Sickle-cell Anemia and Latent Diastolic Dysfunction: Echocardiographic Alterations

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Introduction

Sickle-cell anemia (SCA) is a disease that can cause systemic complications, such as multiple organ dysfunction due to vaso-occlusion and endothelial activation. The genetic cause of the disease is a substitution of the amino acid glutamic acid for valine in the position 6 of the beta globin chain[1]. Stress factors in the vascular microenvironment (cellular dehydration, hypoxemia, increased corpuscular hemoglobin concentration, decreased red blood cell transit time in the microcirculation, and decreased blood pH) trigger intracellular hemoglobin polymerization, forming paracrystalline structures that cause sickling of erythrocytes and increased blood viscosity, hemolysis, and vaso-occlusion[1,2]. Simultaneously, free hemoglobin in the plasma sequesters nitric oxide (NO), leading to decreased NO bioavailability and increased endothelial adhesion (in physiological conditions, NO inhibits of platelet aggregation, platelet activation, transcription of platelet adhesion proteins)[1].

The increase in cardiac output (CO), the afterload reduction due to the peripheral vasodilation as a response to hypoxemia, the increase in blood viscosity secondary to the morphological alterations, and the loss of the deformability of the sickle red blood cells are factors involved with the systolic ventricular overload and progressive enlargement of the cardiac chambers[3-5].

Case Report

In the present paper, we report the adverse effects after volume expansion observed in a single patient with SCA. Initial examination showed borderline left ventricular systolic function, without evident diastolic dysfunction on echocardiography, which was performed as part of a study protocol for cardiac complications in adults with SCA and was previously approved by the local ethics committee.

We present the details of the case below. The patient was a 40-year-old male SCA patient without history of symptoms except for the complaint of sporadic palpitations related to moderate physical effort at presentation. Cardiac function was evaluated using two-dimensional echocardiography in *M*-mode, pulsed wave Doppler, continuous wave Doppler, color Doppler, and tissue Doppler[6,7]. Baseline laboratory examinations showed serum hemoglobin levels of 10.1 mg/dL, lactate dehydrogenase (LD) levels of 1,002 U/L, ferritin levels of 280.9 ng/mL, NT-pro-BNP levels of 250.0 pg/ml; the electrophoretic profile of hemoglobin determined by high-performance liquid chromatography showed 82.6% HBS and 3.8%, HA2, with the remainder being HBF.

After the initial examination, the patient underwent normal saline infusion. After 12 min of infusion (400 ml), he complained of palpitation and dyspnea. Physical examination showed an elevated jugular venous column and pulmonary crepitations. Echocardiography was repeated and isolated periods of supraventricular bigeminy and supraventricular extrasystoles were observed (Table 1); these findings persisted for up to 10 min after the infusion was stopped. When echocardiography was repeated again after restarting intravenous normal saline infusion, important variations were observed in chamber sizes and parameters indicating diastolic function compared with the values obtained at baseline. The left atrium (LA), which initially showed a small increase in volume (34.0 ml/m^2), showed marked dilatation (56.0 ml/m^2); the ejection fraction was normal, as assessed by the Teicholtz (60%) and Simpson (54%) methods (Figures 1 and 2).

Discussion

With regard to the parameters of diastolic function analyzed in the present case, a progression to an abnormal diastolic filling pattern was observed in the second echocardiographic examination, as shown in Table 1. The E/A ratio showed a marked increase, compatible with an abnormal diastolic filling pattern, as observed in type II diastolic dysfunction. These findings were corroborated by the appearance of the L wave and the inversion of the S/D flow in the pulmonary vein[7]. Other characteristic indicators of diastolic dysfunction, such as increased isovolumic relaxation time and E wave deceleration time, were compatible with myocardial overload.

The expected change in diastolic function during pressure overload of LA would be a reduction of E and mitral E velocities and the maintenance of an elevated E/E' ratio proportional to the degree of diastolic dysfunction. In the present case, mitral flow velocities were paradoxically decreased; however, E' velocity increased. Thus, mitral flow velocities were not considered to be a reliable marker of diastolic dysfunction for this patient. The pulmonary venous flow was a more accurate

Keywords

Ventricular Dysfunction; Heart Rate; Anemia, Sickle Cell; Echocardiography, Doppler

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Table 1 – Echocardiographic measures at baseline and after the volume load (400 mL of 0.9% saline solution)

