Left Ventricular–Aortic Coupling in Sickle Cell Disease underlies Diastolic Dysfunction

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Abstract

Left ventricular (LV) diastolic dysfunction (DD) is associated with increased mortality in sickle cell disease (SCD) but its mechanisms are not well known, preventing the development of effective therapies. Our hypothesis was that DD in SCD may be due to changes in aortic properties. We studied 31 SCD patients (32±7yrs) and 12 normal controls (29±10yrs) who underwent echocardiography and MRI on the same day. LV diastolic function was assessed from echocardiography. MRI included velocity-encoded images of the aorta to measure ascending aortic cross-sectional area, stroke volume, distensibility, as well as volumes of the forward (FFV) and backward (BFV) blood flow. Compared to controls, SCD patients had increased aortic area, stroke volume, and both FFV and BFV, while distensibility was similar. DD was found in 5/31 patients (16%), in whom the increase in BFV and BFV/FFV ratio was even more pronounced, when compared to the remaining patients. Our findings suggest a potential mechanism of DD in SCD patients. Increased cardiac output induced by chronic anemia might be associated with aortic dilation, which may increase LV afterload (BFV), ultimately leading to LV DD. If confirmed in larger studies, these aortic changes could be targets for specific therapies as a way to prevent the development of DD in SCD.

1. Introduction

Sickle cell disease (SCD), which is an inherited blood disorder characterized by red blood cells with an abnormal, rigid and sickle shape, is one of the most common genetic diseases worldwide and is an important cause of morbidity and mortality [1]. SCD is associated with anemia, small vessel occlusion and tissue ischemia, which can occur in different organs, as well as progressive vasculopathies, including pulmonary hypertension and peripheral arterial endothelial dysfunction.

Left ventricular (LV) alterations in SCD have been widely described, including LV dilation [2-5], an increase in LV mass [2-6], as well as diastolic dysfunction (DD) [4]. Today, 25% of SCD deaths are related to cardiovascular causes, and DD is a known independent risk factor for mortality in SCD patients [7]. However, the etiology of DD in SCD remains unclear, preventing the development of effective therapies.

Several studies focused on the effects of SCD on large central arteries indicated changes in aortic size [2,3] and arterial stiffness indices [3,6,8], which were shown to be associated with indices of LV DD [3]. However, to the best of our knowledge, other potential determinants of LV DD, such as proximal aortic hemodynamics, have never been investigated in SCD patients. Indeed, the only previously reported cardiovascular hemodynamic indices were either cardiac output [9] or flow measured in peripheral arteries [10].

Accordingly, our aims were: 1) to perform a comprehensive evaluation of SCD-related changes in the ascending aorta, including its size, stiffness and blood flow, and 2) to study the interaction between changes in aortic properties and LV DD. To achieve these aims, we used a multimodality approach that involved echocardiography and cardiovascular magnetic resonance imaging (MRI).

2. Materials and methods

2.1. Study group

Subjects from the University of Chicago Medical Center were recruited from the adult SCD outpatient program. A total of 31 African-American patients with SCD and 12 healthy subjects of a similar age were enrolled. Each subject underwent transthoracic echocardiography (TTE) and cardiovascular MRI within 4 hours. Subjects were excluded if clinically unstable, defined as having vaso-occlusive crisis, acute chest syndrome or unscheduled blood transfusions within 3 weeks of the study, or had standard contra-indications to MRI. Each subject provided written consent to participate

in this study, which was approved by the institutional human subjects review board.

2.2. Echocardiography

TTE images were obtained using an iE33 ultrasound imaging system with an S5 transducer (Philips). Digital cine loops were acquired by an experienced sonographer and subsequently reviewed off- line, to measure left atrial volume, transmitral flow early filling and atrial filling peak velocities (E and A, respectively), as well as the mitral annulus early peak longitudinal velocity on the septal and lateral walls (e'). These parameters were used to diagnose LV DD, according to the latest guidelines of the American Society of Echocardiography [11].

