p < 0.001$ , respectively) and those of group 2 who died were more depressed.

LEFT VENTRICULAR POSTERIOR WALL DYNAMIC CHANGES (TABLE 4)

The systolic peak wall thickening rate and the normalised value among the various groups were not significantly different. The diastolic peak wall thinning rate of group 2 survivors, however, was already significantly slower than group 1 ( $p < 0.001$ ), while that of group 2 patients who died was more

Table 2 Conventional indices of M mode echocardiography

Mean (SD) measurement	Group 1	Group 2		p Values		
		Survived	Died	Group 1 v group 2, survived	Group 1 v group 2, died	Group 2, survived v group 2, died
Left ventricular end diastolic dimension (cm)	3.87 (0.33)	4.25 (0.57)	5.07 (0.57)	<0.05	<0.001	<0.001
Left ventricular end systolic dimension (cm)	2.45 (0.17)	2.82 (0.5)	3.92 (0.6)	<0.05	<0.001	<0.001
Fractional shortening (%)	35.5 (4.5)	33.0 (3.8)	22.25 (7.5)	<0.05	<0.001	<0.001
Ejection fraction	64.0 (5.0)	59.5 (7.5)	37.05 (17.0)	>0.1	<0.001	<0.001
Left ventricular wall end diastolic thickness (cm)	0.41 (0.06)	0.52 (0.1)	0.7 (0.27)	<0.01	<0.001	<0.01
Left ventricular wall end systolic thickness (cm)	0.95 (0.1)	1.02 (0.17)	1.05 (0.27)	>0.3	>0.5	>0.9
Wall fractional thickening	1.35 (0.25)	1.0 (0.39)	0.54 (0.26)	<0.01	<0.001	<0.05

Table 3 Left ventricular dimension dynamics

Mean (SD) measurement	Group 1	Group 2		p Values		
		Survived	Died	Group 1 v group 2, survived	Group 1 v group 2, died	Group 2, survived v group 2, died
Peak left ventricular shortening rate (cm/s)	8.79 (1.50)	8.84 (1.88)	6.69 (1.78)	>0.9	<0.05	<0.05
Peak velocity of circumferential fibre shortening (circumference/s)	2.2 (0.5)	2.1 (0.4)	1.3 (0.3)	>0.9	<0.001	<0.01
Peak left ventricular dimension relaxation rate (cm)	16.34 (4.10)	12.80 (2.90)	8.9 (2.3)	<0.01	<0.001	<0.02
Normalised peak left ventricular dimension relaxation rate (circumference/s)	4.2 (1.0)	3.1 (0.6)	1.9 (0.8)	<0.001	<0.001	<0.02

Table 4 Left ventricular posterior wall dynamics

Mean (SD) measurement	Group 1	Group 2		p Values		
		Survived	Died	Group 1 v group 2, survived	Group 1 v group 2, died	Group 2, survived v group 2, died
Peak wall thickening rate (cm/s)	3.69 (0.75)	3.62 (0.81)	3.75 (1.2)	>0.9	>0.9	>0.9
Normalised peak wall thickening rate/s	6.4 (1.3)	5.38 (1.5)	4.64 (2.6)	>0.05	>0.05	>0.05
Peak wall thinning rate (cm/s)	11.56 (2.8)	6.92 (2.3)	4.64 (0.8)	<0.001	<0.001	<0.05
Normalised peak wall thinning rate/s	29.1 (8.2)	14.0 (5.8)	7.2 (1.7)	<0.001	<0.001	<0.05

depressed ( $p < 0.05$ ). The same was true when the peak wall thinning rate was normalised by the left ventricular wall end diastolic thickness.

Cross sectional echocardiographic evaluation of left ventricular motion showed no dyskinesia in any of the subjects studied.

The mean intraobserver variation of all the static indices between two studies of the same patient was 4.5 (1.5)% and that of dynamic indices was 7.5 (2)%.

## Discussion

Desferrioxamine given subcutaneously was first introduced to treat thalassaemic patients in our unit in 1979, and by now almost all patients are on iron chelation treatment at home. Since 1981 these patients have had regular echocardiographic studies, and the data in the present report represent our earlier experience with patients before chelation treatment was started. The patients were grouped retrospectively according to their outcome because it seemed reasonable to assume that the myocardial state of group 2 patients who subsequently died of cardiac compensation was preterminal, while that of the group 2 survivors was only mildly deranged. Thus theoretically the patients studied had different degrees of myocardial dysfunction. Although the mean age of the group 2 patients who died was marginally greater than the other groups, their mean body sizes (height and weight) were not significantly different.

