Systolic and diastolic function in middle aged patients with sickle β thalassaemia. An echocardiographic study

I Moyssakis, R Tzanetea, P Tsaftaridis, I Rombos, D P Papadopoulos, V Kalotychou, A Aessopos

Objective: To evaluate the right and left ventricular systolic and diastolic function in middle aged patients with sickle β thalassaemia.

Methods: Forty three patients with sickle β thalassaemia were recruited for echocardiographic study while 55 controls, matched for age and sex, served as the control group. Parameters measured included: dimensions and wall thickness of left (LV) and right (RV) ventricle and left atrium, LV mass, and cardiac index. LV and RV contractility variables—ejection fraction, circumferential fibre shortening velocity, end systolic stress, and systolic stress/volume index ratio, mitral and tricuspid annulus systolic excursion, and Tei index—were also calculated. The study also evaluated parameters of RV and LV diastolic function including early and late atrioventricular flow velocities (E and A wave respectively), E/A ratio, deceleration time (DT), isovolumic relaxation time (IVRT) as well as pulmonary and hepatic veins systolic to diastolic (S/D) ratio.

Results: Chamber enlargement, greater LV mass index, cardiac index, and RV wall thickness were found in the anaemic group compared with controls. The LV and RV contractility variables of the patients were similar to controls. Conversely the LV and RV Tei index was significantly greater in the patient group. Diastolic dysfunction was present in the anaemic patients resulting from the increased LV and RV A-wave, the longer LVIVRT, RVIVRT, and RVDT, as well as the higher hepatic and pulmonary veins S/D ratio.

Conclusions: The results show that in middle aged patients with sickle β thalassaemia the diastolic function is abnormal in both ventricles but still more in RV, whereas the systolic function remains unchanged.

Sickle cell disease is a hereditary haemolytic anaemia characterised by the synthesis of the haemoglobin S (HbS, sickle cell haemoglobin). Homozygous sickle cell disease (SS) results from the inheritance of two sickle cell genes (β+). Coinheritance of a β gene and a β thalassaemia gene (βthal) results in different types of sickle β thalassaemia (Sβ) depending on the mutation, which is carried by the β thalassaemia gene, and the amount of HbA synthesised. If the β gene is inherited with a βthal thalassaemia gene, in which some β chains are present, the genotype is Sβ+ and if the β thalassaemia gene is β0, in which β chains are absent, the genotype is Sβ0. It is well known that whether the interacting β thalassaemia gene is β0 the clinical picture is similar to sickle cell anaemia whereas, when the interacting β thalassaemia gene is of β+ type it has milder clinical signs and symptoms.1 Cardiac abnormalities in sickle cell disease have been well described but mainly in sickle cell anaemia. However, little is known about heart involvement in sickle β thalassaemia.

The purpose of this study was to investigate the changes in systolic and diastolic function of the left and right ventricle (LV and RV respectively) in middle aged patients with sickle β thalassaemia.

METHODS

Study population

Forty three consecutive patients between 45 and 66 years (15 men, 28 women, aged mean (SD) 54 (10) years) with sickle β thalassaemia and no underlying heart disease and 55 (18 men, 37 women, aged 53 (11) years) healthy volunteers were recruited in our study. Patients with sickle β thalassaemia were recruited from the haemoglobinopathies unit of Laiko General Hospital, Athens, Greece. Inclusion criteria were, diagnosis of sickle β thalassaemia, made by solubility screening test for sickling, haemoglobin electrophoresis, and β/β chain synthesis to confirm the thalassaemic genotype. All patients were Sβ+ type, with haemoglobin concentrations higher than 70 g/l; they had painful crises and red cell transfusions rarely (less than five per year) while none was receiving drugs such as digoxin, diuretics, or vasodilators. The study protocol was approved by the institutional committee on human research and all subjects gave informed consent.

