Subclinical Left Ventricular Systolic Impairment in Steady State Young Adult Patients with Sickle-cell Anemia

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Short title: Systolic impairment in sickle-cell anemia

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ABSTRACT

Purpose: Chronic volume overload in sickle-cell anemia (SCA) is associated with left ventricular (LV) enlargement and hypertrophy. The effect of the disease on LV systolic function remains debated. The aim of our study was to investigate LV systolic function in SCA patients using 2D speckle-tracking imaging.

Methods: We compared 30 steady state asymptomatic adult SCA patients (17 women, mean age 24.7±5.1 years) with 30 age and sex-matched healthy subjects (17 women, mean age 25.0±4.9 years). In addition to conventional echocardiographic parameters including LV ejection fraction (EF) and LV mass index (LVMi), global longitudinal strain (GLS) and strain rate (GLSR) were measured.

Results: GLS (-17.9±2.0% vs. -19.7±2.5%, $p=0.004$) and GLSR (-0.92±0.09s^{-1} vs. -1.07±0.17s^{-1}, $p<0.0001$) values were lower in SCA patients while LVEF values (60.1±3.8% vs. 61.7±4.7%, $p=0.30$) were not different. LVMi was increased in SCA patients (100.7±23.5g/m² vs. 72.4±15.2g/m², p0.0001) and GLSR was significantly lower in the subgroup of patients with LV hypertrophy (-0.88±0.09s^{-1} vs. -0.96±0.08s^{-1}, $p=0.02$). In SCA patients LVMi was correlated to GLS ($r=0.58$, $p=0.001$) and GLSR ($r=0.45$, $p=0.015$) pleading in favor of a pathological LV remodeling.

Conclusions: Asymptomatic SCA patients exhibited a subclinical alteration of LV systolic function. Myocardial dysfunction appears to be linked to the degree of LV hypertrophy. 2D speckle-tracking imaging might be useful for long-term follow-up and to study the natural course of LV dysfunction in SCA patients.

Keywords: echocardiography, left ventricular function, speckle-tracking, strain, Sickle-cell anemia

BACKGROUND

Sickle-cell disease is one of the most common inherited blood disorders worldwide [1]. Besides chronic anemia, many pathophysiological processes contribute to the complexity of the disease including hemolysis and repeated vaso-occlusive events with ischemia-reperfusion injury leading to endothelial cell dysfunction [1, 2]. Concomitantly to the life expectancy improvement observed over the past years, the prevalence of heart disease in adult patients has also increased representing now up to one fourth of all deaths [3].

In patients with homozygous sickle cell disease, also called sickle-cell anemia (SCA), a diastolic dysfunction, as well as left ventricular (LV) remodelling, including dilation and hypertrophy, have been previously described [4]. These modifications are best explained by an adaptative response to the volume overload effect of chronic anemia [5, 6].

While chronic volume overload in valvular heart disease such as mitral or aortic regurgitation [7] and prolonged anemia induced by iron deficiency in rat models [8] induce LV systolic dysfunction, its' occurrence in SCA disease is still debated with conflicting results in past studies [5, 6, 9–12]. Recently, ultrasound speckle-tracking imaging has emerged as a strong and sensible tool that allows early diagnosis of LV systolic dysfunction [13].

We hypothesized that a systolic LV dysfunction that could be diagnosed by speckle-tracking imaging may exist during steady-state SCA disease in adult patients.

METHODS

Study population

We enrolled 30 patients with SCA, aged 18 years and older, in stable condition and in sinus rhythm. All these patients were referred to our echocardiography laboratory for routine outpatient evaluation of cardiac function and/or systematic screening for pulmonary arterial hypertension. The diagnosis of homozygous sickle-cell disease was based on molecular genetic techniques. Patients who had developed acute chest syndrome, vaso-occlusive crisis or an acute complication within the previous 4 months, including fever, surgery, blood transfusion or hospital admission whatever the reason, were excluded in order to specifically focus on a group of steady state patients free of confounding factors that could be linked to an impaired LV function. The other exclusion criteria were the use of cardiovascular medication at the time of enrollment, hypertension, history of heart failure, moderate or severe valvular heart disease, atrial fibrillation, pregnancy and the presence of an associated comorbidity including autoimmune diseases, HCV or HIV infections and kidney failure defined by a glomerular filtration rate <60ml/mn/1.73m². Clinical and biological data were collected from records of the reference centre for sickle-cell disease (Tenon Hospital, Paris, France). From the general population, 30 age- and sex-matched healthy subjects without history of cardiac or pulmonary disease and with normal electrocardiograms were recruited as control subjects. Blood pressure was measured in patients and controls in supine position at the end of the echocardiographic examination using a Dash 3000 monitor (GE Healthcare; Horten, Norway). Informed consent was obtained from each patient. The study was approved by the institutional committee on human research.