2.3. MRI acquisitions

MRI was performed using a 1.5T scanner (Achieva, Philips) with a 5-element phased array cardiac coil. First, retrospectively gated cine images were acquired using a steady-state free precession (SSFP) sequence with the following acquisition parameters: repetition time (TR)=2.9ms, echo time (TE)=1.5ms, flip angle=60°, acquisition matrix=192x168, pixel spacing=1.3mm and temporal resolution<40ms. Standard long-axis including four-chamber, two-chamber, and three-chamber views, as well as short-axis slices (thickness=8mm, gap=2mm) covering the entire heart were obtained. Then, axial phase-contrast images were acquired in the mid-ascending aorta perpendicular to the aorta at the level of the center of the right pulmonary artery, using a 2D through-plane velocity-encoded sequence with retrospective gating with breath-holding. Acquisition parameters were: TR=4.2ms, TE=2.6ms, flip angle=15°, number of excitation=1, voxel size=1.4x1.4x10mm^3, acquisition matrix=140x133, temporal resolution=29ms and encoding velocity=200cm/s.

2.4. Analysis of MRI data

SSFP short-axis images were analyzed using commercial software (ViewForum, Philips), providing maximal left atrial volume and LV end-diastolic (LVEDV), end-systolic (LVESV) volumes, mass (LVM), and ejection fraction (LVEF). Of note, volumes (LVEDVi, LVESVi) and mass (LVMi) were indexed for body surface area (BSA).

Aortic phase-contrast images were processed using custom, previously validated ArtFun software (U1146 INSERM/UPMC) [12]. First, ascending aorta contours were automatically detected on each phase of the cardiac cycle on modulus images. Such segmentation resulted in aortic lumen area variations throughout the cardiac cycle (Figure 1.A). Furthermore, superimposition of such aortic contours on velocity images provided aortic flow curves (Figure 1.B), which were then processed using automated peak detection and area under curve calculation.

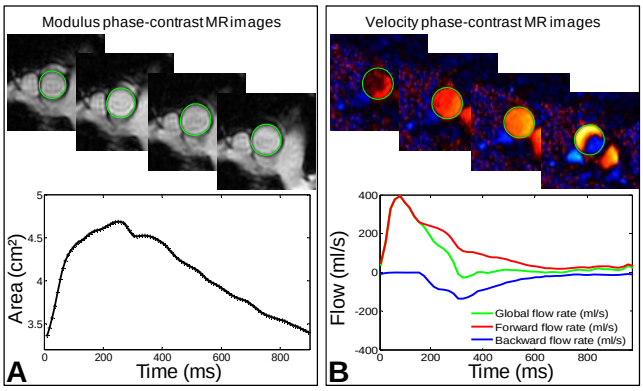

Figure1. A. Segmentation of aortic borders on modulus MRI images providing cross-sectional area. B. Superimposition of aortic contours on velocity images providing aortic global, forward and backward flow curves.

First, ascending aorta diastolic (DA) and systolic (SA) areas were calculated, respectively as the minimum and maximum of the aforementioned cross-sectional area variation curve. Aortic distensibility was then estimated as: (SA–DA)/(DA·PP), where PP is pulse pressure calculated as the difference between systolic (SBP) and diastolic (DBP) brachial blood pressures recorded during MRI. DA indexed to BSA (DAi) was also reported.

Then, ascending aortic flow curves were used to estimate aortic global stroke volume (SV). We further studied the separate contributions of forward and backward components to the global flow by using MRI velocity data [13]. For each velocity-encoded image of the cardiac cycle, pixels corresponding to the velocities encoded in the direction of ejected blood flow from the LV ('positive' pixels) were used to calculate forward flow, and pixels corresponding to the velocities encoded in the opposite direction of ejected blood flow ('negative' pixels) were used to calculate backward flow. Then, time integrals of aortic forward and backward flow curves were calculated, resulting in forward (FFV) and backward (BFV) flow volumes, respectively. Finally, backward to forward flow volumes ratio was computed. Flow volumes indexed to BSA (SVi, FFVi, BFVi) were provided.

