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Cardiac Abnormalities in Children With Sickle Cell Anemia

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Sickle cell anemia (SCA) results in chronic volume overload of the heart due to hemodilution. Previous echocardiographic studies of cardiac function in children with SCA have not accounted for these abnormal loading conditions. The objectives of this study were to (1) determine how the degree of anemia and transfusion status relate to cardiac findings and (2) evaluate cardiac function using load-independent parameters of function. We evaluated 77 patients with SCA, ages 2 to 22 years (mean ± SD = 11.7 ± 4.7), using physical examination, electrocardiography, and echocardiography. We compared two groups of patients. Group 1 consisted of 57 non-transfused patients, and Group 2 consisted of 20 patients on a chronic transfusion protocol. Group 1 patients exhibited a significantly lower hemoglobin, higher cardiac output, and larger left ventricular (LV) end-diastolic dimension and LV mass than groups 2 (P < 0.05). However, the velocity of circumferential fiber shortening-wall stress index (a load-independent measure of systolic function) was normal and not statistically different between the two groups. Conversely, the LV myocardial performance index (a measure of combined systolic and diastolic function) was significantly higher in Group 2 (P < 0.001), possibly indicating impaired myocardial diastolic function. SCA in children results in a volume-overloaded heart with a significant increase in LV dimensions and mass, both proportional to the degree of anemia. Despite these abnormal loading conditions, systolic function is preserved. Patients on a chronic transfusion protocol may develop diastolic dysfunction despite iron chelation therapy. Am. J. Hematol. 70:306–312, 2002.

Key words: sickle cell anemia; cardiac disease; child

Children with sickle cell anemia (SCA) constitute the largest subgroup of patients with chronic anemia in the United States. To compensate for the chronic anemia, these patients increase their cardiac output to maintain oxygen delivery [1]. Cardiac output is dependent on heart rate and stroke volume, and the increase in cardiac output is believed to be due mainly to an increase in the stroke volume [2]. To accommodate this increase in stroke volume, the heart enlarges. Therefore, "normal" values for ventricular dimensions in the general population are not applicable in these patients. In a study by Lester et al., the increased ventricular dimensions in sickle cell patients were apparent after 2 years of age [1]. Despite these increased dimensions, resting parameters of ventricular function—based on shortening fraction, ejection fraction, and the mean velocity of circumferential fiber shortening (V_{cfc})—were found to be comparable to that of control subjects.

It is important to accurately evaluate cardiac function in children with SCA, as it may be compromised from iron overload [3–5], chronic volume overload [6,7], or micro-infarcts [8]. The problem with commonly used indices of cardiac systolic function, like shortening fraction, ejection fraction, and V_{cfc}, is that they are dependent

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on left ventricular loading conditions. Therefore, any condition that causes a change in ventricular volume (i.e., loading) can artificially alter these indices, despite the fact that intrinsic myocardial contractility has not changed. Since children with SCA are volume overloaded due to their anemia, they represent one such subgroup of patients in which the conventionally used indices of systolic function might not be a true reflection of intrinsic cardiac function. Because it is known that patients with SCA can develop abnormalities of both systolic and diastolic function [9–11], it is important to assess the cardiac function in these volume-overloaded patients using a *load-independent* measure. One such measurement is the stress–velocity (V_{cfc}–wall stress) index. This index provides a measure of cardiac contractility that is independent of loading conditions and heart rate [12]. It has the added advantage of comparing patient values to a defined population of normal individuals. It is, however, limited only to assessment of left ventricular systolic performance.

The myocardial performance index (MPI) is a relatively new index for assessing combined systolic and diastolic function of the heart. It is a quick and easy index to obtain and is not dependent on the geometric shape of the ventricle. This may be especially beneficial for measuring the right ventricular function, where the complex geometric shape has limited accurate assessment of function by non-invasive means. Previous studies have found a good correlation of MPI with invasive measures of systolic and diastolic function [13]. MPI has also been found to be independent of variability in heart rate (range 50–120 beats/min) or age in the pediatric population [14]. MPI has not been previously used to evaluate cardiac function in diseases associated with iron overload.