Standard echocardiography

Transthoracic echocardiography was performed in all patients with the use of the Vivid 7 system (GE Healthcare; Horten, Norway) and transferred to a workstation equipped with the Echopac PC software (GE Vingmed Ultrasound; Horten, Norway) for offline analysis. All exams were acquired and analyzed off-line blinded to the clinical data by a senior cardiologist (NH). All measurements were averaged over 3 consecutive cardiac cycles. All projections were obtained according to the recommendations of the American Society of Echocardiography [14, 15]. From M-mode, the following measurements were made at end diastole: LV internal diameter, inter-ventricular septal and posterior wall thicknesses. LV mass was derived and indexed to body surface area (LVMi), relative wall thickness was also calculated (posterior wall thicknesses × 2 / LV internal diameter) and LV remodeling was categorized as recommended [15]. LV hypertrophy was defined by an LVMi > 95g/m² in women and >115g/m² in men. Further classification as either concentric hypertrophy (relative wall thickness > 0.42) or eccentric hypertrophy (relative wall thickness ≤ 0.42) was made. From 2-dimensional mode, end systolic left and right atrial areas were measured, LV volumes and ejection fraction (LVEF) were derived from Simpson's modified biplane method. From pulsed wave Doppler mode, LV outflow tract time-velocity integral, early and late peak diastolic velocities of the mitral (E and A) inflow and the E-wave deceleration time were measured. LV ejection volume and output were calculated and indexed to body surface area as recommended [14]. The peak e' velocity was used to calculate the E/e' ratio using pulsed tissue Doppler imaging of the lateral mitral annulus [16]. Diastolic dysfunction was defined by E/A ratio <1.0 and/or a deceleration time >240 ms; E/A ratio ≥1.0 and E/e'ratio >10; E/A ratio higher than the 95th percentile for age or deceleration time <140 ms and E/e' >10. This classification of LV diastolic function has a prognostic value on mortality in patients with SCA [17].

From continuous wave Doppler, peak tricuspid regurgitation was recorded in multiple views and the highest level of velocity was selected. Elevated pulmonary systolic pressure was defined by a peak tricuspid regurgitation jet velocity ≥ 2.5m/s, severe elevation by a peak tricuspid regurgitation jet velocity ≥ 2.9m/s [18].

Speckle-tracking imaging

For 2D speckle-tracking imaging, sector size and depth were adjusted to achieve optimal visualization of all LV myocardium at the highest possible frame rate (mean value 87 ±14 frames/s). Multiple consecutive cardiac cycles of the 3 standard apical views (4, 2 and 3 chambers views) were acquired during breath holding. In each view, the myocardium was automatically divided by the software into 6 segments. The analyzed values within the middle points for all resulting 18 segments were averaged to obtain the global longitudinal strain (GLS) and the global longitudinal peak systolic strain rate (GLSR); in accordance with current conventions GLS and GLSR values were presented as negative (segment shortening) [13]. The adequacy of tracking was verified manually, and the region of interest was readjusted to achieve optimal tracking. The segment was excluded if no acceptable border was traced. GLS and GLSR values were not calculated if > 1 segment per view were excluded.

Statistical analysis

All quantitative data are expressed as mean ± standard deviation (SD); qualitative data are expressed as number and as percentage. For case-control analysis, the Wilcoxon signed rank test was used for univariate analysis of continuous variables and the McNemar's test was used to compare categorical data.

Using the Mann-Whitney U test and the chi-square test a secondary analysis compared the subgroup of patients with and without LV hypertrophy. The Pearson's correlation test was used to assess the univariate relations between variables.

