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Left Ventricular Diastolic Dysfunction in Congenital Chronic Anaemias During Childhood as determined by Comprehensive Echocardiographic Imaging including Acoustic Quantification

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Aims: To evaluate prospectively the left ventricular performance in thalassaemia major and sickle cell disease using comprehensive echocardiographic imaging including acoustic quantification during early childhood.

Methods and Results: Twenty-three patients with thalassaemia and 26 patients with sickle cell disease underwent echocardiographic examination including M-mode, 2-D, Doppler and acoustic quantification. All patients were matched for age, sex, weight and height with 20 normal controls. All patients were below 13 years of age. Thalassaemia and sickle cell disease patients were significantly anaemic when compared with normals ($P<0.0001$). All patients had normal left ventricular systolic parameters. Acoustic quantification-derived left ventricular volumes, filling rates, and emptying rates were not different in thalassaemia patients from controls. Left ventricular volumes, however, were larger in sickle cell disease patients than in controls. In contrast, by Doppler technique, left ventricular filling occurs mainly in early diastole (E wave) in thalassaemia patients and mainly in late diastole (A wave) in sickle cell disease patients, ($P=0.03$ and 0.01 respectively). E/A ratio was lower and diastolic filling period was shorter than normal in sickle cell disease but not in thalassaemia patients. Patients in both groups had left ventricular mass (determined by M-mode) significantly higher than normal ($P<0.0001$).

Conclusion: The left ventricular systolic performance is well preserved in patients with chronic anaemia due to thalassaemia major and sickle cell disease during early childhood. In both diseases, however, there is left ventricular hypertrophy and measurable abnormalities in the diastolic filling detected by Doppler. Such changes do not fit a specific cardiomyopathic pattern due to diastolic dysfunction i.e. restrictive physiology vs delayed relaxation. Acoustic quantification of left ventricular diastolic parameters (filling rates) was less sensitive than Doppler in detecting these early diastolic abnormalities in both diseases.

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Key Words: left ventricular dysfunction; congenital chronic anaemias.

Introduction

Thalassaemia major and sickle cell disease are both genetically inherited anaemias of childhood. The haemodynamic load posed on the cardiovascular system due to the anaemia caused by both diseases is well recognized. The myocardium, however, is affected by a different pathophysiologic mechanism[1,2].

Echocardiography has been an important tool in monitoring the cardiac function in these patients. Specific diastolic abnormalities can now be demonstrated by Doppler echocardiography[3–18]. Acoustic quantification, a newly applied echocardiographic technique[19,20], is currently increasingly applied together with Doppler technique in that regard.

The main objective of this study was to evaluate the left ventricular performance, both systolic and diastolic,

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Table 1. Demographic data on patients and controls.

Parameter	Thalassaemia patients	SCD patients	Controls
N	23	26	20
Age (years):			
mean ± SD	11 ± 2·7	10·2 ± 2·6	9 ± 2·7
range	3–14	5–14	3–13·2
95% CI	10–12	9·1–11·2	7·2–10·7
Sex:			
male	7	19	12
female	16	7	8
Weight (kg):			
mean ± SD	29 ± 6·6	26·9 ± 7·7	26·7 ± 6·7
range	13–42	12·7 ± 47·5	19–38
95% CI	27–31	24–30	22·6–30·8
Height (cm):			
mean ± SD	130 ± 13·3	130·5 ± 16·1	128·8 ± 15·9
range	91–151	100–165	112–157
95% CI	126–135	123–138	119–138
BSA (M^2):			
mean ± SD	1 ± 0·2	0·98 ± 0·2	1 ± 0·2
range	0·6–1·3	0·6–1·48	0·8–1·3
95% CI	1–1·1	0·9–1·1	0·87–1·1
Hg (g)*			
mean ± SD	7·7 ± 1	8·9 ± 1·5	12 ± 1
range	6–10	7–13	10–13
95% CI	7·4–8·1	8–9·5	11–12·5
Hct (%)*			
mean ± SD	22·8 ± 3	26·6 ± 4·7	35–2·6
range	18–30	18–38	29–37
95% CI	21·7–23·8	25–29	33–36·5

*P is <0·0001 when thalassaemia or SCD patients were compared with each other or with normal controls.

in a group of children with thalassaemia major and sickle cell disease by comprehensive echocardiographic imaging including acoustic quantification, and to compare the latter technique with the conventional Doppler.