The objectives of our study were as follows:

1. Define the echocardiographic, ECG, and physical examination findings in a large cohort of children with SCA.
2. Evaluate systolic performance in SCA children using load-independent measures of cardiac contractility (V_{cfc}–wall stress index).
3. Evaluate systolic and diastolic function using MPI in children with SCA.
4. Define how the above findings relate to the degree of anemia and transfusion status.

METHODS

Study Population

We prospectively evaluated 77 patients with SCA, ages 2 to 22 years, between August 1999 and March 2001. These patients were recruited during their routine clinic visits. Two groups of patients were studied. The first consisted of 57 non-transfused patients, and the second consisted of 20 patients on a chronic transfusion protocol. All patients in Group 2 were transfused every 3–4 weeks and all were on iron chelation therapy with deferoxamine. Indications for chronic transfusion protocol included a history of cerebrovascular accident ($n = 17$), recurrent acute chest syndrome ($n = 2$), and increased transcranial Doppler velocity ($n = 1$).

Patients who had echocardiograms performed during a sickle cell crisis were not included in the study. Hemoglobin SC and hemoglobin S β-thalassemia patients were excluded. One patient was excluded after a large atrial septal defect was found during the echocardiogram, and another was excluded due to the presence of concomitant systemic lupus erythematosis with cardiomyopathy and renal failure. This study was approved by the Institutional Review Boards of Childrens Hospital Los Angeles and University of Southern California/Los Angeles County Hospital. Prior to enrollment in the study, informed consent was obtained from each patient and/or legal guardian.

Cardiac Evaluation

Physical examination, electrocardiogram (ECG), and echocardiogram were performed on all patients. The physical examination involved palpation, inspection and auscultation of the heart for the grade of murmur and for any signs of heart failure, including a gallop rhythm, cardiomegaly, hepatomegaly, jugular venous distention, or coarse rales on lung auscultation. A single observer (ASB) did all exams. A 12-lead ECG was done at the same time, and the amplitudes of the S waves in lead 1 and of the V1 and R waves in lead V6 were measured. Evidence of ST segment changes or T wave abnormalities was also evaluated [15].

Echocardiographic evaluation. Standard two-dimensional, M-mode, and Doppler echocardiograms were performed in the supine and left lateral decubitus positions using a Sonos 5500 echocardiography machine (Agilent, Inc., Andover, MA) and a 3–7 MHz transducer. Standard parasternal, apical, subxiphoid, and suprasternal views were used. The left ventricular systolic (LVSD) and diastolic (LVDD) dimensions were measured directly using M-mode echocardiography according to the recommendations of the American Society of Echocardiography [16]; these values were then used to calculate the shortening fraction (SF), a quantitative measure of systolic function. Cardiac Index (CI) was calculated from two-dimensional and Doppler echocardiography using previously described equations for volumetric flow [17]. We used two-dimensional echocardiography to determine left ventricular mass [18,19] by the area–length method [20,21]. The V_{cfc}, which measures rate of shortening of the left ventricle, was derived by dividing the shortening fraction by the left ventricular ejection time [12]. Meridional wall stress (WS) is defined as the force per unit area acting at the equatorial plane of the ventricle in the direction of the apex to base axis. It was calculated by a formula that uses the mean blood pressure, the LV systolic dimension, and the LV posterior wall thickness [22]. The relationship of the V_{cfc}–WS is then compared to normal values and reported as a *Z*-score. Individuals with a *Z*-score below negative 2 are considered to have diminished ventricular contractility. The MPI was calculated as the sum of the isovolumetric contraction and relaxation times standardized for the ejection time using Doppler echocardiography (Fig. 1) [13]. In the normal pediatric population, an MPI value of 0.32 ± 0.10 has previously been reported [23]. Higher MPI values indicate worsening combined systolic/diastolic function. A single observer (ASB) made all measurements on three to five cardiac cycles using a digitizer interfaced with a computer. The observer was blinded to the history of transfusion and hemoglobin levels.

Statistical Analysis

Cardiac dimensions for the SCA patients were compared to values from the normal predicted equations [24], and each observed value was then expressed as a standard deviation (SD) from the normal predicted value (*Z*-score).

The means of all the continuous variables were compared between the two groups using the two-sample Student's *t*-test and the Mann–Whitney *U*-test. For categorical variables, Fisher's exact test was applied to test the equality of distributions between the two groups.

