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Evaluation of Left Ventricular Systolic Function in Pediatric Sickle Cell Anemia Patients Using the End-Systolic Wall Stress-Velocity of Circumferential Fiber Shortening Relationship

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OBJECTIVES The aim of this work was to evaluate myocardial contractility using the end-systolic wall stress (ESSm)-velocity of circumferential fiber shortening (VCFc) relationship in sickle cell anemia (SCA) patients compared with a similar age group of African-American (AA) control patients.

BACKGROUND Abnormalities of myocardial function have been documented in SCA patients using load-dependent echocardiographic indexes. Whether the systolic dysfunction results from impaired myocardial contractility or altered loading conditions is unknown because controlled studies using a load-independent measure of contractility have not been performed.

METHODS Fifty healthy AA patients and 57 SCA patients age 3 months to 18 years were studied. Simultaneous indirect arterial pulse tracing, phonocardiogram, electrocardiogram, and M-mode tracing of the left ventricular (LV) short-axis were recorded. The LV dimensions, corrected ejection time (ETc), percent fractional shortening (%FS), VCFc, and ESSm were determined. The ESSm-VCFc relationship was calculated and compared between groups. Duration and severity of anemia and effects of exchange transfusion on the ESSm-VCFc relationship were determined.

RESULTS The SCA patients had increased LV dimensions in systole and diastole, and increased indexed LV mass. Load-dependent measurements of LV function (ETc, %FS, and VCFc) were lower in SCA patients, and afterload, as measured by ESSm, was increased. The ESSm-VCFc relationship demonstrated reduced contractility in SCA patients compared with control subjects. Degree and duration of anemia along with exchange transfusions did not impact contractility.

CONCLUSIONS Sickle cell anemia patients have significant LV dilatation and increased LV mass due to abnormal loading conditions. Contractility, measured by the ESSm-VCFc index, is lower in SCA patients and was not negatively impacted by severity or duration of anemia, or exchange transfusions. The underlying mechanism explaining these findings requires further investigation. (J Am Coll Cardiol 2006;47:2283–8) © 2006 by the American College of Cardiology Foundation

Hemoglobinopathies, such as sickle cell anemia (SCA), are associated with long-standing severe anemia. While this disease process may affect multiple organ systems, the extent to which SCA impacts myocardial function is unclear. Previous studies (1–3) report normal left ventricular (LV) function in patients with severe chronic anemia, while others (4–7) document varying degrees of LV dysfunction with significantly decreased fractional shortening or abnormal systolic time intervals. To date, no consensus exists as to whether myocardial contractility is inherently affected by long-standing severe anemia or is simply altered by chronic volume overload.

In previous echocardiographic studies assessing LV function in SCA patients, contractility was evaluated using the ejection phase indexes fractional shortening, ejection fraction, velocity of circumferential shortening, or systolic time intervals (1–7). These measurements are highly dependent on and influenced by myocardial loading conditions as well as heart rate, both of which are abnormal in SCA patients. Use of these indexes of systolic function in this population may explain the broad spectrum of results and apparent inconsistencies documented in the literature. Ideally, to discriminate between inherent ventricular dysfunction and the effects of altered loading conditions, myocardial contractility should be evaluated using load-independent indexes of ventricular function. Two decades ago, Colan et al. (8) described a non-invasive echocardiographic technique for analysis of myocardial contractility using the relationship between LV end-systolic wall stress (ESSm) and rate-corrected velocity of circumferential fiber shortening (VCFc). This relationship is preload independent, normalized for heart rate, and incorporates afterload. It accurately reflects the state of myocardial contractility irrespective of

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Abbreviations and Acronyms

AA	= African American
BSA	= body surface area
ESSm	= meridional end-systolic wall stress
ETc	= corrected ejection time
Hgb	= hemoglobin
Hgb SS	= hemoglobin sickle cell
LV	= left ventricle/ventricular
LVEDD	= left ventricular end-diastolic dimension
SCA	= sickle cell anemia
VCFc	= velocity of circumferential fiber shortening
%FS	= percent fractional shortening

loading conditions. Since its introduction, this relationship has been used to study myocardial mechanics in several clinical and pathophysiologic settings (9–13), and application in SCA patients may be ideal to help differentiate changes in contractility from abnormal loading conditions, which are known to influence global cardiac function.