Intraobserver and interobserver variabilities for LV deformation parameters, LV volume, LVEF and LVMi measurements were assessed in 20 studies by 2 independent observers (NH and DA). Using the Bland-Altman approach, the 95% limit of agreement was calculated. In addition, the coefficient of variation (CV) defined as the ratio of the SD of the difference of paired samples to the average of the paired samples and the intra-class correlation coefficient (ICC) were calculated. For intraobserver variability the CV and the ICC were respectively

4.1% and 0.93 for GLS, 4.3% and 0.92 for GLSR, 8.1% and 0.96 for LV end diastolic volume index, 4% and 0.83 for LVEF and 5.5% and 0.99 for LVMi. The 95% limits of agreement were -1.63 to 2.35% for GLS, -0.10 to 0.13 for GLSR, -17.1 to 14.7 ml/m² for LV end diastolic volume index, -7.1 to 6.8% for LVEF and -15.4 to 12.2g/m² for LVMi. For interobserver variability the CV and the ICC were respectively 6.6% and 0.88 for GLS, 6.2% and 0.91 for GLSR, 7.6% and 0.96 for LV end diastolic volume index, 3.6% and 0.85 for LVEF and 7.8% and 0.98 for LVMi. The 95% limits of agreement were -1.2 to 3.7% for GLS, -0.05 to 0.18 for GLSR, -11.0 to 16.5 ml/m² for LV end diastolic volume index, -5.5 to 6.8% for LVEF and -15.1 to 21.7 g/m² for LVMi.

SPSS software version 17.0 (SPSS, Inc, Chicago, IL) was used for calculation. A $p<0.05$ indicated statistical significance.

RESULTS

Patients' mean age was 24.7±5.1 years and 17 patients (57%) out of a total of 30 were women. Percentages of patients with histories of thoracic vaso-occlusive events or cerebral vasculopathy were 30% and 7% respectively. The mean hemoglobin level was 8.5±0.9 g/dl and in 11 cases (36%) it was ≤ 8g/dl. Patients and controls were matched for age and gender and there was no significant difference between the 2 groups for body surface area and body mass index. Diastolic and mean blood pressures were significantly lower in patients than in controls; the heart rate was not higher in patients (Table 1), only 3 patients had heart rates > 90/min and none >100/min.

Morphological and hemodynamic characteristics are summarized in Table 2. LV dimensions and mass were greater in patients than in controls. In patients, the LV hypertrophy was mainly eccentric; only 1 patient had concentric hypertrophy. The mean tricuspid regurgitant jet velocity was higher in the patient group including 13 patients (43%) with elevated pulmonary systolic pressures and none with severe elevation.

LVEF measurements were > 50% in all patients. Despite similar LVEF between the 2 groups, the GLS and the GLSR values were significantly decreased in the SCA group (Table 2, Figure 1). LV speckle analysis was not feasible in 1 patient and 1 control subject, because of poor image quality. Patients presented a diastolic dysfunction and had a higher E/e' ratio (Table 2).

In order to assess the potential impact of blood pressure or heart rate on the relationship between GLS and SCA, 3 linear regression analyses including respectively, mean arterial blood pressure, diastolic blood pressure and heart rate were done. The results of the 3 analyses were similar and confirmed the independent link between GLS and SCA ($r^2=0.15$, $p=0.002$).

The GLSR was significantly lower in patients with LV hypertrophy (Table 3). A correlation was found between LVMi and GLS ($r=0.58$, $p=0.001$) as well as with GLSR ($r=0.45$, $p=0.015$). There was a significant inverse correlation between the hemoglobin level and LVMi ($r=-0.43$, $p=0.017$) as well as LV end-diastolic diameter index ($r=-0.36$, $p=0.047$). The hemoglobin level was not statistically correlated to LVEF ($r=-0.04$, $p=0.83$), E/e' ratio ($r=-0.28$, $p=0.13$), GLS ($r=0.15$, $p=0.44$) and GLSR ($r=0.28$, $p=0.14$).