A Pearson correlation was computed on the pairs of LV MPI and each of the demographic and echocardiographic variables. A multiple regression was then applied to the same set of variables, simultaneously adjusting for the effect of each other. All statistical analyses were performed with the software, The SAS Systems for Windows (Version 8, 1999, SAS Institute Inc., Cary, NC).

RESULTS

Of the 77 patients evaluated, 46 (60%) were males and 31 (40%) were females ranging in age from 2 to 22 years (mean ± SD = 11.7 ± 4.7 years). Group 1 (non-transfused) subjects had significantly lower mean hemoglobin than Group 2 (transfused) patients. The mean ± SD hemoglobin for Group 1 was 8.1 ± 1.3 g/dL (range 6.4–11.6 g/dL), and that for Group 2 was 10.0 ± 0.9 g/dL (range 8.1–11.6 g/dL). There was no significant difference between the groups with regard to age, gender, or ethnicity. The demographic characteristics of the study groups are summarized in Table I.

There were more loud (≥ grade 2) murmurs in Group 1 (84%) when compared to Group 2 (40%) ($P < 0.001$).

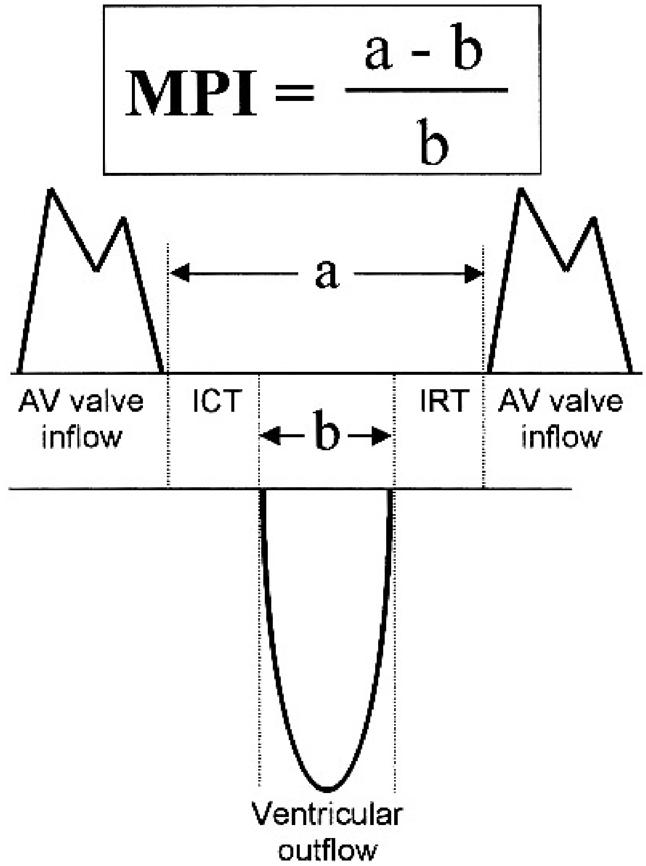

Fig. 1. Myocardial performance index (MPI). MPI is the sum of the isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) corrected for the ventricular ejection time as shown in the formula above. Interval "a" represents the duration from atrioventricular valve (AVV) opening to closing for either the mitral or the tricuspid valves. Interval "b" represents the ventricular ejection period for either the right or left ventricles.

TABLE I. Comparison of Demographic Characteristics Between Transfused and Non-Transfused Patients

Patient characteristics		Total (n = 77)	Group 1 (non-transfused) (n = 57)	Group 2 (transfused) (n = 20)	P value
Age	Mean ± SD	11.7 ± 4.7	11.6 ± 4.8	11.9 ± 4.5	0.76
Gender	% (n) male	60% (46)	58% (33)	65% (13)	0.61
	% (n) female	40% (31)	42% (24)	35% (7)	
Ethnicity	% (n) black	90% (69)	93% (53)	80% (16)	0.19
	% (n) hispanic	10% (8)	7% (4)	20% (4)	

TABLE II. Comparison of Clinical Characteristics Between Transfused and Non-Transfused Patients[a]