Parameter	Baseline	Value at overload
Aortic root diameter (cm)	3.1	3.3
Left atrial diameter (cm)	4.4	4.4
Left atrial volume (end of the ventricular systole), ml/m^2	34.0	56.0
Maximum right atrial volume (ml)	44.0	47.0
LV end-diastolic diameter (cm)	5.5	5.5
LV end-systolic diameter (cm)	3.8	3.7
Thickness of the interventricular septum (cm)	0.80	0.90
Thickness of LV posterior wall (cm)	0.80	0.80
RV end-diastolic diameter (cm)	2.4	2.3
Left ventricular mass (g)	122	142
LEV mass/volume ratio	0.80	0.90
Teichholz ejection fraction	58%	60%
Simpson ejection fraction	50%	54%
Mitral E/A ratio	1.27	2.67
Deceleration time (ms)	0.150	0.217
Isovolumic relaxation time (ms)	0.046	0.096
E wave (cm/s)	86.8	80.8
A wave (cm/s)	68.5	30.2
Mitral/Septal S' wave (cm/s)	8.70	8.70
Mitral/Septal E' wave (cm/s)	12.80	13.40
Septal/mitral E/E' ratio	6.78	6.03
Septal/mitral E'/A' ratio	1.47	2.4
TEI index	0.23	0.34
Acceleration time/ejection time	0.48	0.47
Mitral gradient	28.0	25.0
Systolic flow/diastolic flow of the pulmonary vein	>1	<1

marker of the alteration from the normal pattern to an abnormal diastolic filling pattern. It is possible that this phenomenon is related to a hyperdynamic cardiac state secondary to anemia, probably because of increased recruitment of cardiac muscle fibers during volume overload (evidenced by the increased E' velocity and increased ejection fraction).

An important characteristic that was also evaluated was the rate of global ventricular performance, or the Tei index, a parameter indicated for the standardization and comparison of results obtained by different studies. In this patient, the Tei index increased from 0.23 to 0.34 after normal saline infusion. This worsening of performance can be explained by the increase in the duration of isovolumic contraction and relaxation, combined with decreased ventricular compliance. It is interesting to note that the heart rate did not change in the observation period.

The echocardiographic follow-up used independent measures of volume load because the hemodynamic characteristics of SCA, such as increased CO, may mask diastolic dysfunction, thus leading to the underdiagnosis of the condition. The patient described in this case showed two biochemical markers associated with unfavorable outcomes. Elevated LD values are indicators of marked hemolysis and predictors of clinical complications in SCA, mainly those associated with endothelial activation and chronic inflammation.[8-10] Another characteristic was the elevation in NT-pro-BNP levels, which were at 250.0 pg/ml at baseline in the present case; this may suggest the subclinical impairment of cardiac function. NT-pro-BNP levels > 160.0 pg/mL have been associated with the diagnosis of pulmonary hypertension, and they are considered an independent risk factor for high mortality.[8-10]

The importance of this case lies in the fact that cardiopulmonary complications are the main cause of death in SCA patients. In particular, in the present case, a normal echocardiographic pattern was observed before volume stress. This suggests that some SCA patients can present with potentially fatal complications even if few abnormalities are observed at examination. Additional studies are needed to better understand the alterations in ventricular/atrial