Methods

Patients

Thalassaemia Patients

Twenty-three patients with thalassaemia major who are enrolled in a regular blood transfusion programme at our institution were included in this study. These patients are admitted regularly to the hospital (same day procedure) where they receive a monthly blood transfusion. Their demographic data are summarized in Table 1. The echocardiographic examinations were performed on admission and just prior to the monthly blood transfusion, which constitutes a considerable volume in these young subjects.

Sickle Cell Disease Patients

Twenty-six patients with sickle cell disease were included. These patients were admitted to the hospital for treatment of acute vaso-occlusive crises and underwent their cardiac evaluation immediately prior to their discharge from the hospital after complete recovery. None of these patients was receiving intravenous fluids at the time of the echocardiographic examination (Table 1).

Normal Controls

Twenty age, sex and body surface area matched normal controls were included. They were evaluated either for an innocent heart murmur or trivial lesion such as a tiny muscular ventricular septal defect, patent foramen ovale, etc. Some of the control subjects were matched with more than one patient due to the smaller number of the control subjects and the unequal distribution of gender among the three groups. The study was approved by the institutional public relations and medical support services department.

Echocardiographic Examination

A comprehensive echocardiographic examination was obtained on each patient including two-dimensional, M-mode, Doppler and acoustic quantification. Hewlett-Packard Sonos 1500 and 5500 echocardiographic systems were used for all patients. All studies were performed by the same echocardiographic technologist (MP), to eliminate inter-observer variability. All M-mode, Doppler and acoustic quantification parameters were obtained from 5–10 cardiac cycles and averaged. Nine of the thalassaemia patients underwent more than one echocardiographic examination (total 37 studies). The difference between one study and the subsequent one (at least one month apart) was 3–7%, which was considered acceptable intra-observer variability. Each echocardiographic examination included, in order, the following modalities and left ventricular parameters:

(1) *M-mode* of the left ventricular parasternal long axis view: left ventricular end-systolic dimension, end-diastolic dimension, end-diastolic thickness of interventricular septum and posterior wall. All these parameters were indexed for the body surface area and expressed in millimetres (mm). The left ventricular fractional shortening (SF%) was calculated and expressed as percentile. The left ventricular muscle mass was calculated from the equation (Devereux *et al.*): left ventricular mass=0.80 $(1.04 \times (\mathrm{IVS}+\mathrm{EDD}+\mathrm{PW})^{3}-(\mathrm{EDD})^{3})+0.6$ and expressed in gm/M^2 body surface area.
(2) *Two-dimensional echocardiogram*. Using sequential imaging from standard windows.
(3) *Doppler interrogation* of all valves and great vessels: The mitral valve Doppler signal (left ventricular inflow) was obtained from the four-chamber view

