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<td><strong>Author(s)</strong></td>
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<tr>
<td><strong>Citation</strong></td>
<td>Heart, 2003, v. 89 n. 6, p. 669-670</td>
</tr>
<tr>
<td><strong>Issued Date</strong></td>
<td>2003</td>
</tr>
<tr>
<td><strong>URL</strong></td>
<td><a href="http://hdl.handle.net/10722/42168">http://hdl.handle.net/10722/42168</a></td>
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Heart 2003;89:669-670
doi:10.1136/heart.89.6.669

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Early detection of left ventricular dysfunction in patients with β thalassaemia major by dobutamine stress echocardiography

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Myocardial iron deposition, among other factors, contributes to left ventricular (LV) dysfunction in patients with β thalassaemia major. Nonetheless, conventional indices have not been particularly useful for its early detection. Importantly, cardiac function deteriorates rapidly once clinical symptoms develop. Dobutamine stress echocardiography (DSE) is well accepted in the evaluation of myocardial dysfunction caused by coronary artery disease in adults. In children, DSE has been used for early detection of LV dysfunction in long term childhood cancer survivors. In this study, we assessed the usefulness of DSE for early detection of LV dysfunction in thalassaemia patients.

METHODS
Twenty six patients (17 females) with β thalassaemia major with a mean (SD) age of 17.4 (8.3) years (range 4–33 years) were studied. Their body surface area (BSA) was 1.12 (0.20) m². None had congestive heart failure clinically and all were in New York Heart Association (NYHA) functional class I at initial assessment. Monthly blood transfusion was started at a median of 11 months (range 3–96 months), while deferoxamine was started at a median age of 30 months (range 25–114 months). Post-transfusion haemoglobin was targeted at 14 g/dl (8.7 mmol/l), and echocardiographic studies were performed within one week of transfusion to minimise confounding influence of anaemia. Only one of the patients had undergone splenectomy. Twenty healthy subjects (13 females) aged 10.4 (4.5) years (range 4–15 years), with a BSA of 1.40 (0.23) m², were recruited as controls. The institutional ethics committee approved the study and parents or subjects themselves gave informed consent.

Transthoracic echocardiography was performed using Vingmed System 5 (Horton, Norway) ultrasound machine. Echocardiographic assessments were performed after 15 minutes of rest and after 10 minutes of dobutamine infusion (5 μg/kg/min). Cineloop data were digitised for offline analysis. Blood pressure was measured using an oscillometric device (Critikon, Dinamap, Tampa, Florida, USA). After the first DSE assessment, a repeated non-stressed echocardiographic assessment was performed in patients at an interval of two years.

Standard parasternal short axis view was used to derive the following: LV end systolic dimension (LVEDD), LV end-diastolic dimension (LVESD) and LV posterior wall thickness at systole (LVPWS). The fractional shortening (FS) and ejection fraction (EF) of the left ventricle were calculated according to standard formulae: FS = \( \frac{LVEDD - LVESD}{LVEDD} \) × 100% and EF = \( \frac{LVEDD - LVESD}{LVEDD} \) × 100%. The aortic ejection time (ET) and RR interval were measured by pulsed Doppler and from surface ECG, respectively. Rate corrected velocity of circumferential fibre shortening (Vcfc) was calculated by Vcfc = RR × FS/ET, while LV systolic meridional wall stress (WS) was calculated by WS = \( \frac{0.337 \times LVESP \times LVESD}{LVPWS} \). The peak systolic pressure was used to estimate LV end systolic pressure (LVESP) as this avoided the need for carotid tracing which is technically demanding in children. Average values of indices obtained from three consecutive cardiac cycles were used for analysis. The reference LV myocardial contractility index, a relatively load independent index based on the relation between Vcfc and WS, was derived from controls using linear regression at baseline and under dobutamine stress. Patients with data points lying below the 95% confidence limit were regarded as having impaired myocardial contractility.

Data are expressed as mean (SD). Differences in indices between patients and controls were compared using unpaired Student's t test, while differences between first and second assessments in patients were compared using paired Student's t test. A probability value of p < .05 was considered significant.

RESULTS
There were no significant differences in echocardiographic indices between patients and controls in the first assessment at rest (table 1). Three of the 26 patients, however, had a reduced contractility index. During dobutamine stress, patients had a significantly lower FS, EF, and Vcfc, and a higher WS (table 1). For the normal subset, LV systolic pressure was calculated by Vcfc = RR × FS/ET, while LV systolic meridional wall stress (WS) was calculated by WS = \( \frac{0.337 \times LVESP \times LVESD}{LVPWS} \). The peak systolic pressure was used to estimate LV end systolic pressure (LVESP) as this avoided the need for carotid tracing which is technically demanding in children. Average values of indices obtained from three consecutive cardiac cycles were used for analysis. The reference LV myocardial contractility index, a relatively load independent index based on the relation between Vcfc and WS, was derived from controls using linear regression at baseline and under dobutamine stress. Patients with data points lying below the 95% confidence limit were regarded as having impaired myocardial contractility.