The objectives of this study, therefore, were to: 1) assess LV systolic function in SCA patients using load-dependent and load-independent indexes of myocardial contractility compared with African-American (AA) control subjects; 2) determine impact of patient age and duration of SCA upon myocardial contractility; and 3) determine the influence of anemia severity and exchange transfusions upon myocardial contractility.

METHODS

Study population. This prospective study consisted of 107 subjects divided into two groups. The SCA study group, documented (hemoglobin [Hgb] SS) by electrophoresis, consisted of 57 subjects ages 1 to 18 years. All SCA patients were recruited and studied during outpatient visits, and none were *in crisis* at the time of echocardiogram. The Hgb levels (g/dl) for the SCA patients were recorded from the last blood draw obtained before participation in the study. Duration of anemia was defined as time from clinical diagnosis of SCA to time of enrollment in study. Clinical records were reviewed for frequency, duration, and indication for exchange transfusions within the SCA population. A group of 50 similar age healthy AA volunteers served as control patients. The control subjects were recruited from the general population and ranged in age from 3 months to 18 years. None of the 107 subjects had known cardiovascular disease on the basis of history, physical exam, electrocardiogram (ECG), or complete two-dimensional echocardiography. No subject was taking cardiovascular medications at the time of enrollment. Informed consent was obtained from all subjects, and the project was approved by the institutional review board.

Recordings. A complete two-dimensional echocardiogram was performed on each subject using an ultrasound imaging system with a size-appropriate transducer. Each study was performed at rest without sedation to confirm normal anatomy and function. The detailed methodology used in this study has been previously described (8). Briefly, simultaneous indirect carotid or brachial arterial pulse tracing, phonocardiogram, ECG, and M-mode tracing of the LV short-axis was recorded on a hard copy at high speed (100 mm/s). Peripheral blood pressure was recorded simultaneously using a Dinamap Vital Signs Monitor 8100T (Critikon Inc., Thomasville, Georgia). The average of three to five blood pressure readings was used for data analysis. All echocardiographic measurements made from hard copy were blinded to the subjects SCA status.

Meridional end-systolic wall stress was calculated using a previously detailed formula (8) from data obtained by averaging three consecutive cardiac cycles. End-systolic pressure was estimated through linear interpolation onto the arterial tracing at a time in the cardiac cycle just before aortic valve closure (S2 on phonocardiogram). Left ventricular posterior wall and septal thickness along with internal dimension were measured in the short-axis M-mode plane at end systole and end diastole. The LV corrected ejection time (ETc) was measured from the arterial tracing from the onset of rapid upstroke to the onset of the dicrotic notch and normalized to a heart rate of 60 beats/min by dividing by the square root of the preceding R-R interval on the simultaneously recorded ECG. Left ventricular mass, % fractional shortening (%FS), and VCFc was calculated using standard mathematical formulae.

Statistical analysis. Demographic, dimensional, and functional data are reported as mean ± SD. Comparison of the normally distributed variables between groups was performed using the Student *t* test. Simple linear regression by the least squares method was used to calculate ESSm-VCFc equations. Multivariate regression models were used to compare the ESSm-VCFc relationship for the SCA and AA control patients and to determine the impact of the anemia variables (duration, severity, exchange transfusions) on the ESSm-VCFc relationship.