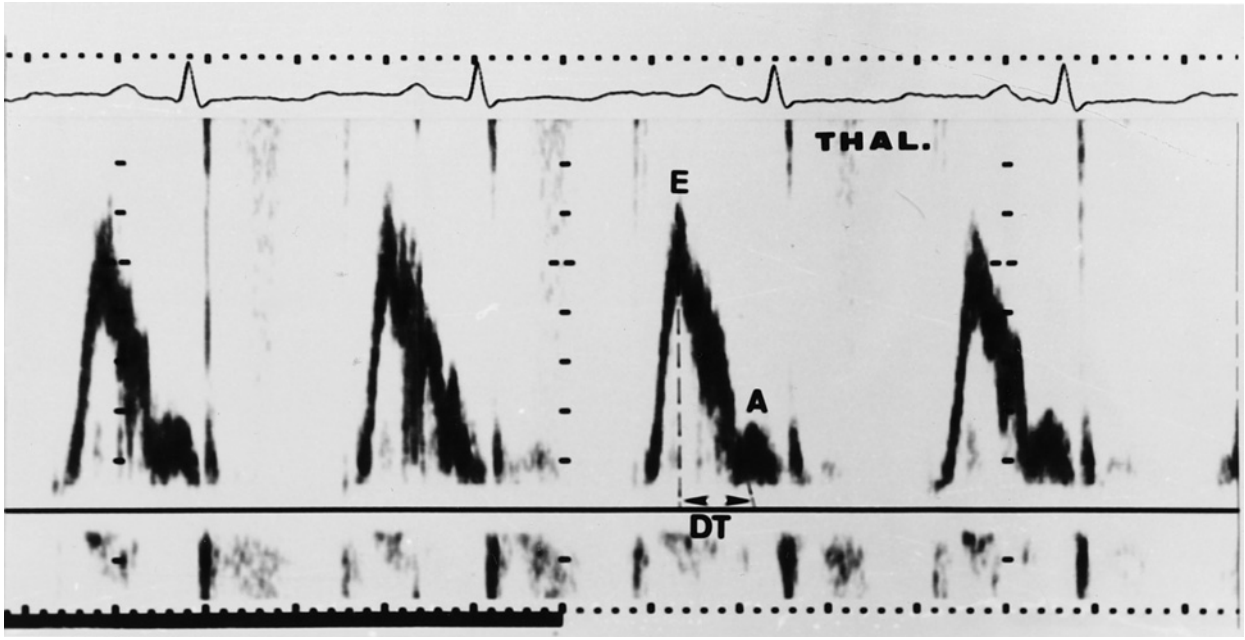

Figure 1. Mitral flow Doppler signal from a patient with thalassaemia major (Thal) showing increased flow velocity in early diastolic (E wave). DT=deceleration time.

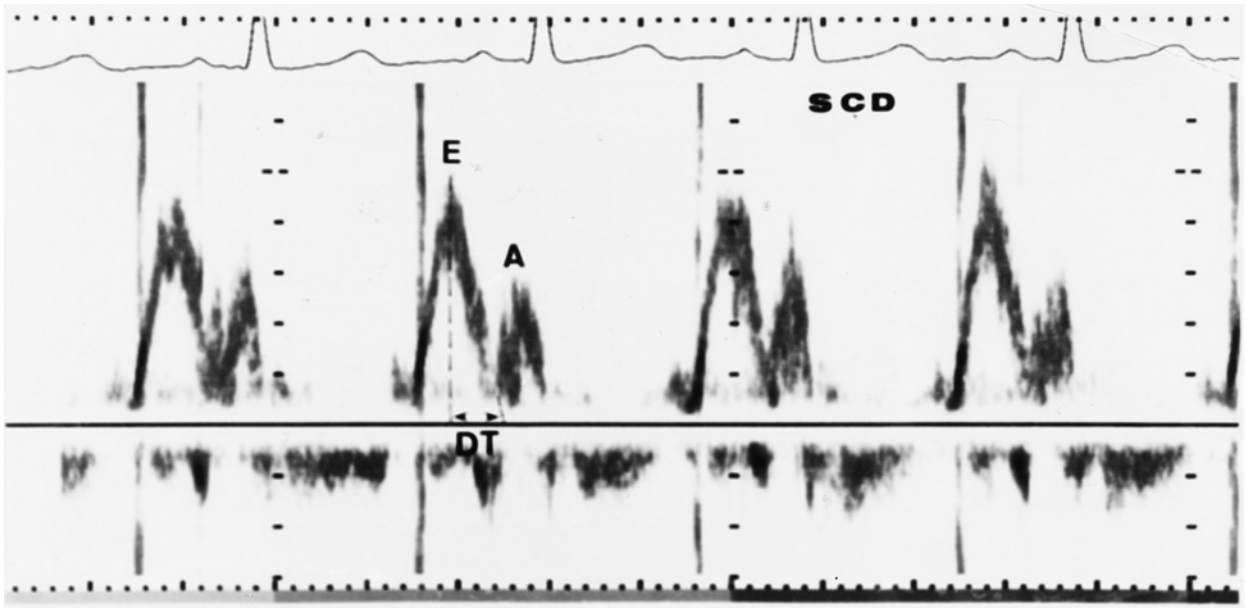

Figure 2. Mitral flow Doppler signal from a patient with sickle cell disease (SCD) showing increased flow in late diastole (A wave) with decreased E/A ratio.

where the left ventricular was displayed in the correct anatomic position with the apex down. The sample volume was kept in its smallest configuration and at the tips of the mitral valve leaflets in all patients. All measurements were made on frozen images on-line using the available software package of the ultrasound system. The following parameters were measured: peak of E wave (cm/s), peak of A wave (cm/s), E/A ratio, the deceleration time (in m/s), which is the time from the peak filling to an extrapolation of the rate of decline of the velocity to baseline (Figs 1 and 2), and the total diastolic filling period (in m/s).