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RESULTS
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Twenty four of the 26 patients underwent a second assessment. One patient, who had impaired LV contractility under dobutamine stress, died of congestive heart failure, while the other declined reassessment. Of the remaining 24 patients, 14 (normal subset) had a normal LV contractility index under dobutamine stress two years earlier, while 10 (abnormal subset) had subnormal LV contractility. For the normal subset, there were no significant differences in echocardiographic indices between the first and second assessments (table 1). All of these patients remained in NYHA functional class I. However, for the abnormal subset, there was a significant reduction in FS, EF, and Vcfc on follow up assessment (table 1). All had a subnormal myocardial contractility index at follow up even in the absence of stress. Furthermore, eight of the 10 patients in the abnormal subset had worsening of the NYHA functional class on follow up, seven in class II and one in class III. Thus a subnormal myocardial contractility index under dobutamine stress has a sensitivity of 80% and a

**Abbreviations:** DSE, dobutamine stress echocardiography; EF, ejection fraction; ET, ejection time; FS, fractional shortening; LV, left ventricular; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; LVESP, left ventricular end systolic pressure; LVPWS, left ventricular posterior wall thickness at systole; NYHA, New York Heart Association; Vcfc, velocity of circumferential fibre shortening; WS, wall stress.
The velocity relation is relatively age independent. Nonetheless, previous studies have shown that the stress–controls was not entirely matched to those of the patients. β be useful for early detection of LV dysfunction in patients with myocardial contractility. Thirdly, aortic ET was not assessed diagnosis rather than over diagnosis of patients with impaired confidence intervals, which, however, would result in under low dose dobutamine infusion regimen reserve rather than coronary arterial flow limiting lesions, a >10 effects has been reported to occur with an infusion rate of µg/kg/min. As we were assessing myocardial contractile including superimposed myocarditis and immunogenetic profile do interact to result in eventual LV failure.

The optimal dobutamine dose for assessment of LV reserve in children remains controversial. Nonetheless, frequent side effects has been reported to occur with an infusion rate of >10 µg/kg/min.1 As we were assessing myocardial contractile reserve rather than coronary arterial flow limiting lesions, a low dose dobutamine infusion regimen1 was used.

Certain limitations deserve comment. Firstly, the age of the controls was not entirely matched to those of the patients. Nonetheless, previous studies have shown that the stress–velocity relation is relatively age independent.1 Secondly, the relatively small number of controls might have widened the confidence intervals, which, however, would result in under diagnosis rather than over diagnosis of patients with impaired myocardial contractility. Thirdly, aortic ET was not assessed simultaneously with M mode echocardiography, but nonetheless usually within a 30 second interval.

In conclusion, findings of this study suggest that DSE may be useful for early detection of LV dysfunction in patients with β thalassaemia major.

| Table 1 | Comparison of echocardiographic indices between patients and controls at rest and under dobutamine stress (left hand columns), and comparison of indices between first and second echocardiographic assessment in “normal” and “abnormal” subsets (right hand columns) |

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline assessment</th>
<th>Dobutamine stress assessment</th>
<th>First versus second assessments</th>
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<tr>
<td>Patients</td>
<td>Controls</td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>RR [s]</td>
<td>0.80 (0.15)</td>
<td>0.79 (0.16)</td>
<td>0.78 (0.13)**</td>
</tr>
<tr>
<td>ET [s]</td>
<td>0.30 (0.03)</td>
<td>0.30 (0.03)</td>
<td>0.29 (0.05)**</td>
</tr>
<tr>
<td>FS [%]</td>
<td>0.38 (0.05)</td>
<td>0.41 (0.05)</td>
<td>0.47 (0.07)**</td>
</tr>
<tr>
<td>EF [%]</td>
<td>0.76 (0.06)</td>
<td>0.80 (0.16)</td>
<td>0.84 (0.08)**</td>
</tr>
<tr>
<td>Vcfc [circ/s]</td>
<td>1.11 (0.16)</td>
<td>1.23 (0.21)</td>
<td>1.42 (0.24)**</td>
</tr>
<tr>
<td>WS (g/cm²)</td>
<td>64.34 (14.23)</td>
<td>72.67 (11.65)</td>
<td>59.89 (22.80)**</td>
</tr>
<tr>
<td>Ferritin (µmol/l)</td>
<td>– – – –</td>
<td>4235 (792)</td>
<td>4935 (831)</td>
</tr>
</tbody>
</table>

Values are mean (SD). *p<0.05; **p<0.01; ***p<0.001.

References