2.5. Statistical analysis

Mean values and SD were provided for continuous variables. A nonparametric Mann–Whitney test was used for comparisons between SCD patients and normal controls, as well as for the evaluation of differences in aortic indices between SCD patients with and without LV DD. All reported p-values are two-sided and a p-

value<0.05 indicated statistical significance. Statistical analysis was performed using Stata 10 IC (StataCorp).

3. Results

Controls and SCD patients' baseline characteristics along with MRI indices of LV systolic function, and TTE indices of LV diastolic function are summarized in Table 1. Gender distribution, BSA and blood pressures did not differ between the two groups. While LV ejection fraction was similar, indexed LV volumes and mass were significantly increased in SCD patients, as compared to controls. While diastolic E and A velocities were significantly increased in SCD patients, E/A ratio was similar between the two groups. Finally, septal and lateral mitral annulus velocities, e', were significantly lower in SCD patients, resulting in a significant increase in E/e' ratio. DD was found in 5 (16%) patients with SCD.

Table 1. Baseline characteristics and MRI, TTE indices of LV function in controls and patients with SCD. *: p<0.05 for comparisons between the two groups.

	Controls(*n*=12)	SCD(*n*=31)
Age, yrs	29±10	32±7
Women *n* (%)	7 (58)	18 (58)
BSA, m^2	1.92±0.30	1.80±0.19
Heart rate, bpm	74±14	70±15
SBP, mmHg	125±19	121±20
DBP, mmHg	71±12	66±18
Hemoglobin level, g/dL	-	8.5±2.5
LVEF, %	62±5.9	58±5.0
LVEDVi, ml/m^2	79±12	123±28*
LVESVi, ml/m^2	31±7.2	53±15*
LVMi, g/m^2	50±13	78±20*
E velocity, cm/s	85±13	97±15*
A velocity, cm/s	51±21	60±16*
E/A	1.9±0.6	1.7±0.5
Septal e', cm/s	10.6±1.9	9.1±1.4*
Lateral e', cm/s	14.5±3.2	13.3±3.2
Septal E/e'	8.2±1.5	10.8±2.3*
Lateral E/e'	6.1±2.0	7.6±2.2*

MRI aortic indices are summarized in Table 2. While no significant differences in aortic distensibility were found between SCD patients and controls, aortic area, stroke volume, forward and backward flow volumes were significantly higher in SCD patients.

Finally, in the SCD group, the aforementioned increase in backward flow was even more prominent in patients with DD, when compared to patients with normal diastolic function (Table 3). Of note, aortic distensibility was considerably reduced in patients with DD, although this difference was not statistically significant.

Table 2. MRI indices of aortic geometry, stiffness and hemodynamics for controls and SCD patients. *: p<0.05 for comparisons between the two groups.

	Controls(*n*=12)	SCD(*n*=31)
DAi, cm^2/m^2	2.7±0.3	3.4±0.7*
Distensibility, 10^{-3} kPa^{-1}	24±15	27±20
SVi, ml/m^2	22±3.9	31±5.9*
FFVi, ml/m^2	25±4.3	36±6.6*
BFVi, ml/m^2	2.0±0.9	3.3±1.6*
BFV/FFV, %	7.7±3.1	9.1±4.2

Table 3. MRI indices of aortic geometry, stiffness and hemodynamics for SCD patients with and without DD. *: p<0.05 for comparisons between the two groups.