(4) *Acoustic quantification*. Following the conventional echocardiographic examination, the four-chamber view was obtained and the settings of the system were adjusted to obtain the optimal left ventricular border detection as described previously[19]. The following left ventricular indexes were measured on each patient: end-diastolic volume and end-systolic

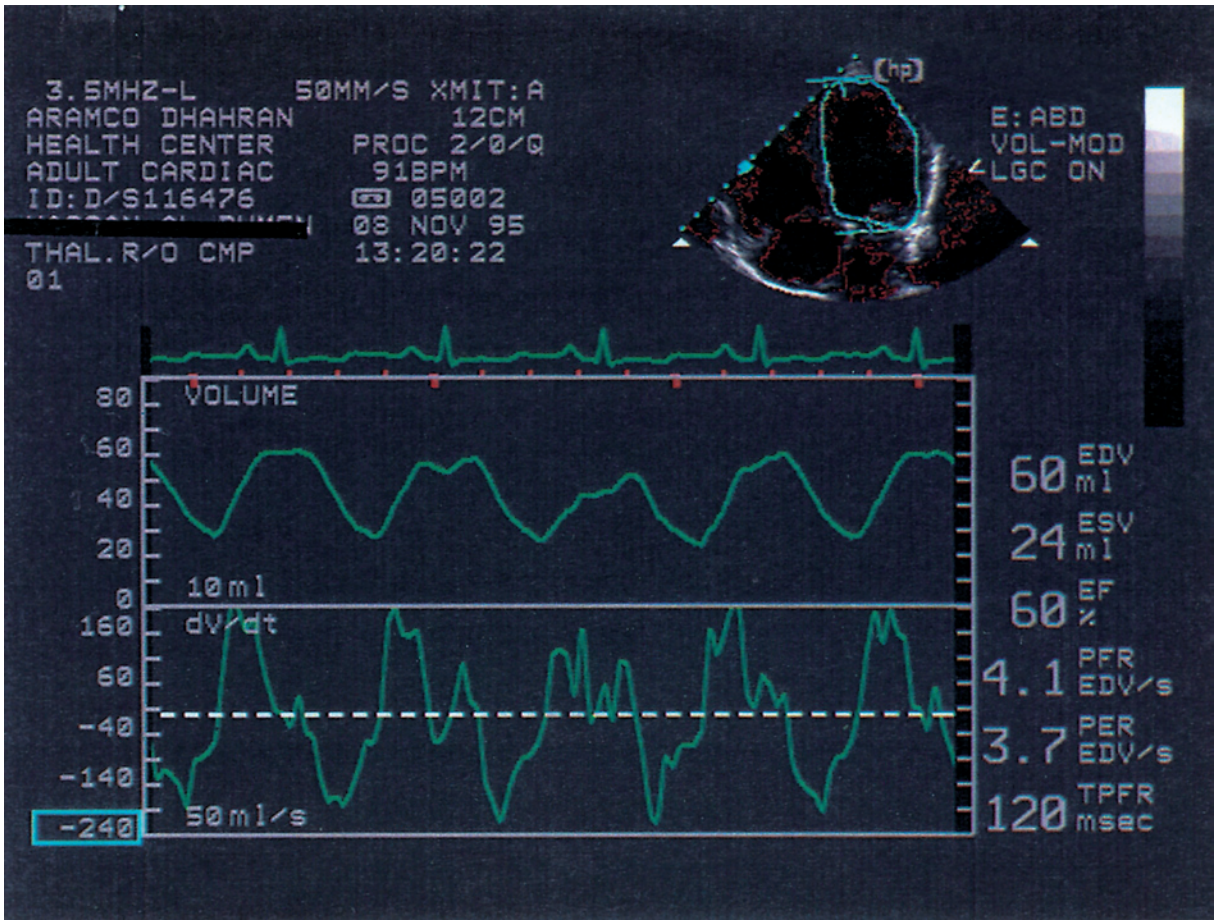

Figure 3. Waveform recording of acoustic quantification of the left ventricle of a patient with thalassaemia major.

volume both in ml/M^2 body surface area, peak filling rate normalized for end-diastolic volume, peak ejection rate normalized for end-diastolic volume, time to peak filling rate (in m/s), and ejection fraction (EF%) (Fig. 3).