RESULTS

Patient demographics and anemia status. Gender and age distribution, heart rate, blood pressure, and body surface area (BSA) for the two groups are detailed in Table 1. No significant difference was identified between groups for age distribution, mean arterial blood pressure, or heart rate. Mean BSA was lower in the SCA patients. Sixty-eight

Table 1. Patient Demographics

	Healthy AA Patients	SCA Patients	p Value
Age (mean)	9.9 ± 5.1	9.4 ± 4.1	0.56
Blood pressure, mm Hg (mean)	72.5 ± 11.2	71.9 ± 8.4	0.75
Body surface area (g/m^2)	1.21	1.05	0.05
Male gender (%)	34/50 (68%)	27/57 (47%)	0.03
Heart rate (mean)	77 ± 19.6	83 ± 13.4	0.08

AA = African American; SCA = sickle cell anemia.

Table 2. Dimensional Data

	Healthy AA Patients	SCA Patients	p Value
LV end-diastolic diameter (cm)	4.00 ± 0.76	4.47 ± 0.66	<0.01
LV end-diastolic diameter indexed ($BSA^{0.5}$)	3.77 ± 0.31	4.44 ± 0.49	<0.01
LV end-systolic diameter (cm)	2.35 ± 0.48	2.76 ± 0.46	<0.01
LV end-systolic diameter indexed ($BSA^{0.5}$)	2.20 ± 0.23	2.79 ± 0.49	<0.01
LV posterior wall thickness—diastole (cm)	0.68 ± 0.24	0.66 ± 0.19	0.70
LV posterior wall thickness—systole (cm)	1.26 ± 0.35	1.28 ± 0.33	0.75
Interventricular septum diastole (cm)	0.69 ± 0.19	0.71 ± 0.21	0.82
LV mass (g)	86.90 ± 60.91	97.41 ± 55.77	0.35
LV mass indexed (g/m^2)	66.14 ± 23.51	89.14 ± 32.16	<0.01
LV mass indexed ($g/BSA^{1.4}$)	62.35 ± 20.3	88.20 ± 28.6	<0.01

AA = African American; BSA = body surface area; LV = left ventricular.

percent (34 of 50) of the AA control patients were male gender versus 47% (27 of 57) of the SCA patients, resulting in a statistically significant difference in gender distribution between groups (p = 0.03).

The mean Hgb level of the SCA group was 8.4 ± 1.4 g/dl. Of the 57 SCA patients, 11 received chronic monthly transfusions and iron chelation therapy. Indications for chronic transfusions were history of cerebral vascular events (n = 8), recurrent pain crisis (n = 2), and recurrent acute chest syndrome (n = 1). The mean Hgb concentration for the exchange transfusion patients was similar, 8.5 ± 0.9 g/dl, to that of the non-exchange transfused SCA patients, 8.0 ± 1.5 g/dl.

M-mode echocardiography. Left ventricular chamber dimensions and mass are detailed in Table 2. The LV systolic and diastolic dimensions were significantly increased in SCA patients compared with control patients for both indexed ($BSA^{0.5}$) and non-indexed values. To verify that assumptions in the LV mass formula were not violated, both components of the LV wall were measured. In addition to similar posterior wall thicknesses (SCA 0.66 ± 0.19 cm vs. 0.68 ± 0.24 cm, p = 0.7), there was no difference in septal thickness between groups (SCA 0.71 ± 0.21 cm vs. 0.69 ± 0.19 cm, p = 0.8). Indexed LV mass (g/m^2 and $BSA^{1.4}$) was greater in patients with SCA than control subjects.