Computer assisted analysis of M mode echocardiography is an established method of assessing myocardial function. It has been used to study a large variety of cardiac disorders in both adults and children.<sup>6-14</sup> Provided that adequate precautions are taken (selecting only the good quality echocardiographs with continuous leading edges of the septal and wall surfaces for digitisation, high speed recording of maximally expanded echocardiographic tracings, recording the left ventricular endocardium at the level of the tip of the mitral valve as a constant site of reference, and taking the mean of the results of at least three cardiac cycles) the results obtained are reliable, reproducible, and interpretable. The reproducibility of computer assisted analysis of M mode echocardiography has been previously shown<sup>17</sup> and the present study confirms it. As only one of us (KCL) was responsible for recording and digitising the echocardiographs, the variation was low. The rates of systolic and diastolic changes vary little with heart rate<sup>14</sup>; these indices, which are obtained by non-invasive means, may be ideal for monitoring myocardial performance. The method, however, has not previously been used to evaluate the myocardial function of thalassaemic patients.

Dilatation of left ventricular chambers in patients with thalassaemia has previously been shown,<sup>1-3</sup> and the results of the present study confirm this. Henry *et al* showed that the fractional shortening or ejection fraction, which were better indices of myocardial function, were only abnormal when the myocardial impairment in thalassaemia was extreme.<sup>3</sup> This phenomenon was also confirmed by our results, as those indices were still normal in group 2 survivors, but abnormal in those who died. We also found that although both the systolic and diastolic dimensional and posterior wall dynamic indices were abnormal in those with preterminal myocardial dysfunction, abnormalities of the diastolic dynamic indices alone were already present. The diastolic abnormalities seemed to become more pronounced as the myocardial impairment worsened. When the diastolic indices were normalised by the corresponding end diastolic dimension or wall thickness, an attempt to take account of chronic volume overloading and body sizes made the abnormalities more obvious. There was, however, considerable overlap among groups. Further evaluation in a longitudinal manner is necessary to confirm the usefulness of the method in monitoring these patients' myocardial function.

The phenomenon of abnormal left ventricular diastolic function with otherwise normal systolic function detected by computer assisted analysis of M mode echocardiography has been shown in such conditions as systemic hypertension and postoperative aortic stenosis, in which pathological left ventricular hypertrophy is present.<sup>6,7</sup> Using the same method, Shapiro and Smith have shown that in normal subjects physiological hypertrophy of the left ventricular wall from physical training does not give rise to any early diastolic abnormalities.<sup>17</sup> These studies confirm our belief that the depressed diastolic indices found in our group 2 patients who survived are evidence of myocardial impairment from iron deposition rather than the simple result of myocardial hypertrophy secondary to chronic anaemia. Our evaluation of a small group of patients with thalassaemia intermedia who were chronically anaemic but who were not receiving blood transfusions showed normal diastolic findings, which accords with this suggestion (unpublished observations). Additionally, our present finding of a progressive increase in end diastolic wall thickness in group 2 without the corresponding increase in end systolic wall thickness has similar implications. This again suggests that the isolated increase in end diastolic wall thickness is not the result of simple hypertrophy of the myocardial contractile fibres alone, otherwise both their end systolic and end diastolic wall thicknesses would be correspondingly

increased. Their myocardiums must have contained an appreciable proportion of non-contractile tissue, possibly reactive or replacement fibrosis, or both, together with myocardial cell death secondary to myocardial iron deposition. This is in keeping with the pathological findings in hearts with haemochromatosis.<sup>18</sup> Thus it is likely that the diastolic abnormalities found in the thalassaemic patients are the early functional result of such a pathological process. When both the diastolic and systolic functions are affected, severe myocardial cell loss and fibrosis must have been present. Whether fibrosis will regress with successful iron removal by chelation is unknown. If the answer is no, iron chelation treatment may only halt the progression of myocardial dysfunction that is already present rather than reverting it. This would imply that optimal treatment of thalassaemic patients should include early institution of iron chelating drugs well before the development of any myocardial dysfunction. Further longitudinal studies are required to clarify the issue.

Grossman and McLaurin suggested that many of the signs and symptoms of cardiac failure that had previously been attributed to abnormal early systolic performance may be caused largely by altered diastolic properties of the ventricular chambers.<sup>19</sup> Our findings confirm this, and point to the importance of evaluating the diastolic functions of the transfusion dependent thalassaemic patients. Our results show that with the use of computer assisted analysis of M mode echocardiography, abnormalities of left ventricular function are detected in children with  $\beta$  thalassaemia major before their myocardial dysfunction becomes overt. Abnormalities in diastole appear earlier and may be used to differentiate different grades of myocardial dysfunction. When both the diastolic and systolic abnormalities are present the myocardial dysfunction is terminal and the prognosis is poor. Our study should stimulate further research to validate the usefulness of the method used and to cast further light on the mechanisms of myocardial dysfunction as well as the effect of iron chelation treatment in these patients.

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Accepted 26 October 1988