DISCUSSION

In this study we found that in addition to morphological modifications including hypertrophy and dilation, LV systolic function assessed by 2D speckle tracking imaging was impaired in a population of steady state SCA young asymptomatic adult patients with preserved LVEF. The severity of LV hypertrophy was linked to the impairment of global longitudinal LV deformation parameters. The GLS was linked to SCA independently to blood pressure and to heart rate. LV remodeling was inversely associated to the hemoglobin level.

Despite not being a pure form of anemia [19], the LV remodeling observed in homozygous sickle-cell disease is commonly attributed to chronic anemia as reduced blood oxygen-carrying capacity induces an increased cardiac output [4]. As described in this study and noted previously by others, an important stroke volume increase associated with a relatively mild heart rate elevation contribute to the cardiac output increase [12]. Modifications in LV preload and afterload could explain the stroke volume increase; the significant reduction of the mean arterial blood pressure while the cardiac index is increased underlines the decrease in peripheral vascular resistances [20]. Volume overload contributes to the increased cardiac output by inducing an increase in LV preload and a substantial LV enlargement[21, 22]. According to Laplace's Law, this volume overload increases the peak systolic wall stress resulting in wall thickening to normalize the systolic stress. Wall thickening and fiber elongation contribute to the pattern of eccentric hypertrophy in which the ratio of wall thickness to chamber radius remains normal [23].

Regarding the LV systolic function assessment, conflicting results in previous studies are partly explained by the multitude of different echocardiographic parameters used to assess myocardial contractility including load-dependant measures such as the LVEF calculation [6, 12, 24–26]. In our study, deformation parameters were significantly reduced while the LVEF was similar in both groups. Myocardial deformation assessed by strain and strain-rate is the result of a complex interaction between the intrinsic contractile force and the extrinsic loading conditions applied to a tissue with variable elastic properties [27]. Therefore, it could be argued that the observed modifications of LV longitudinal deformation may not only be the result of an alteration in contractility but may reflect modifications of loading conditions or in myocardial stiffness. In our study the afterload was lower and the preload higher in the SCA group and it is admitted that under these conditions deformation values should increase [28, 29]. This argument pleads in favor of the occurrence of a LV systolic impairment in young adult SCA patients. Similarly, a recent meta-analysis reported an impairment of a relatively load independent LV systolic function assessment parameter (end-systolic stress to end-systolic volume index) despite preservation of load dependant parameters in SCA patients [30].

An interesting parallel can be made concerning LV remodeling between patients suffering from chronic anemia and endurance athletes in whom a comparable cardiac remodeling has been reported [31]. In contrast with the results of our study, LV strain and strain rate values in endurance athletes have been reported to be normal or increased [32, 33]. Besides, while increased LV mass is associated with improved deformation indices in endurance athletes [32], LV hypertrophy is associated with an impairment of LV function in our population further supporting the hypothesis that a LV myocardial impairment exists in sickle-cell disease patients. Similar findings have been reported in the course of hypertrophic cardiomyopathy [32] and myocardial fibrosis is associated with depressed strain values in these patients [34]. Moreover, as morphological and functional LV parameters are linked, LV mass may be helpful in routine practice for the identification of a subgroup of SCA patients athigh risk of LV dysfunction.

In case of severe organic mitral regurgitation, prolonged burden due to volume overload might result in LV dysfunction and irreversible myocardial damage. If a significant LV myocardial morphological and/or functional involvement is/are identified, current guidelines recommend the correction of the regurgitation in asymptomatic patients [7]. The LV abnormalities observed in SCA patients are multifactorial including the combination of chronic anemia and microvascular dysfunction[4]. In our study, LV deformation parameters revealed a LV impairment in a population of young adult SCA patients with normal LVEF, suggesting a promising role of these parameters for the detection of LV dysfunction at an early stage before major and irreversible damage of the myocardium occurs. As cardiovascular mortality in adult SCA patients is high[3] our findings may provide clinicians a useful method of identification of a category of patients at high risk of developing long-term congestive heart failure and/or premature death. Moreover these patients may benefit from more regular follow up and more aggressive clinical interventions in order to improve their prognosis.

