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Echocardiographic Parameters to Identify Sickle Cell Patients with Cardio-pathology

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Abstract

Background—Sickle cell disease (SCD) affects millions of people and causes chronic hemolytic anemia leading to vasculopathies like pulmonary hypertension and abnormalities in cardiac function that increase complications and mortality. It is therefore crucial to identify cardiac abnormalities in SCD. We aimed to assess the prevalence of echocardiographic parameters in SCD to help identify cardiopulmonary risk.

Methods—Ninety-one patients (53% male), median age of 30, body surface area (BSA) of 1.79 m², hemoglobin of 8.8 g/dL, and creatinine of 0.7 mg/dL identified. We retrospectively measured laboratory and echocardiographic parameters in SCD patients: left ventricular (LV) dimensions, LV ejection fraction (LVEF), LV myocardial performance index (MPI), LV mass index (MI), left atrial volume index (LAVI), tricuspid regurgitation velocity (TRV), tricuspid annular plane systolic excursion (TAPSE), right heart dimensions.

Results—Prevalence of left heart abnormalities were 32%: increased LV end diastolic diameter (EDD), 78%: LV MPI, 21%: diastolic dysfunction, 38%: decreased LVEF, 24%: increased LVMI and 47%: increased LAVI. Right heart abnormalities were 39%: TAPSE, 38%: increased TRV, and 59%: increased pulmonary systolic pressure (PASP). Multivariate logistic regression analysis was significant for increased LVMI and LAVI in those with hemoglobin < 8 g/dL (odds ratio (OR) 7.4, 95% confidence interval (CI) 2.23-24.6, p 0.001) and (OR 3.32, 95% CI 1.18-9.33, p 0.023).

Conclusions—We confirmed increased prevalence of abnormal LVEDD, LVMI, diastolic function, LAVI and PASP in SCD. In addition we identified abnormal LV MPI (78%), TAPSE (29%). These parameters may be useful and readily accessible echocardiographic prognostic tools in this population.

Keywords

Hemoglobin; cardiomyopathy; tricuspid annular plane systolic excursion; myocardial performance index; left atrial volume index; diastolic function

Introduction

Sickle cell disease (SCD) is an autosomal recessive disease that affects millions of people worldwide and occurs in 1 out of every 365 African-Americans and 1 out of every 16,300 Hispanic-Americans births, with an estimated 100,000 Americans affected.¹ It is caused by a point mutation in the gene that encodes β -globin. This mutation causes polymerization during times of deoxygenation and, subsequently, sickling of hemoglobin.² The most common form of SCD is due to inheriting two mutant hemoglobin S alleles; this genotype is associated with more severe hemolytic anemia and increased risk of cardiovascular complications. Because the sickled hemoglobin is less deformable and causes obstruction of the microvasculature, it produces ischemia-reperfusion injury to vital organs. Additionally, the sickled cells are more likely to undergo chronic intra- and extravascular hemolysis, resulting in reduced red cell lifespan and anemia.³

These vaso-occlusive episodes and chronic hemolytic anemia create ongoing stress on the cardiopulmonary system, leading to its dysfunction, and hence increase morbidity and premature mortality.³ Common cardiopulmonary abnormalities seen in SCD are pulmonary hypertension, right ventricular (RV) and left ventricular (LV) enlargement, and an increase in LV mass⁴ and LV diastolic dysfunction, which is an independent predictor of mortality.¹ Additionally, recent studies, particularly one by Niss et al.⁵, reported that an increase in left atrial (LA) volume was also present in most individuals with SCD. LA volume index (LAVI), which is the LA volume adjusted for body surface area, has been shown to be a powerful prognostic marker of adverse cardiac events in many different clinical conditions.⁶ Because LA enlargement is linked to LV function and performance, LAVI is useful for the diagnosis and evaluation of heart failure in the setting of preserved LV ejection fraction.⁷

Because cardiac complications have a grave prognosis on morbidity and mortality in SCD patients, it is essential to diagnosis potential cardiac problems early. Echocardiography is a useful non-invasive tool for identifying such structural and functional abnormalities of the heart.

In this study, we aimed to better define and identify additional useful non-invasive diagnostic and prognostic echocardiographic tools in our sickle patients. We propose that these echocardiographic tools will help to better evaluate the cardiovascular status of sickle cell patients.