	SCD without DD(*n*=26)	SCD with DD (*n*=5)
Age, yrs	31±6.8	35±7.6
DAi, cm^2/m^2	3.3±0.7	4.0±0.6
Distensibility, 10^{-3} kPa^{-1}	29±21	14±8.7
SVi, ml/m^2	32±6.2	30±4.7
FFVi, ml/m^2	36±6.9	35±5.4
BFVi, ml/m^2	3.0±1.4	4.8±1.5*
BFV/FFV, %	8.2±3.5	14±5.1*

4. Discussion

In this multimodality imaging study involving echocardiography and MRI, we found differences in aortic geometry and hemodynamics between SCD patients and normal controls. We also found that SCD-related changes were more pronounced in the presence of DD. Our main findings were that: 1) proximal aorta was dilated, its elasticity was unchanged and all global, forward and backward flow components were increased in SCD patients, as compared to controls, 2) indices of aortic backward flow volumes were able to discriminate between SCD patients with and without DD.

Cardiac alterations in SCD have been previously studied. In agreement with published literature, we found in our SCD patients a preserved LV ejection fraction [2,4] along with LV dilation [2-4] and an increase in LV mass [2-4,6]. Such LV enlargement has been hypothesized to reflect a remodeling mechanism to adapt to the elevation in stroke volume induced by the chronic anemia-related decrease in blood oxygenation to match metabolic demand. Consistently, we observed in SCD patients an elevation of stroke volume measured in the ascending aorta from velocity MRI data.

Previous studies focusing on the dilating and stiffening effect of SCD on large central arteries resulted in conflicting findings. Indeed, it was previously demonstrated that aortic size was either unchanged [3] or increased [2], while arterial stiffness has been shown to

be either decreased [8] or increased [3,6] in SCD patients. In our study, we found that aortic area was significantly increased and that stiffness was unchanged in SCD patients when compared to controls. These discrepancies might be due to differences in study populations as well as in techniques used to evaluate arterial stiffness. Indeed, we calculated local distensibility in the proximal ascending aorta, while in most previous studies [6,8], arterial stiffness was assessed from measurements performed in the carotid, brachial, radial and femoral arteries. Furthermore, the previously used stiffness-related brachio-radial [6], carotid-radial [8] or carotid-femoral [8] pulse wave velocities are global, as they include arterial segments with different elasticity, and do not always reflect aortic elasticity, which is known to decrease towards peripheral sites.

We further evaluated SCD-related changes in aortic hemodynamics, while studying separately the forward and backward flow components provided by MRI velocity-encoded data. Indeed, aortic blood flow includes a forward (=antegrade) flow originating from the LV and going through the aorta, and a backward (=reverse) flow, coming back towards the heart. This physiological phenomenon has been described in the literature for a long time; it can be amplified in case of various cardiovascular diseases, such as aortic aneurysms or ischemic heart disease, but it is always present even in healthy subjects. In a recent study [13] including 96 healthy subjects aged from 19 to 79 years, we observed that such backward flow increased with age. Besides, we found that the independent correlate of backward flow was age-related aortic remodeling, namely aortic cross-sectional dilation and aortic arch elongation. Thus, backward flow might mostly represent local flow disorganization due to geometric changes. In our SCD patients, we found that aortic dilation was accompanied by increased backward flow volume, when compared to healthy subjects.

Importantly, indices of backward flow volume were able to discriminate SCD patients with and without diastolic dysfunction. Thus, LV dysfunction in SCD might begin with an increase in stroke volume, associated with aortic dilation along with an increase in aortic backward flow. Such increased afterload could induce an impairment of LV diastolic function.

Our study has several limitations. First, we calculated aortic distensibility using brachial blood pressure, rather than central pressure, which could have obscured potential changes in the true proximal aortic local stiffness. Also, the cross-sectional nature of our study does not allow identifying causes and effects involved in the LV-aortic interplay alterations in SCD. Finally, subject groups were small, especially the number of SCD patients with diastolic dysfunction.

Despite these limitations, we found a significant increase in ascending aortic area, as well as global, forward and backward flow in SCD. Such elevation in backward flow was even more pronounced in patients with diastolic dysfunction. If confirmed in larger and longitudinal studies, these aortic changes could become useful as they may allow an early detection of LV diastolic dysfunction and could ultimately be targets for specific therapies, as a way to prevent or delay the development of cardiovascular diseases and thus potentially improve outcomes in these patients.

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