Patient characteristics	Total ($n = 77$) mean ± SD	Group 1 (non-transfused) ($n = 57$) mean ± SD	Group 2 (Transfused) ($n = 20$) mean ± SD	P value[b]
BSA	1.27 ± 0.40	1.27 ± 0.42	1.27 ± 0.33	0.949*
Hb	8.6 ± 1.4	8.1 ± 1.3	10.0 ± 0.9	<0.001*
Hct	25.2 ± 4.5	23.6 ± 3.9	29.7 ± 2.7	<0.001*
Retic	12.1 ± 5.9	13.0 ± 6.0	9.5 ± 4.6	0.022*
HR *Z*-score	−0.11 ± 0.64	−0.10 ± 0.67	−0.12 ± 0.56	0.913
LVDD *Z*-score	1.46 ± 1.64	1.71 ± 1.66	0.75 ± 1.37	0.024
LVSD *Z*-score	0.53 ± 1.82	0.73 ± 1.85	−0.03 ± 1.64	0.111
SF *Z*-score	1.51 ± 2.31	1.52 ± 2.41	1.49 ± 2.08	0.956
AA *Z*-score	1.41 ± 1.14	1.56 ± 1.19	0.99 ± 0.89	0.052
V_{cfc} *Z*-score	0.27 ± 1.68	0.28 ± 1.72	0.24 ± 1.60	0.923
LV mass *Z*-score	4.24 ± 2.12	4.77 ± 2.18	2.73 ± 0.85	<0.001*
WT *Z*-score	1.63 ± 2.27	1.73 ± 2.31	1.35 ± 2.19	0.471*
CI	4.8 ± 1.5	4.9 ± 1.6	4.3 ± 0.9	0.185*
LV MPI	0.259 ± 0.088	0.233 ± 0.075	0.333 ± 0.079	<0.001
RV MPI	0.196 ± 0.103	0.191 ± 0.106	0.211 ± 0.093	0.277*
WS	38.0 ± 11.6	37.6 ± 12.2	39.1 ± 9.8	0.619

[a]*Abbreviations:* BSA, body surface area; Hb, hemoglobin; Hct, hematocrit; Retic, reticulocyte count; HR, heart rate; LVDD, left ventricle diastolic dimension; LVSD, left ventricle systolic dimension; SF, shortening fraction; AA, aortic annulus; V_{cfc}, velocity of fiber shortening; LV mass, left ventricle mass; WT, wall thickness; CI, cardiac index; LV MPI, left ventricle myocardial performance index; RV MPI, right ventricle myocardial performance index; WS, wall stress; SD, standard deviation.

[b]P values *without* asterisks were derived by the 2-sample *t*-test.

*P values *with* asterisks were derived by the Mann–Whitney *U*-test.

There were no signs of heart failure on physical exam in any of these patients.

ECG analysis found no statistical difference between the amplitude of the S waves in leads 1 and V1 between groups. The R wave in lead V6, however, was significantly taller in Group 1 compared to Group 2 ($P = 0.04$) and correlated weakly with the degree of anemia ($r = -0.40$). There was no pathologic evidence of ST segment changes, T wave changes, or arrhythmias in these patients.

Of the clinical variables, body surface area, heart rate, LVSD, SF, V_{cfc}, WT, CI, RV MPI, and wall stress were not significantly different between the two groups (Table II). The LVDD and LV mass were significantly greater in Group 1 than in Group 2 ($P = 0.024$ and $P < 0.001$, respectively). Aortic annulus was higher in Group 1 but did not reach statistical significance ($P = 0.052$). In addition, the individual V_{cfc}–WS index values fell within normal limits for both groups, indicating normal systolic performance (Fig. 2). The LV MPI was significantly higher in Group 2 as compared to Group 1, indicative of impaired LV myocardial performance.

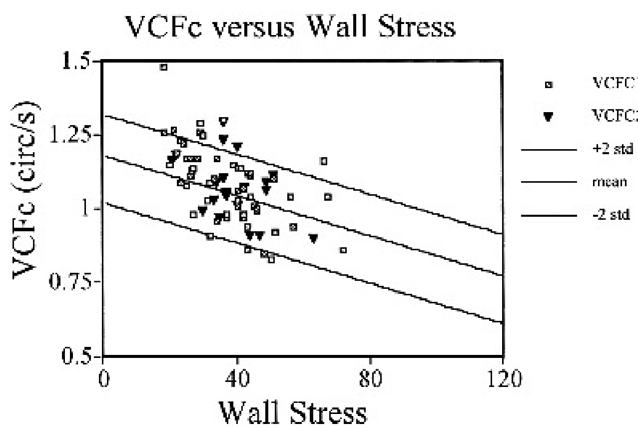

Fig. 2. V_{cfc} versus wall stress. Individual values for patients in each group are plotted on this graph depicting the V_{cfc}–wall stress relationship with mean and standard deviations for the normal population.