Statistical Analysis

All results are expressed as mean ± standard deviation with both range and 95% confidence limits. Student *t*-test, paired *t*-test, Mann–Whitney rank sum and Chi-square (χ^2) analysis were used to compare between the groups. A *P* value of 0·05 was considered statistically significant.

Results

Demographic and haematologic parameters (Table 1)

Thalassaemia and sickle cell disease patients were well matched with the normal controls for age, sex, weight, height and body surface area. The haemoglobin and haematocrit were lower in thalassaemia patients than sickle cell disease patients ($P<0.0001$) and in both diseases than in control subjects ($P<0.0001$). Serum ferritin in thalassaemia patients was 5262 ± 2124, range 1169–8608 and 95% (CI) 4454–6070.

Left Ventricular Systolic Performance

In both diseases, the left ventricular systolic performance was preserved. Both M-mode derived percentage of shortening fraction (SF%) and acoustic quantification derived ejection fraction (EF%) and emptying rates were normal in both patient groups (Table 2).

Left Ventricular Diastolic Parameters

The diastolic properties of the left ventricle assessed by M-mode measurements, Doppler spectral signal analysis and, acoustic quantification are presented in Table 2.

(A) Left Ventricular Geometry

In patients with thalassaemia major and those with sickle cell disease, the left ventricular muscle mass was

Table 2. Echocardiographic parameters of patients and controls.

LV parameter	Thalassaemia patients n=37	SCD patients n=26	Normals n=20
M-Mode:			
End-diastolic dimension (mm/M^2)	4·5 ± 0·6	4·6 ± 0·9	4·2 ± 0·6
End-systolic dimension (mm/M^2)	2·8 ± 0·5	2·7 ± 0·6	2·5 ± 0·4
Inter-ventricular septum (mm/M^2)	0·7 ± 0·2	0·8 ± 0·2†	0·6 ± 0·1
Posterior wall (mm/M^2)	0·6 ± 0·1*	0·6 ± 0·1†	0·5 ± 0·07
SF%	38 ± 5·3%	40 ± 4·5%	39 ± 5%
Left ventricular muscle mass g/M^2	81 ± 21*	79 ± 22†	56 ± 8·9
Doppler:			
E wave (cm/s)	126 ± 17*	113 ± 17‡	113 ± 17
A wave (cm/s)	68 ± 14	76 ± 19†	60 ± 10
E/A ratio	1·9 ± 0·5	1·6 ± 0·4†‡	1·95 ± 0·5
Deceleration time (msec)	143 ± 49	118 ± 52	177 ± 90
Diastolic filling period (msec)	315 ± 53	276 ± 67†‡	364 ± 120
Acoustic quantification:			
End-diastolic volume (ml/M^2)	39 ± 10	45 ± 9†‡	36 ± 7·3
End-systolic volume (ml/M^2)	18 ± 6	20 ± 6†	15 ± 3·8
EF%	56 ± 7%	54 ± 7·8%	58 ± 6%
Peak filling rate normalized for end-diastolic volume	4·7 ± 0·7	4·7 ± 0·8	4·6 ± 0·9
Peak ejection rate normalized for end-diastolic volume	3·9 ± 0·6	4 ± 0·7	3·9 ± 0·4
Time-to-peak filling rate (msec)	110 ± 30	122 ± 44	124 ± 32
R–R interval (msec)	709 ± 88	732 ± 76	732 ± 127
Blood pressure (mmHg):			
Systolic	103 ± 14	106 ± 9	106 ± 7
Diastolic	58 ± 8	63 ± 6	61 ± 9
Mean	73 ± 8	77 ± 7	75 ± 5

*=$P \leq 0{\cdot}05$ compared with controls.
†=$P \leq 0{\cdot}02$ compared with controls.
‡=$P0{\cdot}01$ compared with thalassaemia.

significantly greater than normal ($P<0.0001$, Table 2). This was due to increased ventricular dimensions, (although it did not reach statistical significance), and wall thickness that reached statistical significance for the posterior wall in both diseases and for the intraventricular septum in sickle cell disease patients. In other words, these ventricles were mildly dilated and also had thicker walls.