A similar study using deformation imaging was recently conducted on a pediatric population of sickle cell disease patients with contrasting results as deformation indices were not modified [35]. It could be hypothesized that the LV systolic impairment, as found in our population of adults, occurs later in the course of the disease. Age related deterioration of LV systolic function was previously described [30]. Moreover, in a population of adult patients presenting with sickle-cell crisis, the usefulness of deformation indices assessed by speckle tracking for detecting LV systolic function impairment has already been reported [36]; our study identified LV dysfunction in a population of steady-state patients. Contrastingly, no impairment in LV systolic function was reported in a study based on 3-dimensional LV speckle tracking echocardiography [37]. This promising new method performed on a pre-commercial prototype software still suffers from technical limitations such as low temporal resolution. Besides, in addition to SCA patients, hemoglobin sickle-cell (SC) patients were also included in this study. It has already been described that SC patients have very different clinical and biological characteristics [38]. Therefore, the results must be compared to ours with caution.

Consistently with previous studies [10, 17, 39, 40], we also found a LV diastolic function impairment. Diastolic dysfunction is known to be an independent risk factor for mortality in SCA [17]. It is worth noting that the E/e’ ratio is normal in healthy endurance athletes [32, 33].

Several limitations of our study need to be acknowledged. First, our population was relatively small as we decided to focus on strict inclusion criteria in order to reduce any bias by selecting only steady state homozygous sickle-cell disease patients free of confounding factors that could be linked to LV systolic impairment. Despite this limitation, we found a significant impairment of deformation indices. Second, we only evaluated the LV longitudinal deformation parameters as they appear to be the most efficient and reproducible parameters in speckle tracking technology [41]. Moreover, it has been earlier described that the natural course of myocardial diseases is characterized by the impairment of the longitudinal function that occurs before the onset of circumferential and radial alterations [42]. Finally, the prognostic implications of LV deformation parameters were not assessed in this study and need further investigations.

Steady state young adult patients suffering from homozygous sickle-cell anemia exhibited a subclinical impairment of myocardial contractility. 2D speckle-tracking imaging might constitute a useful tool for long-term follow-up and to study the natural course of LV dysfunction in these patients. Additional studies are required to further understand the prognostic implications of deformation parameters.

DISCLOSURES

The authors have no disclosures.

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FIGURE LEGENDS

Figure 1. Comparison of LV global longitudinal strain measures between a sickle-cell anemia patient and an age and sex-matched control subject. Despite similar LV ejection fractions, LV peak global longitudinal strain value (white curve; arrow) is significantly decreased in the sickle-cell anemia patients' measure.

GLS = Global longitudinal Strain; LVEF = Left ventricular ejection fraction; SCA = Sickle-cell Anemia.

Table 1: General characteristics of the study subjects

	SCA patients (n=30)	Controls (n=30)	p value
Age (years)	24.7±5.1	25.0±4.9	0.08
Women	17 (57)	17 (57)	matched
Body Mass index (g/m²)	21.0±3.2	22.0±2.9	0.23
Body surface area (m²)	1.75±0.18	1.78±0.19	0.26
Systolic Blood Pressure (mmHg)	114.2±9.3	119.0±11.1	0.11
Diastolic Blood Pressure (mmHg)	65.5±8.6	70.8±7.0	0.008
Mean Blood Pressure (mmHg)	81.7±7.9	86.9±7.4	0.02
Heart rate (beats/min)	72.5±10.3	67.7±11.4	0.07

Data are expressed as mean ± SD or as number (%)