Case Report

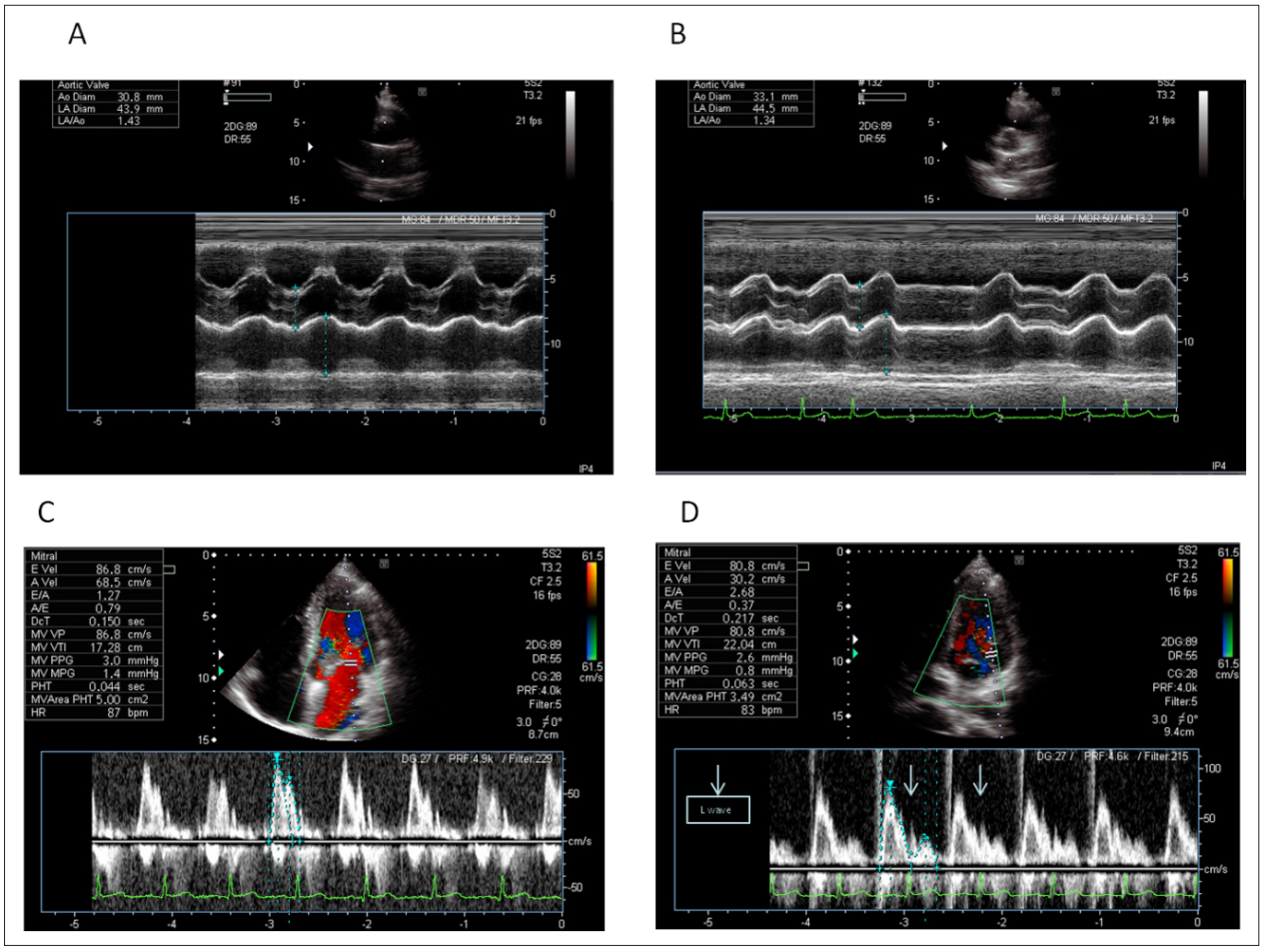

Figure 1 – *(A) Parasternal view in M-mode showing the aorta and the left atrium. (B) The same view as figure A, with ECG showing isolated ventricular extrasystoles. (C) Baseline spectral Doppler recording of the mitral flow. (D) Postinfusion spectral Doppler recording, showing mitral reflux and the development of the L wave.*

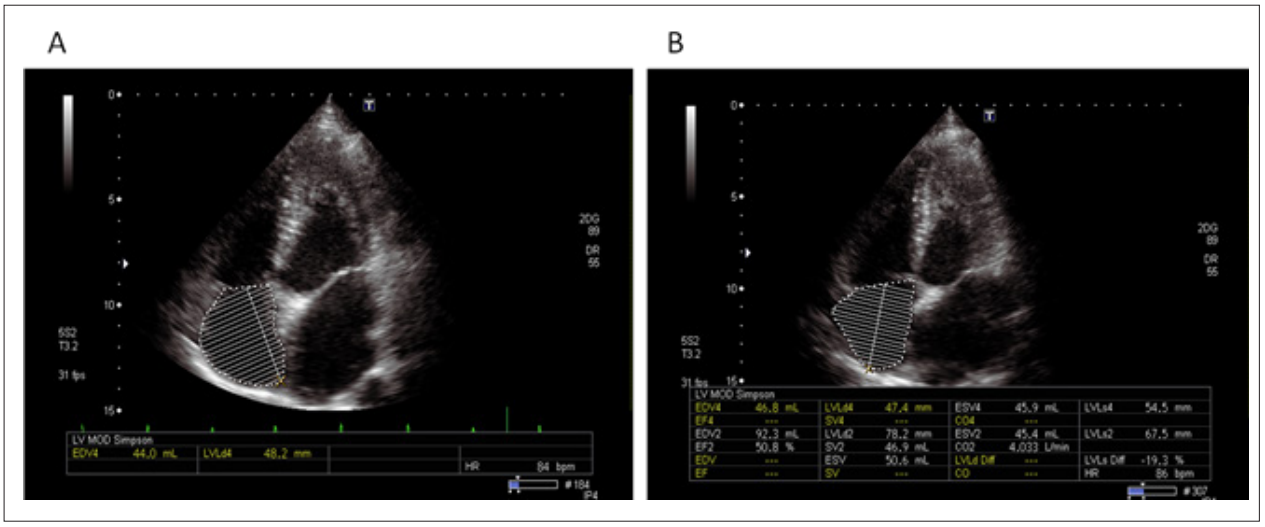

Figure 2 – *Apical views of the four chambers before (A) and after (B) volume expansion, showing left atrial volumes of 34 mL/m² and 56 mL/m², respectively.*

compliance and diastolic function as well as to identify patients at risk of hemodynamic decompensation and adverse outcomes.

Author contributions

Conception and design of the research: Fattori A, Oliveira DC, Coelho OR; Acquisition of data and Writing of the manuscript: Fattori A, Oliveira DC; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Fattori A, Oliveira DC, Castilho RF, Coelho OR; Statistical analysis and Obtaining financing: Fattori A; Fattori A, Oliveira DC, Castilho RF, Coelho OR.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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