(B) Doppler Mitral Inflow Dynamics

In thalassaemia major patients, mitral inflow analysis (Fig. 1) showed increased flow during early diastole (E wave). A wave, E/A ratio, diastolic filling period, and the deceleration time were not different from control.

In sickle cell disease, on the other hand (Fig. 2), the flow is increased in late diastole (A wave) while the E wave was not different from control. However, E/A ratio, and diastolic filling period were lower than normal.

The main difference between thalassaemia patients and sickle cell disease patients was in the higher E wave and E/A ratio in thalassaemia patients and shorter diastolic filling period in sickle cell disease patients.

(C) Acoustic Quantification

Acoustic quantification volumetric parameters (end-diastolic volume and end-systolic volume) (Fig. 3) showed significantly dilated left ventricle in sickle cell disease when compared with both controls and thalassaemia patients. The left ventricular volumes, although larger in thalassaemia patients than controls, did not reach statistical significance. Both filling and emptying rates (peak filling rate and peak ejection rate) did not differ from controls in either group.

Discussion

In chronic anaemia of childhood, as in thalassaemia major and sickle cell disease, there is a two-fold burden imposed on the cardiovascular system, namely the haemodynamic effect of the anaemia and the influence of the myocardial insult caused by iron overload in thalassaemia syndrome or the sickling process in sickle cell disease. The increase in the preload and afterload caused by the anaemia will eventually result in left ventricular hypertrophy as well as dilatation. Development of congestive heart failure in children and young adults is usually related to co-existing complications of the disease and not due to the anaemia itself. The major morbidity and mortality in thalassaemia patients develop as a result of iron overload and cardiomyopathic changes as time passes while they are receiving chronic blood transfusions [1]. Chronic anaemia itself does not

lead to congestive heart failure in the absence of underlying myocardial disease[2]. Echocardiography has been well utilized for assessment of the left ventricular performance in patients with severe anaemia. Several left ventricular diastolic abnormalities have been documented in both diseases using conventional echocardiographic modalities (i.e. M-mode, two-dimensional and Doppler)[3–18]. More recently acoustic quantification (or automated endocardial border detection) has been used to obtain both volumetric data and filling rates of left ventricle[19,20].

Left Ventricular Performance in Thalassaemia Major as Determined by Echocardiography

The left ventricular systolic performance has been documented to be normal in thalassaemia patients at rest in the early course of the disease (i.e. young subjects). M-mode echocardiography showed normal fractional shortening at rest[3,4]. However, exercise testing revealed overall abnormal systolic performance in transfusion-dependent patients at peak exercise[5,6]. The left ventricle of these patients is usually dilated and has increased muscle mass[7,8]. More recently, Doppler echocardiography has evolved as a main non-invasive modality for evaluating the left ventricular diastolic abnormality. Such an abnormality is usually described in terms of abnormal relaxation or restrictive physiology with decreased chamber compliance[9,10]. Several studies have been reported on the left ventricular diastolic performance of thalassaemia patients using Doppler echocardiography[11–15]. Although most of these studies reported a wide range of diastolic abnormalities in these patients, there has been a large discrepancy in the age groups and study designs, which precluded a general agreement between these studies in their findings. Some studies suggested restrictive physiology and decreased left ventricular chamber compliance[11], which was not confirmed by other investigators[12]. The influence of chronic blood transfusion and chelation therapy was also controversial among those investigators[4–6,13–15].

In our study, patients with thalassaemia major showed abnormal mitral flow velocity curve because of increasing E wave (Fig. 1). A wave, E/A ratio, diastolic filling period, and the deceleration time were all normal. Therefore, although abnormal, this pattern does not fully fulfil the criteria of a restrictive physiology[9,10].

Left Ventricular Performance in Sickle Cell Anaemia as Determined by Echocardiography

Patients with sickle cell anaemia are also known to have dilated ventricles and abnormal left ventricular diastolic properties as determined by conventional echocardiography. Both systolic and diastolic dimensions and wall thickness are increased compared with controls[16]. The left ventricular muscle mass is usually increased[17]. Their systolic function, however, remained normal[17,18].