LV functional data, wall stress, and ESSm-VCFc index. The SCA patients had longer ETc, and lower %FS and VCFc values than the control patients (Table 3); however, the measured values for SCA patients were within normal limits for age. Myocardial afterload, measured as ESSm, was increased in the SCA group despite similar mean and end-systolic blood pressures. Load-independent evaluation of myocardial performance using the ESSm-VCFc relationship demonstrated lower myocardial contractility in the SCA group (VCFc = 1.40 to 0.007 [ESSm]) compared with control subjects (VCFc = 1.48 to 0.007 [ESSm], p < 0.01 for population linear regression equations). The Y-intercept, VCFc, for the SCA patients was lower than for control patients with similar slopes for the linear regression equations. Figure 1 plots individual points for the ESSm-VCFc relationship for each of the 57 SCA patients onto the regression line of the healthy AA control population with confidence limits (±2 SD). Seven of the 57 SCA patients (12%) had values for the ESSm-VCFc relationship that were ≥2 SD below the mean for the control population. Forty-four of 57 SCA patients (77%) had values for the ESSm-VCFc relationship that were below the mean regression line for the healthy AA control patients. Only one SCA patient had an increased contractility value for the ESSm-VCFc relationship that was ≥2 SD above the mean for the control population.

Impact of anemia. The LV systolic and diastolic dimensions increased with increasing degrees of anemia. Specifically, there was a negative correlation between Hgb concentration and left ventricular end-diastolic dimension (LVEDD) Z-score (r = −0.6). Load-dependent indexes of ventricular function (% FS, VCFc, ETc) were not adversely affected by patient age, increasing severity or duration of anemia. Similarly, the contractility index, ESSm-VCFc relationship, was unaffected by patient age, or increasing severity of anemia. Because long-term severity of anemia may not be properly represented by a single Hgb value, we evaluated the relationship between ventricular dilation (LVEDD Z-score), a more reflective measure of the chronic severity of anemia, to the ESSm-VCFc relationship and found no correlation. Yet, as a continuous variable, longer

Table 3. Functional Data and Contractility Index

	Healthy AA Patients	SCA Patients	p Value
Shortening fraction (%)	41 ± 4.3	38 ± 5.8	<0.01
ETc (ms)	334 ± 23.7	350 ± 27.9	<0.01
VCFc (circ/s)	1.23 ± 0.14	1.09 ± 0.19	<0.01
ESSm (g/m^2)	32.8 ± 13.5	41.0 ± 15.3	<0.01
ESSm-VCFc relationship (contractility index)	VCFc = 1.48–0.007 (ESSm) R^2 = 0.30	VCFc = 1.40–0.007 (ESSm) R^2 = 0.45	<0.01

AA = African American; ESSm = meridonial end-systolic wall stress; ET_c = corrected ejection time; SCA = sickle cell anemia; VCFc = velocity of circumferential fiber shortening.

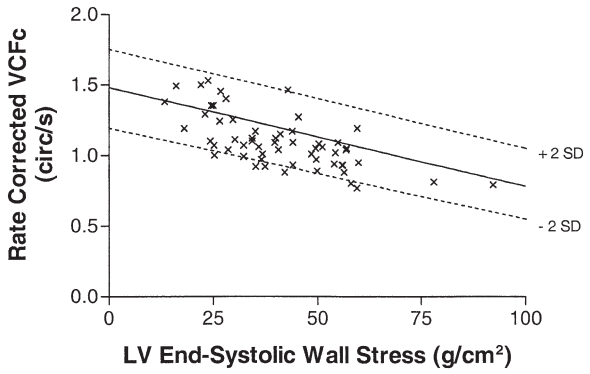

Figure 1. Linear regression equation for the meridional end-systolic wall stress-velocity of circumferential fiber shortening (VCFc) relationship for the African American control population with ± 2 SDs onto which individual sickle cell anemia data points for the meridional end-systolic wall stress-VCFc relationship are plotted. **Solid line** = healthy African-American patients; VCFc = 1.48 to 0.007 (meridional end-systolic wall stress), r = 0.7; n = 50; **X** = sickle cell anemia patients, n = 57. LV = left ventricular.

duration of anemia tended to negatively impact the ESSm-VCFc relationship (p = 0.08). When analyzing Hgb as a dichotomous variable (18 of 57 SCA patients with Hgb <8 gm/dl), no differences in functional indexes (load dependent/independent) were demonstrated among the SCA patients based on Hgb levels. Notably, in the seven SCA patients with depressed contractility, no increase in severity or duration of anemia was identified compared with the remaining SCA patients. Age distribution within the depressed contractility subgroup ranged from 3.7 to 13.0 years, similar to the distribution of the entire SCA population. Of the seven patients with depressed contractility, three were receiving monthly exchange transfusions. Load-dependent and independent indexes were similar between the 11 SCA patients who received routine exchange transfusions versus the remaining non-exchange transfused patients.