Echocardiographic evaluation

Comprehensive echocardiographic examination with pulsed, continuous, and colour Doppler was performed with a Hewlet Packard Sonos 1000 ultrasound System, using a 2.5 MHz transducer by the same cardiologist and was recorded on tape. The measurements were performed, independently, by two cardiologists unaware of the subject’s status. From the two dimensional guided M-mode echocardiogram, LV end systolic and end diastolic diameters as well as interventricular septum and posterior wall thickness at end diastole were measured for the calculation of fractional shortening (FS) and LV mass with the Penn convention formula. Measurements of LV mass were divided by body surface area to obtain LV mass index. The LV ejection fraction (EF) was determined by the biplane Simpson’s method. The LV stroke volume was also calculated as the product of the cross sectional area of the LV outflow tract and velocity time integral of the LV outflow velocity.3 The LV cardiac output was derived as the product of the stroke volume and heart rate and, divided by body surface area; the LV cardiac index was calculated. Furthermore, we measured several parameters of RV and LV diastolic function.

Abbreviations: RV, right ventricle; LV, left ventricle; DT, deceleration time; FS, fractional shortening; EF, ejection fraction; TAPSE, tricuspid annular plane systolic excursion; IVRT, isovolumic relaxation time; ESS, end systolic stress; MAPSE, mitral annular plane systolic excursion.
of less than 0.05 was considered significant.

With the echocardiographic findings, a probability (p) value was used to test the correlations between serum ferritin concentrations and the echocardiographic parameters of LV systolic function such as the circumferential fibre shortening velocity (Vcf) as the ratio FS to ejection period, the meridional end systolic stress (ESS), the ratio end systolic stress/end systolic volume index (ESS/ESVI), and the mitral annular plane systolic excursion (MAPSE). We also evaluated the myocardial performance index (Tei index) of LV and RV. Using pulsed Doppler from the mitral and tricuspid inflow velocity curves the following parameters were calculated: peak early velocity (E-wave), peak velocity at the time of atrial contraction (A-wave), E/A ratio, deceleration time (DT) of the peak early velocity, and the isovolumetric relaxation time (IVRT). For the calculation of the RV diastolic variables at least three beats from the end inspiration and three beats from the end expiration were recorded and their values were averaged. Flow velocities of the hepatic veins and upper pulmonary veins were also recorded for systolic to diastolic forward flow velocity ratio (S/D) calculation. The intraobserver and interobserver mean percentage error (absolute difference between two measurements divided by the mean and expressed in percentage) of Doppler measurements were respectively (for the LV: 3.1% and 3.3% for E-wave, 3.3% and 3.6% for A-wave, 3.5% and 4.2% for DT, 3.5% and 4.3% for IVRT whereas for the RV: 6.3% and 6.9% for E-wave, 6.5% and 7% for A-wave, 5.6% and 5.9% for DT, 5.2% and 5.5% for IVRT). Continuous wave Doppler echocardiogram recorded in the apical four chambers or parasternal short axis view was used to estimate the peak systolic pressure gradient across the tricuspid valve. A tricuspid gradient greater than 30 mm Hg was considered indicative of pulmonary hypertension.

**Statistical analysis**

Data are expressed as mean (SD). Differences between groups were compared using the unpaired Student’s t test as appropriate. Linear correlation and regression were used to test the correlations between serum ferritin concentrations with the echocardiographic findings. A probability (p) value of less than 0.05 was considered significant.

### RESULTS

As table 1 shows, the patients with sickle β thalassaemia had lower levels of diastolic blood pressure, packed cell volume, and haemoglobin and increased concentrations of serum ferritin compared with controls.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SJT</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA (cm)</td>
<td>42 (16)</td>
<td>35 (12)</td>
<td>0.05</td>
</tr>
<tr>
<td>EDD (cm)</td>
<td>52.30 (7.50)</td>
<td>49.10 (6.30)</td>
<td>0.05</td>
</tr>
<tr>
<td>ESD (cm)</td>
<td>34.50 (5.10)</td>
<td>31.20 (3.80)</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>109 (28)</td>
<td>86 (19)</td>
<td>0.01</td>
</tr>
<tr>
<td>RV diameter (cm)</td>
<td>29.50 (6.20)</td>
<td>26.60 (7.10)</td>
<td>0.05</td>
</tr>
<tr>
<td>RV thickness (cm)</td>
<td>0.32 (0.07)</td>
<td>0.29 (0.06)</td>
<td>0.05</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>4.80 (1.80)</td>
<td>3.70 (1.20)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

LA, left atrium; EDD, end diastolic diameter; ESD, end systolic diameter; CI, cardiac index; SJT, sickle β thalassaemia.