SCA = Sickle Cell Anemia

Table 2: Echocardiographic measurements in patients and controls

	SCA patients (n=30)	Controls (n=30)	p value
LVEDD index (mm/m^2)	30.8±3.2	28.3±2.1	0.0009
LV mass index (g/m^2)	100.7±23.5	72.4±15.2	0.0001
LV mass index (g/m^2) in women (n=17)	98.6±19.2	66.6±13.4	0.0001
LV mass index (g/m^2) in men (n=13)	107.3±26.5	80.0±14.6	0.03
LV hypertrophy	14 (47)	1 (3)	< 0.0001
LV eccentric hypertrophy	13 (43)	1 (3)	0.0002
LVEDV index (ml/m^2)	80.9±16.0	59.5±13.0	< 0.0001
LV ejection volume index (ml/m^2)	56.4±9.6	47.3±7.6	0.0004
Cardiac index (L/min/m^2)	4.1±0.7	3.2±0.6	0.0001
TR velocity (m/s)	2.4±0.2	2.1±0.2*	< 0.0001
TR velocity > 2.5m/s n, %	13 (43.3)	1 (3.7)*	0.001
Left atrial area (cm^2)	23.8±3.8	18.0±3.9	< 0.0001
Right atrial area (cm^2)	17.7±2.9	14.4±3.5	0.0001
Diastolic function			
E (cm/s)	94.6±16.0	79.9±14.1	0.0003
A (cm/s)	49.5±11.7	46.2±11.0	0.33
E/A	2.0±0.5	1.8±0.4	0.04
E-wave deceleration time (ms)	169.5±34.6	153.3±30.7	0.02
e' (cm/s)	17.4±3.7**	19.0±3.5	0.11
E/e'	5.8±2.5**	4.5±2.1	0.0003
Diastolic dysfunction	6 (20)	0 (0)	0.03

Systolic function			
LVEF (%)	60.1±3.8	61.7±4.7	0.30
Global longitudinal strain (%)	-17.9±2.0**	-19.7±2.5**	0.004
Global longitudinal strain rate (s^{-1})	-0.92±0.09**	-1.07±0.17**	<0.0001

*n=27, **n=29

Data are expressed as mean ± SD or as number (%)

A= Late peak diastolic velocity of the mitral inflow; E = Early peak diastolic velocity of the mitral inflow; e’ = early diastolic mitral annular tissue Doppler velocity, E/e’ = ratio between peak velocities of mitral E wave and early-diastolic mitral annulus; LVEDD = Left ventricular end-diastolic diameter; LVEDV = Left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; TR velocity = tricuspid regurgitant maximal velocity; SCA = Sickle Cell Anemia

Table 3: Comparison of clinical and echocardiographic data according to LV Mass index in Sickle cell Anemia patients

	LV hypertrophy (n=14)	Normal LV morphology (n=16)	p value
Age (years)	24.3 ± 5.3	25.0 ± 5.1	0.80
Women	10 (71)	7 (44)	0.13
Systolic Blood Pressure (mmHg)	114.4 ± 10.0	113.9 ± 9.0	0.88
Diastolic Blood Pressure (mmHg)	64.1 ± 7.8	66.7 ± 9.3	0.51
Heart rate (beats/min)	70.9 ± 10.6	73.9 ± 10.1	0.37
Hemoglobin (g/dl)	8.3 ± 0.6	8.8 ± 1.1	0.21
LV mass index (g/m^2)	119.2±17.0	84.6±14.8	< 0.0001
Cardiac index (L/min/m^2)	4.2 ± 0.6	3.9 ± 0.8	0.13
TR velocity (m/s)	2.4 ± 0.2	2.4 ±0.2	0.52
E (cm/s)	100.2 ± 13.3	89.6 ± 17.0	0.05
A (cm/s)	48.8 ± 13.0	50.1 ± 10.7	0.49
E/A	2.2 ± 0.5	1.9 ± 0.4	0.15
E-wave deceleration time (ms)	163.6 ± 21.9	174.6 ± 42.9	0.65
e' (cm/s)	16.6 ± 4.0*	18.0 ± 3.4	0.38
E/e'	6.7 ± 3.4*	5.1 ± 1.3	0.10
Diastolic dysfunction	5 (36)	1 (6)	0.04
LV Ejection Fraction (%)	59.4 ± 3.8	60.8 ± 3.8	0.42
Global longitudinal strain (%)	-17.1 ± 2.4*	-18.5 ± 1.5	0.07
Global longitudinal strain rate (s$^{-1)}$	-0.88 ± 0.09*	-0.96 ± 0.08	0.02

*n=13.

Data are expressed as mean ± SD or as number (%)

TR velocity = tricuspid regurgitant maximal velocity; E = Early peak diastolic velocity of the mitral inflow; A= Late peak diastolic velocity of the mitral inflow; e’ = early diastolic mitral annular tissue Doppler velocity, E/e’ = ratio between peak velocities of mitral E wave and early-diastolic mitral annulus; SCA = Sickle Cell Anemia