Methods

Study Design

This was a retrospective study of adult patients with SCD seen at The University of Texas Comprehensive Sickle Cell Center in Houston who had echocardiograms from 1/2013 to 12/2016 meeting the inclusion criteria. All genotypes of SCD were included. The exclusion criteria were acute vaso-occlusive pain crisis, acute coronary syndrome, pregnancy, acute pulmonary embolism, and circulatory shock. Demographic, clinical, laboratory, and therapeutic data were also collected. Doppler-echocardiograms performed on the subjects in steady state were retrospectively analyzed. Two echocardiography board-certified physicians reviewed the images and measured the following parameters using the current American Society of Echocardiography (ASE) guidelines⁸: LV end-diastolic dimension, LV ejection fraction, LV myocardial performance index (MPI), LV mass index, fractional shortening, E/e' ratio, E-tissue Doppler imaging, LAVI, LV diastolic function, pulmonary arterial systolic pressure (PASP), tricuspid regurgitation velocity (TRV), right ventricular (RV) tricuspid annular plane systolic excursion (TAPSE), RV size, RV hypertrophy, and right atrial (RA) volume index.

Study Procedures

Height (cm) and weight (kg) were obtained at the time of the transthoracic echocardiogram. Body surface area (BSA) was calculated using the Mosteller formula [(weight × height/ 3600)]. In the parasternal long view, the LV end diastolic diameter (LVEDD), intraventricular septal diameter (IVSD), and LV posterior wall diameter (LVPWd) were measured in millimeters (mm) at end diastole. LV end systolic diameter (LVESD) was measured in mm. In the apical views, 2-dimensional (2D) volumetric measurements were used to obtain the LA and RA volumes. The RV size (mm) was obtained by measuring the basal RV inflow, and the RV TAPSE was obtained in M-mode (cm). When RV M-mode was not available, the linear measurement of the systolic excursion of the tricuspid annulus was used in the 2D 4-chamber apical view. Mitral and tricuspid regurgitation velocity were graded as 1+ to 3+, from mild to severe, respectively, by visual estimate. Using continuous wave Doppler, the following were obtained in the 4-chamber apical view: TRV (m/sec), mitral valve closure to opening time (MCOT) (ms), and LV ejection time (LVET) (ms). Pulse wave Doppler was used to measure the mitral E-velocity, mitral A-velocity, and deceleration time (ms). The mitral E'-velocity and A'-velocity of the lateral wall were obtained by using tissue Doppler. In the subcostal view, linear measurement of the RV wall thickness in 2D was obtained (mm), and the diameter (cm)/collapsibility of the inferior vena cava was noted.

The following calculations were performed: the fractional shortening was calculated as $[(LVEDD-LVESD)/LVEDD] \times 100$. LV mass was calculated using the cube formula with the linear method $(0.8 \times 1.04 \times [(IVSD + LVEDD + LVPWd)^3 - LVEDD^3] + 0.6 \text{ g})$. The LVEF was obtained by using the Simpson's biplane method of discs in the 4- and 2-chamber apical views. LV MPI was calculated using the formula $(MCOT-LVET)/LVET$. The PASP was calculated with the modified Bernoulli equation $[PASP = 4(TRV)^2 + RA \text{ pressure}]$, where the RA pressure was estimated as 3 mmHg if the IVC diameter was ≥ 2.1 cm and

collapse >50%, 15 mmHg if the IVC diameter was >2.1 cm and collapses <50%, and 8 mmHg if neither of those criteria were met. All calculations for indexed measurements were obtained by dividing the BSA with the respective parameter measured.^{8–11}

ASE guidelines and cutoff values were utilized to define abnormalities. Abnormal parameters were defined as such: indexed abnormal LV and RV dimensions according to ASE gender cutoff values; LV volumes: LDEDV (ml/m²): > 74 for men and > 61 for women; LVESV (ml/m²): >31 for men and >24 for women; LV mass: >95 g/m² in women and >115 g/m² in men; LAVI: > 34 cm²/m²; LVEF: <52% in males and <54% in females; FS: <18%; LVMI: >0.39 ± 0.05; TAPSE: <17mm. Abnormal diastolic function was defined by current ASE algorithm.¹¹