DISCUSSION

Rationale for present study. The impact of SCA on LV dimensions and function has been extensively studied; yet no consensus exists as to the long-term effects on myocardial contractility. Lester et al. (1) evaluated 64 pediatric SCA patients and found significantly increased LV dimensions and mass compared with healthy AA control patients that increased in correlation to severity of anemia and percent Hgb SS concentration. At rest, the SCA patients had similar load-dependent functional indexes compared with control subjects. Other investigators have confirmed these results (2,3). In contrast, Balfour et al. (4) and San et al. (5) documented varying degrees of LV dysfunction in SCA patients that worsened with advancing age. Lewis et al. (6) and Lau et al. (7) documented similar findings in patients with anemia related to thalassemia. In each case the authors proposed that the abnormal loading conditions associated with anemia lead to chamber dilation and myocardial remodeling that progressed to ventricular dysfunction. These studies are limited by the use of load-dependent indexes of ventricular function. By using a load-independent functional assessment, the present study was performed in an effort to differentiate the relative contributions of altered myocardial load versus decreased contractility to explain the previously observed functional abnormalities in SCA patients.

Results of present study. DIMENSIONAL MEASURES AND AFTERLOAD. The present study corroborates previously published clinical (3–5) and autopsy (14) studies that demonstrate enlargement of the left heart chambers and increased LV mass in patients with SCA. Left ventricular mass is increased secondary to compensatory hypertrophy that occurs in response to ventricular dilation, and the severity of dilation progressed with increasing degree of anemia. Despite myocardial remodeling/hypertrophy, the SCA patients had increased wall stress compared with control subjects. Similar increased wall stress measurements were noted by Bahl et al. (15) in a study of young adults with severe chronic anemia (Hgb <7 g/dl) due to nutritional deficiencies, and by Bosi et al. (16) in a study of young adults with β thalassaemia major. In each case, the increased wall stress occurs because the magnitude of eccentric hypertrophy is inadequate to normalize the mass to volume ratio that results from chronic anemia. The anemic patients reported by Bahl et al. (15) had hyperdynamic ventricular function with increased %FS and VCFc, which increased with progressive hemodilution. In contrast, the thalassaemia patients studied by Bosi et al. (16) had depressed %FS and VCFc compared with control patients, which they attributed to myocardial iron toxicity. Bahl et al. (15) concluded that chronic severe anemia led to a hyperdynamic state with improved LV function and decreased peripheral resistance, and that chronic severe anemia alone does not lead to ventricular dysfunction in patients with no other underlying cardiac or systemic disease. Our results, and those of Bosi et al. (16), would suggest that factors associated with chronic hemoglobinopathies contribute to the lower functional indexes found in these patients.

Contractility. At the onset of this study, we expected to find similar contractility indexes between SCA patients and control subjects. The SCA patients were asymptomatic from a cardiac standpoint, and several previous studies (1–3), using load-dependent measures, had documented normal systolic function. Also, a recent publication by Batra et al. (13), which, to our knowledge, is the only other investigation in SCA patients using the wall stress-VCFc relationship, showed contractility to be normal. However, differences in methodology exist between the Batra et al. (13) study and the present study, which may provide insight into the discrepant findings. Batra et al. (13) study used mean arterial blood pressure to calculate end-systolic wall stress values. Our data showed an R^2 correlation of only 0.7 between mean and end-systolic blood pressures. While this suggests these blood pressures are similar, they are not equivalent, and use of a surrogate (mean blood pressure)

may introduce inaccuracies into the calculation of end-systolic wall stress. Additionally, Batra et al. (13) compared their SCA patients with historical control subjects published by Colan et al. (17), which represent a relatively homogeneous, predominantly Caucasian population. The validity of results obtained when using this control group to assess a disease state that predominantly affects AA could be challenged. Therefore, to avoid bias, our data was obtained in a prospective manner using control patients with a similar age and racial distribution.