Because of the significantly elevated LV MPI in Group 2, all 16 variables were investigated for a possible association with the level of LV MPI. Bivariate analysis showed that transfusion status, age, hemoglobin, hematocrit, and cardiac index were significantly correlated with LV MPI. However, multivariate analysis revealed transfusion status was the only independent variable significantly correlated with a worse MPI (adjusted $P =$ 0.012) (Table III). Transfusion status alone explained 25% of the variation in the level of LV MPI. None of the patients had evidence of significant pulmonary hypertension. The left ventricle was round in the short axis in all patients, indicating that the right ventricular pressure was half-systemic or less. Quantitative estimation of the RV pressure was not possible since none of the patients had significant tricuspid valve regurgitation.

Serum ferritin levels were available in only the chronically transfused patients (Group 2) and were a mean ± SD of 3,075 ± 2,413 ng/mL (normal 10–300 ng/mL). In

TABLE III. Correlation Between LV MPI and Other Patient Characteristics[a]

Patient characteristics	Pearson correlation coefficient	Unadjusted *P* value*	Adjusted *P* value**
Transfusion status	0.502	<0.001	0.012
Age	0.265	0.020	0.383
BSA	0.202	0.079	0.877
Hct	0.309	0.006	0.376
Hb	0.283	0.013	0.441
CI	0.239	0.036	0.512
Retic	0.222	0.053	0.220
RV MPI	0.196	0.087	0.139
V_{cfc} (*Z*-score)	0.032	0.785	0.913
WT (*Z*-score)	0.069	0.551	0.609
LV mass (*Z*-score)	0.215	0.060	0.216
LVSD (*Z*-score)	0.079	0.491	0.552
LVDD (*Z*-score)	0.077	0.503	0.844
HR (*Z*-score)	0.038	0.743	0.705
SF (*Z*-score)	0.032	0.779	0.629
AA (*Z*-score)	0.152	0.187	0.962
WS	0.071	0.541	0.242

[a]See Table II for abbreviations.
*Derived by Pearson correlation.
**Derived by multiple regression adjusting for all other factors.

this group, 90% ($n = 18$) of the patients had a ferritin level greater than 1,000 ng/mL, and 55% ($n = 11$) had a ferritin level greater than 2,000 ng/mL.

DISCUSSION

To our knowledge, this is the largest study evaluating cardiac dimensions and function in children with SCA. This is also the first study to evaluate systolic function while accounting for abnormal loading conditions, and to evaluate the combined systolic and diastolic function using MPI.

Clinical Findings

Signs of heart failure including pulmonary edema, hepatomegaly, and a prominent third heart sound have been reported as common findings in adults with SCA [25]. However, there were no signs of heart failure observed on physical examination in our pediatric population. Heart murmurs have been commonly reported in patients with SCA, with an incidence of 72–100% [26–28]. In this study, the incidence was 87% with the degree of murmur correlating with the severity of anemia.

ECG. Significant abnormalities (69.5%) have been reported in electrocardiograms of adult patients with SCA. These findings have included first-degree heart block (10.6%), incomplete right bundle branch block (5.8%), incomplete left bundle branch block (0.9%), left ventricular hypertrophy (18.4%), right ventricular hypertrophy (6.7%), myocardial infarction (1.9%), and nonspecific S-T and T wave changes (29.1%) [25]. These electrocardiographic abnormalities are, however, not specific for patients with SCA. A higher incidence of dysrhythmias has been reported in patients with elevated iron [29].

In our pediatric population, ECG analysis did not add any new information to that already known by echocardiography. The amplitude of the S waves in lead 1 and of the V1 and R waves in lead V6 are conventionally used to evaluate left ventricular hypertrophy. However, we found only a weak correlation of the amplitude of the R wave in lead V6 with the degree of anemia. There was no evidence of ischemia by ST segment or T wave changes.