Statistical Analysis

Histograms were constructed to examine the distribution of continuous characteristics. Normally distributed characteristics were summarized as mean and standard deviation, but those with skewed distributions were depicted as median and range. Logistic regression models were built for complications. Variables with too few frequencies (N < 9) in one level were excluded from multivariate analysis. The following variables were considered in building logistic regression models: age (<30 years old, ≥ 30 years old), type of sickle cell anemia (SS, SC), BSA (< 1.79 m², ≥ 1.79 m²), baseline hemoglobin (Hb) (< 8 g/dL, ≥ 8 g/dL), baseline creatinine (< 0.7 mg/dL, ≥ 0.7 mg/dL), hydroxyurea, chronic transfusion therapy, hypertension, stroke, ferritin (ng/mL), angiotensin converting enzyme inhibitor, angiotensin receptor blocker, and beta blocker. A forward stepwise procedure was performed to select variables significantly associated with an outcome at the 5% level. The interactions between selected variables were tested, but none of them were significant. All p values were two-sided, and p values less than 0.05 were considered significant. All statistical analyses were performed by using SAS software (version 9.4, the SAS institute, Cary, NC).

Results

Study Population

The total number of subjects was 91. They had a median age of 30 years old, BSA of 1.79 m², Hb of 8.8 g/dL, and creatinine of 0.7 mg/dL. Fifty-three percent were male, 94.5% were Black, and 5.5% were Hispanic. Most (83%) had the homozygous sickle cell genotype; 12%, 3%, and 2% had sickle cell trait, sickle-beta thalassemia (–), and sickle-beta thalassemia (+), respectively. Sixty-five percent had ferritin levels <1000 ng/mL (Table 1).

Significant co-morbidities included a 19% prevalence of hypertension and a history of stroke in 10% of those studied (Table 2). Seventy percent of the subjects were taking hydroxyurea, and 29% had received chronic transfusion therapy. Hydroxyurea increases fetal Hgb which is protective in nature and tends to decrease the severity of SCD in general. Chronic transfusions are indicated for the more severe cases of SCD. Eleven percent of the subjects were taking beta blockers, and 11% were taking angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers (Table 2).

Echocardiography/Doppler Findings

The abnormal transthoracic echocardiogram findings were increased LVEDD in 32% of subjects, LV mass index in 24%, and LAVI in 24%; decreased LVEF in 38%, fractional shortening in 21%, and LV MPI in 78%; 21% had abnormal LV diastolic function. Abnormal findings were also found in the right side of the heart: decreased RV TAPSE (29%), elevated TRV (38%) (defined as >2.5 m/sec)¹², and elevated PASP (59%)(Table 3).

Anemia (odds ratio (OR) 7.4, 95% confidence interval (CI) 2.23-24.6, $p=0.001$), baseline renal dysfunction (OR 6.69, 95% CI 1.93-23.2, $p=0.003$), and being on hydroxyurea (OR 5.3, 95% CI 1.14-24.7, $p=0.034$) were associated with higher odds of having abnormal LV mass index. Hydroxyurea is approved for use in the most severe sickle cell disease genotypes, so this is probably why it was associated with increased abnormal LV mass index when, in fact, it may just be a confounding factor.

Baseline Hb was recognized as an important factor for echocardiographic outcomes. To elucidate its impact, we conducted univariate analysis and depict the results in Table 4.

Having a high ferritin concentration (OR 7.22, 95% CI 1.8-28.9, $p=0.005$) and not being on hydroxyurea (OR 5.09, 95% CI 1.24-20.9, $p=0.024$) were associated with a greater likelihood of abnormal fractional shortening. Additionally, risk factors for abnormal LV MPI were the absence of beta blockers (OR 4.76, 95% CI 1.04-21.8, $p=0.045$) and being normal- or underweight (OR 3.32, 95% CI 1.02-10.9, $p=.047$). Having a high BSA (OR 7.06, 95% CI 2.01-24.8, $p=0.002$), normal- or underweight (OR 6.74, 95% CI 1.82-24.9, $p=0.004$) and being anemic (OR 3.32, 95% CI 1.18-9.33, $p=0.023$) were linked to higher risk of an abnormal LAVI.

Those who had not received chronic transfusion therapy had increased odds of having abnormal RV TAPSE (OR 6.77, 95% CI 1.46-31.4, $p=0.015$).

Hypertension was not significantly associated with having increased LVMI (OR: 0.48, 95%CI $-0.92 - 1.87$, $p=0.501$) and increased LAVI (OR: 1.13, 95% CI $-0.21 - 2.46$, $p = 0.097$)

No significant predictors were noted to contribute to LVEDD and abnormal LVEF.