### DISCUSSION

It is well known that the clinical course for patients with sickle β thalassaemia is similar to that seen in patients with
Thus it is therefore logical to state that there is a good number of studies on sickle cell anaemia and heart involvement but only a few concerning sickle β thalassaemia.

Acquired chronic anaemia, in young or older patients, was found causing systemic hyperfunction attributable to the hyperdynamic state and no impairment of diastolic function. Similarly cardiac abnormalities in sickle β thalassaemia are thought to be secondary to anaemia-related volume overload. However, more factors such as transfusion therapy with iron overload and toxicity, renal, pulmonary and heart injury attributable to vaso-occlusive effect of sickle haemoglobin on the circulation are involved in the sickle syndrome.

In our study, the patients with sickle β thalassaemia had increased dimensions of the left atrium, and left and right ventricle than the controls. Moreover they had a greater LV mass index, a thicker RV wall, and a higher cardiac index.

We found that the LV EF and the other traditional contractility parameters—Vcf, ESS, and MAPSE—were not different between patients and controls. It is possible that the above variables are insensitive because they are load dependent and in sickle β thalassaemia patients high preload and low afterload are present. However, the ratio ESS/ESVI, which is comparatively load independent, was similar in patients and controls.

In this study, impairment of diastolic parameters of RV was not impaired as assessed by the TAPSE. Conversely the LV and RV Tei index expressing global myocardial performance significantly differs between patients and controls, distinguishing global dysfunction. The fact that the Tei index decreases in increased preload and/or decreased afterload and we found opposite results supports the notion of an abnormality mainly in diastolic function in such patients.

Significant differences as far as the parameters of ventricular filling and pulmonary and hepatic vein flow were found between patients and controls. These diastolic variables however are load dependent. Specifically the high preload and low afterload in anaemic patients would be expected to cause physiologically an increase of transstic and transmitral inflow velocities and shortened IVRT and DT, which was not the case. Thus the RV and LV filling pattern show impaired relaxation. Additionally the pulmonary and hepatic vein flow characteristics are also compatible with abnormal relaxation as the increased preload decreases the S/D ratio and our findings are opposite.

Our findings are in accordance with the findings of Braden et al who found abnormal diastolic filling pattern in patients with sickle cell anaemia and coexisting β thalassaemia-2. As in our study, they found significantly greater wall thickness but not chamber enlargement. It is possible that this happens because their population was younger but mainly because of the sickle cell anaemia and coexisting β thalassaemia-2 is less severe than sickle β thalassaemia. Previous studies have also established left sided chamber enlargement and biventricular dysfunction in patients with sickle cell anaemia. However, there is controversy about the frequency of the influence ventricle. Other investigators have found the LV ventricular performance to be normal in these patients, studied by the ejection phase parameters, and only the index ESS/ESVI ratio discriminated the above population from controls. In our study the preserved LV and RV systolic function may be associated with the Sβα type of sickle cell thalassaemia, which is less severe.