Impact of anemia. The functional indexes (load-dependent and load-independent) of our SCA patients were not detrimentally affected by patient age, duration or degree of anemia, or exchange transfusion status. Batra et al. (13) published similar findings in their SCA population. These results may, in part, be explained by the study by Bahl et al. (15), which concluded that anemia alone does not lead to myocardial dysfunction.

Potential mechanisms of depressed contractility. The depressed contractility seen in a subset (12%) of our population of SCA patients is likely multifactorial. The combination of moderate-to-severe anemia and the resultant volume load produces increased cardiac output at rest. The degree to which SCA patients can increase cardiac output and coronary perfusion in response to stress may be limited. An example is provided by Alpert et al. (18) who studied 47 children with SCA during exercise testing and found inducible ischemic ECG changes in 15%, which were seen more frequently in patients with lower Hgb levels despite normal coronary angiography. Also, the degree to which myocardial contractility is affected by vaso-occlusion is unclear. Despite the stimulus for sickling, several published studies (14,19) do not support the existence of an "ischemic sickle cell cardiomyopathy." In contrast, case reports (20,21) describe clinical evidence of myocardial infarction in pediatric SCA patients, and autopsy findings (22,23) document subendocardial fibrosis proposed to be caused by chronic anemia and increased O_2 demand of a dilated hypertrophied ventricle. Finally, although this study did not address genetic variations or polymorphisims, it is possible that dimensional and functional differences seen in SCA patients, previously ascribed to abnormal loading conditions, may, in fact, represent intrinsic genetic differences in myocardial cytoarchitecture not yet described in association with SCA.

Study limitations. Potential limitations using this methodology of wall stress quantification have been previously detailed (8). Also, in a recent publication by Gentles and Colan (24) comparing wall stress to myocardial fiber stress, the authors determined that fiber stress might be a more accurate indicator of ventricular afterload, specifically in clinical settings with abnormal wall thickness to ventricular dimension ratios as are present in SCA patients. To minimize random measurement error and interobserver variability, data was hand-digitized by one observer (R.J.G.), and multiple cardiac cycles were averaged for each calculation of wall stress and VCFc. As is noted in several early reports by Colan et al. (8–11) and corroborated in our data analysis, the squared correlation coefficient (R^2) between the VCFc and ESSm relationship was 0.3 suggesting that other, not yet ascertained, factors beyond those measured influence this indexed relationship. Although this was a prospectively designed and executed study, group size may limit the power of our results. Finally, myocardial injury secondary to volume overload is a slowly progressive phenomenon, which implies more importance to the cumulative effect of chronic anemia than the short-term magnitude of a single Hgb measurement. It is likely that the SCA patients had a significantly variable severity of anemia over the years, which may not be properly represented by a single Hgb measure as was used for data analysis in this study.

Summary and clinical implications. The ESSm-VCFc relationship is a noninvasive echocardiographic measurement that accurately reflects the state of myocardial contractility independent of loading conditions. This relationship allows differentiation of abnormalities in function caused by altered loading conditions versus true abnormalities in intrinsic contractility. Using this relationship, the current study found that abnormalities exist in ventricular systolic function in SCA patients. The routine use of the contractility index in this population of patients may permit targeted therapeutic interventions before the onset of symptoms. Although uncertain, the underlying cause of the ventricular dysfunction is likely multifactorial, and further studies will be necessary to elucidate the mechanisms mediating these clinical observations.

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