Discussion

In this study, we assessed echocardiographic parameters of cardiac function in patients with SCD. While we observed common findings of increased left ventricular dimensions, left ventricular mass, elevated TRV and pulmonary hypertension; we also found that a large proportion of our SCD population had abnormal LV MPI (78%). There was also a significant prevalence of abnormal TAPSE (29%).

Some authors have postulated that MPI not only predicts the outcome of LV systolic and diastolic function after myocardial infarction but can also predict early LV dilatation and cardiac death after myocardial infarction.¹⁵⁻¹⁷ Accordingly, we hypothesize that assessing

LV MPI will allow more insight into cardiac function and may predict cardiac dysfunction prior to its appearance.

As might be expected, we found that patients on hydroxyurea, a drug approved to treat severe SCD genotypes (homozygous sickle cell anemia and sickle beta thalassemia (-)) were more likely to have abnormal LV mass indices because, generally, their disease was more severe.

In children, global RV longitudinal systolic strain – a load independent measure to assess right ventricular systolic function has been shown to be altered, potentially impaired by elevated pulmonary pressure and LV diastolic dysfunction.¹⁹ Because of its simplicity and reproducibility, TAPSE is a common parameter used to assess RV function.^{20,21} Recently, there has been interest in the implications of abnormal TAPSE and LV function.²⁰ Work from Pittsburg showed a correlation between reduced TAPSE and LV dysfunction.²² In our cohort we observe decreased TAPSE in about one-third of our patients possibly reflecting impaired RV systolic function and/or diastolic dysfunction. Because it is known that LV systolic function is generally preserved in the SCD population,^{1,3,5} we speculate that other factors may be affecting the TAPSE in our SCD cohort. Abnormal TAPSE may be indicative of chronic elevation in pulmonary pressures. More studies should be conducted to determine whether TAPSE can serve as a prognostic parameter for cardiac function in SCD patients.

Similar to prior studies, we found that a large proportion (47%) of our SCD population had enlarged LA volumes. Given that the enlargement of the left atrium has been found to be an independent predictor of cardiac events in many other disease cohorts, we propose the LAVI should be thoroughly measured and followed in the SCD. Unlike other studies, only 21% of our subjects had diastolic dysfunction. It is known that pressure and/or volume overload on the left atrium leads to remodeling over time and reflects severity and chronicity of underlying pathologic conditions rather than instantaneous LV diastolic dysfunction and increased filling pressures. The degree and extent of LA dilation are closely coupled with sickle cell severity but not diastolic dysfunction.^{6-7,23} As there is currently a debate about whether having an increased LAVI is correlated with diastolic dysfunction in the SCD population,²³ the use of LAVI may not be an accurate assessment of diastology. Because diastolic dysfunction in SCD is an independent predictor of mortality,¹ it is essential that we use any method possible to allow an early diagnosis. For this reason, assessing LV MPI may be another means to distinguish diastolic function.

Limitations of our study are that is a retrospective, single evaluation, cross sectional study. Although we attempted to account for confounding factors, there may be many other factors not included.

Conclusions

It is important to promptly identify cardiovascular abnormalities in SCD, as these are associated with increased complications and mortality. Our study demonstrates high prevalence of left and right cardiac abnormalities in these patients. Echocardiography – utilizing both conventional and newer tools is essential in making earlier and more accurate

diagnosis of cardiovascular abnormalities in sickle cell patients. Better understanding of the prognostic value of these echocardiographic abnormalities in SCD patients is needed to aid in risk stratification. We propose including LV MPI as a parameter to assess the cardiac function of SCD patients. In addition, as we have found that a large proportion of our SCD population had abnormal TAPSE, we propose that this parameter should be further investigated to assess its prognostic utility over time in assessing cardiac function in SCD patients.