These left ventricular geometric changes may be related to the duration of the anaemic process (i.e. haemoglobin level), which in turn is related to the age of the patient. No specific cardiomyopathic pattern was reported in these patients[18]. In the present study, our patients have Doppler evidence of a diastolic abnormality. The height of the A wave is increased and the E/A ratio is decreased (a pattern seen in delayed relaxation), while the deceleration time was shortened (though it did not reach statistical significance), which is typically seen in restrictive physiology with decreased chamber compliance (Fig. 2).

It is clear that our patients with thalassaemia major and those with sickle cell disease had measurable abnormalities in the diastolic filling of the left ventricle (as determined by Doppler), while preserving their systolic function. These changes, taken together with increased left ventricular muscle mass and dimensions would indicate early diastolic dysfunction. However, it is difficult in our patients and in those reported by others, to fit either thalassaemia patients or sickle cell disease patients in a specific cardiomyopathic pattern due to diastolic dysfunction, i.e., restrictive physiology vs delayed relaxation. This issue is further complicated by the loading effect of the anaemia process itself on the left ventricle and the effect of chronic blood transfusions with fluctuating haemoglobin levels in the thalassaemia patients.

Acoustic Quantification of Left Ventricular Performance in Anaemia Patients

Acoustic quantification was used in these patients in an attempt to better delineate the magnitude of these diastolic abnormalities. This relatively new echocardiographic modality, allows instantaneous on-line assessment of load dependent parameters of systolic performance (e.g., ejection fraction and peak emptying rate) and diastolic performance (e.g., peak filling rate and time-to-peak filling rate)[19,20]. In this study, acoustic quantification confirmed the presence of normal systolic performance in both diseases as found by M-Mode while the magnitude of the diastolic abnormalities (i.e., filling rates) did not reach a level of significance.

The volumetric data showed dilated ventricles in sickle cell disease patients, but not in thalassaemia patients (Table 2). This probably reflects the effect of long-standing lower haemoglobins in sickle cell disease while chronic blood transfusions correct the haemoglobin periodically in thalassaemia patients. The disease process in both patient populations did not affect the filling or emptying rates, which did not differ from those of controls. Therefore, this technique was helpful to

confirm the main findings of other conventional echocardiographic techniques, i.e., preserved systolic function, dilated ventricles and non-specific diastolic abnormalities.

Limitations of the Study

Although this study was prospective, there were some limitations worth mentioning. The number of the patients in each group was relatively small. The number of our patients with thalassaemia major included in the chronic blood transfusions programme was small and we tried therefore, to keep the patient number more or less equal in the three groups. The male:female ratio is reversed between the two groups. Although it is understood that the haemodynamics in both diseases are similar in some aspects (i.e. chronic anaemia leading to dilated ventricles with increased muscle mass), they differ in the basic pathophysiological process, i.e., iron overload vs sickling, which may explain the difference in the diastolic abnormalities. The volumetric data measured by M-Mode vs those measured by acoustic quantification should not be compared as they are obtained by completely different techniques[20]. This study did not specifically address the acute influence of blood transfusion in thalassaemia patients and, therefore, immediate post-transfusion assessment of those patients was not part of this study although reported not to be different in other studies[13].

Many diastolic indices isovolumic relaxation time, pulmonary venous flow tracings, etc. were not part of Doppler assessment of these young patients due to technical reasons (young and small subjects, not sedated, hospital environment, etc.).

There is also some degree of overlap in many of the indices measured between patients and controls, which is well illustrated in the wide range of these values, i.e., many individual patients had values not different from their control. Several statistical analyses, however, were applied to these measured indices to test the differences between the three groups. When there was a disagreement between any of these statistical methods, i.e., when one test showed a significant difference and the other did not, the P value was considered not significant. For example the deceleration time in SCD patients was significantly shorter than controls using the student t-test but not Mann–Whitney rank sum test. Therefore, P was reported as = NS.

Clinical Implications

This study documented the presence of early, non-specific diastolic abnormalities in both groups of young patients. Acoustic quantification is complementary to other conventional techniques in confirming the normal systolic performance, evaluating the volumetric data, and serially following the filling rates in these young subjects. Such diastolic abnormalities, as shown in this report, can be detected very early in the course of the chronic disease provided that all available echocardiographic modalities are used in a complementary fashion. No single imaging modality is sensitive enough to detect these early and subtle abnormalities. Serial follow up of these young subjects, therefore, is a fundamental part of their overall care to address any diastolic abnormalities before the development of systolic dysfunction, which is usually a late sequale of the disease.

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