In this study, impairment of diastolic parameters of RV function was more pronounced than impairment of the respective LV function. The explanation for this may be multifactorial. This dissociation possibly reflects a preferential involvement or a higher susceptibility of the RV. The fact that the RV diastolic variables are correlated positively with the serum ferritin concentrations, support the hypothesis that lung and heart haemochromatosis affects predominantly the RV function. Hyperkinetic circulation and vaso-occlusive effects may have also more effect on the RV, which has

### Table 3

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SFT</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF%</td>
<td>58.50 (8.30)</td>
<td>61 (7.50)</td>
<td>NS</td>
</tr>
<tr>
<td>MAPSE (mm)</td>
<td>13.90 (2.10)</td>
<td>14.60 (1.70)</td>
<td>NS</td>
</tr>
<tr>
<td>ESS (kdyn/cm²)</td>
<td>93 (19)</td>
<td>86 (23)</td>
<td>NS</td>
</tr>
<tr>
<td>ESS=ESVI (kdyn/cm²)</td>
<td>2.29 (0.48/10⁴)</td>
<td>2.52 (0.71/10⁴)</td>
<td>NS</td>
</tr>
<tr>
<td>Vcf (sec)</td>
<td>1.19 (0.50)</td>
<td>1.26 (0.30)</td>
<td>NS</td>
</tr>
<tr>
<td>LV Tei index</td>
<td>0.39 (0.07)</td>
<td>0.36 (0.06)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RV Tei index</td>
<td>0.37 (0.11)</td>
<td>0.32 (0.09)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>12.80 (1.90)</td>
<td>13.40 (1.50)</td>
<td>NS</td>
</tr>
</tbody>
</table>

EF, ejection fraction; MAPSE, mitral annulus plane systolic excursion; TAPSE, tricuspid annulus plane systolic excursion; ESS, meridional end systolic stress; ESVI, end systolic volume index; Vcf, circumferential fibre shortening velocity.

### Table 4

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SFT</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV E cm/sec</td>
<td>61 (19)</td>
<td>56 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>LV A cm/sec</td>
<td>53 (12)</td>
<td>44 (15)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV E/A</td>
<td>1.17 (0.37)</td>
<td>1.28 (0.26)</td>
<td>NS</td>
</tr>
<tr>
<td>LV DT (ms)</td>
<td>185 (34)</td>
<td>178 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>LV IVRT (ms)</td>
<td>83 (17)</td>
<td>76 (11)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RV E cm/sec</td>
<td>53 (10)</td>
<td>49 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>RV A cm/sec</td>
<td>47 (9)</td>
<td>40 (8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV E/A</td>
<td>1.19 (0.22)</td>
<td>1.23 (0.25)</td>
<td>NS</td>
</tr>
<tr>
<td>RV DT (ms)</td>
<td>198 (39)</td>
<td>175 (34)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV IVRT (ms)</td>
<td>52 (13)</td>
<td>46 (11)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hepatic vein S/D</td>
<td>2.20 (1.08)</td>
<td>1.64 (0.90)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulmonic vein S/D</td>
<td>1.43 (0.50)</td>
<td>1.22 (0.30)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

E, peak velocity of early mitral or tricuspid flow; A, peak velocity of late mitral or tricuspid flow; E/A, ratio of early to late peak velocity; DT, deceleration time of early inflow; IVRT, isovolumic relaxation time; S/D, systolic to diastolic forward flow velocity ratio.
substantially a smaller mass than the LV, resulting in faster functional derangement.

In conclusion, our findings show that in middle aged patients with sickle β thalassemia, SB type, the diastolic function is abnormal in both ventricles but more noticeable in the RV. The systolic function remains unchanged. However, these abnormalities seem insignificant and well tolerated, because of sufficient cardiovascular adaptation, suggesting longer living in this population.

Authors’ affiliations
I Moyaissakis, D P Papadopoulos, Cardiology Department, Laiko General Hospital, Athens, Greece
R Tzanetin, I Rombo, V Kaloytchou, A Aessapou, First Department of Internal Medicine, University of Athens Medical School, Laiko General Hospital
P Tsaifardis, Thalassemia Department, Laiko General Hospital
Funding: none.

Conflicts of interest: none.

REFERENCES
Systolic and diastolic function in middle aged patients with sickle β thalassaemia. An echocardiographic study
I Moyssakis, R Tzaneta, P Tsafaridis, I Rombos, D P Papadopoulos, V Kalotychou and A Aessopos

Postgrad Med J 2005 81: 711-714
doi: 10.1136/pgmj.2004.031096