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Abbreviations

2D	Two dimensional
BSA	Body surface area
CI	Confidence interval
HB	Hemoglobin
IVSD	Intraventricular septal diameter
LV	Left ventricle
LVEDD	LV end diastolic diameter
LVESD	LV end systolic diameter
LVET	LV ejection time
LVPWd	LV posterior wall diameter
MCOT	Mitral valve closure to opening time
MPI	myocardial performance index
OR	Odds ratio
PASP	pulmonary artery systolic pressure
RA	Right atrial
RV	Right ventricle
SCD	Sickle cell disease
TAPSE	Tricuspid annular plane systolic excursion

TRV Tricuspid regurgitation velocity

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Table 1

Demographics and baseline laboratory variables

Age (years old), mean $\pm$ SD	33.1 $\pm$ 11.3
BSA (m ²), mean $\pm$ SD	1.80 $\pm$ 0.22
Male	48 (53%)
Overweight (kg/m ²) (body mass index $\geq$ 25)	33 (36%)
Race	
Black	86 (94.5%)
Hispanic	5 (5.5%)
Type of SS anemia	
Sickle cell anemia	75 (83%)
Sickle cell trait	11 (12%)
Sickle-beta thalassemia (–)	3 (3%)
Sickle-beta thalassemia (+)	2 (2%)
Baseline Hb (g/dL)	
8	30 (33%)
>8	61 (67%)
Baseline Hb (g/dL), mean $\pm$ SD	9.0 $\pm$ 1.7
Baseline creatinine (mg/dL), median (min, max)	0.7 (0.2, 7.4)
Ferritin (ng/mL)	
<1000	59 (65%)
>1000	28 (31%)
Unknown	4 (4%)

Table 2

Comorbidities & confounding factors

Disease/factor Number (percentage) of subjects	
Hypertension	17 (19%)
Diabetes	1 (1%)
Coronary heart disease or heart failure	2 (2%)
Chronic kidney disease or end-stage renal disease	3 (3%)
Autoimmune disease	1 (1%)
Stroke	9 (10%)
Hydroxyurea	64 (70%)
Chronic transfusion therapy	26 (29%)
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker	10 (11%)
Beta blocker	10 (11%)
Statin	4 (4%)
Aspirin	6 (7%)

Table 3

Echocardiographic findings

Parameter	Number (percentage) of subjects
LVEDD (abnormal)	29 (32%)
LVEF (%) (abnormal)	35 (38%)
LV MPI	
Abnormal	71 (78%)
Normal	15 (16.5%)
Unknown	5 (5.5%)
LV Mass Index (abnormal)	22 (24%)
Fractional Shortening (abnormal)	19 (21%)
E/E -TDI ratio	
Abnormal	21 (23%)
Normal	65 (71.5%)
Unknown	5 (5.5%)
E-TDI	
Abnormal	7 (7.5%)
Normal	79 (87%)
Unknown	5 (5.5%)
TRV	
Abnormal	35 (38%)
Normal	46 (51%)
Unknown	10 (11%)
LAVI	
Abnormal	43 (47%)
Normal	43 (47%)
Unknown	5 (5.5%)
LV diastolic function	
Abnormal	19 (21%)
Normal	66 (72.5%)
Unknown	6 (6.5%)
PASP	
Abnormal	54 (59%)
Normal	29 (32%)
Unknown	8 (9%)
RV TAPSE	
Abnormal	26 (29%)

Parameter	Number (percentage) of subjects
Normal	61 (67%)
Unknown	4 (4%)
RV size	
Abnormal	13 (14%)
Normal	70 (77%)
Unknown	8 (9%)
RV hypertrophy	
Abnormal	7 (8%)
Normal	72 (79%)
Unknown	12 (13%)
RA volume index	
Abnormal	13 (14%)
Normal	70 (77%)
Unknown	8 (9%)

E – Early mitral inflow velocity

E – TDI - mitral annular early diastolic velocity.

Table 4

Univariate analysis of baseline Hb.

Odds ratio of Hb (8 g/dL vs. >8 g/dL) for echocardiographic parameters

Parameter	OR	95% CI	P value
LVEDD	0.88	0.34 – 2.26	0.79
LVEF (%)	0.72	0.29 – 1.80	0.48
LV MPI	0.59	0.19 – 1.87	0.37
LV Mass Index	5.80	2.06 – 16.3	<0.001
Fractional Shortening	1.65	0.59 – 4.68	0.34
E/E-TDI ratio	5.42	1.89 – 15.5	0.002
E-TDI	3.06	0.64 – 14.7	0.16
TRV	1.90	0.75 – 4.81	0.17
LAVI	2.47	0.95 – 6.42	0.06
LV diastolic function	2.40	0.84 – 6.87	0.10
PASP	2.00	0.73 – 5.50	0.18
RV TAPSE	1.49	0.57 – 3.91	0.41
RV size	0.60	0.19 – 1.84	0.37
RV hypertrophy	3.03	0.63 – 14.7	0.17
RA volume index	1.57	0.60 – 4.12	0.36