Cardiac dimensions and mass. Previous studies have reported enlargement of the left heart chambers in patients with SCA [1]. In the present study, we have shown that the measures of left heart size, including LVDD, LVSD, and aortic annulus dimension, correlate with worsening anemia. The LV mass showed a significant increase in all SCA patients, relative to published normal values [24], and its severity progressed with the degree of anemia. Cardiac output also increased in proportion to the degree of anemia. There was a mild increase in heart rate with worsening anemia, but the mean heart rate was within normal limits (and not significantly different) for both groups. Therefore the increase in cardiac output results from an increase in stroke volume (preload), as manifested by increased LV chamber dimensions.

Systolic function. Left ventricular systolic function has been reported to be within normal limits in children [1] and adults [30] with SCA. Covitz et al. observed normal ejection fraction in 22 adolescents with SCA evaluated by radionuclide angiography [31]. However, none of the parameters utilized in the above studies were true indices of cardiac contractility, because of the potential influence of ventricular loading conditions. Chronic anemia may be accompanied by an elevation in blood volume (increased preload) and by a decrease in blood viscosity as well as systemic vascular resistance (decreased afterload) [32]. Our study showed a clear increase in preload but no change in afterload with increasing anemia. As increased preload or decreased afterload will enhance ventricular ejection, higher than normal functional indices might be expected in patients with SCA. Indeed, we found the shortening fraction, a *load-dependent* index of function, to be elevated in both groups. However, the V_{cfc}–WS index, a *load-independent* measurement of contractility, was within normal limits, irrespective of the degree of anemia or the status of transfusion. Thus we confirm previous reports that LV contractility is normal in children with SCA.

Myocardial performance index. MPI is a combined measure of systolic and diastolic function. Higher MPI values have been found to correlate with worsening myocardial systolic and/or diastolic function [13,23]. LV MPI was significantly elevated in Group 2 patients when compared to the Group 1 patients. Because systolic function was found to be preserved in these chronically transfused patients, the elevated LV MPI most likely is explained by decreased diastolic function. Also, although MPI does not vary with age in the normal pediatric population [14], we found LV MPI increases with increasing age in our SCA patients. Again, given that systolic function is preserved in these patients, the diastolic dysfunction might be related to older age and might be seen earlier in patients with chronic transfusions.

Pulmonary hypertension. Yater and Hansmann first reported cor pulmonale in SCA patients from obliterative thrombosis of the small pulmonary arteries [33]. Since then, various studies have reported cases of pulmonary hypertension in adults with SCA [34,35]. Our study found no echocardiographic evidence of significant pulmonary hypertension in this young population. However, it must be noted that echocardiography is an insensitive measure of pulmonary hypertension; lesser degrees of pulmonary hypertension could not be ruled in these patients.

Limitations

The degree of iron overload with cardiac abnormalities could not be evaluated. Serum ferritin levels were available in only the chronically transfused patients, and measurements of iron load by liver biopsy were available in less than half the patients receiving chronic transfusions, thus limiting the sample size required to conduct a correlation between iron overload and cardiac findings. Serum ferritin is an acute-phase reactant. Ferritin levels, by themselves, serve as useful screening tools, but they do not closely delineate specific changes in iron load [36,37].

MPI is a new index and has some limitations. There may be some load-dependence to the MPI, and it does not measure diastolic function independently.

CONCLUSION

This study demonstrates that a murmur is a common finding in children with SCA and ECG findings are neither specific nor sensitive in determining the degree of ventricular hypertrophy. The chronic anemia in these patients produces a volume-overloaded heart with a significant increase in LV dimensions and mass proportional to the degree of anemia. However, despite their abnormal loading conditions, systolic function and cardiac contractility remained preserved in this relatively young patient population regardless of degree of anemia or transfusion status. Patients on a chronic transfusion protocol may have diastolic dysfunction despite iron chelation therapy. Diastolic function may be impaired with age in patients with SCA. There was no echocardiographic evidence of significant pulmonary hypertension in the pediatric population with SCA.

Future Directions

Diastolic function should be a part of the routine echocardiographic evaluation in patients with SCA. LVMPI may be useful in identifying patients with early cardiac dysfunction. Newer, more specific assessments of diastolic function, e.g., tissue Doppler imaging [38,39], should be performed in chronically transfused patients and older patients with SCA. Data on iron overload needs to be more aggressively obtained and correlated with the effects of desferroxamine and iron chelation therapy on cardiac dysfunction.

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