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CLINICAL RESEARCH

Left atrial volume is not an index of left ventricular diastolic dysfunction in patients with sickle cell anaemia

Le volume atrial gauche ne constitue pas un paramètre de dysfonction diastolique chez les patients atteints de drépanocytose homozygote

Nadjib Hammoudi[a,b,c,*], Magali Charbonnier[d], Pierre Levy[e], Morad Djebbar[a,b], Katia Stankovic Stojanovic[f], Stéphane Ederhy[d], Robert Girot[b,f], Ariel Cohen[b,d], Richard Isnard[a,b,c], François Lionnet[b,f]

[a] *Department of Cardiology, AP—HP, Pitié-Salpêtrière Hospital, 75651 Paris, France*
[b] *University Paris 6, Faculté de Médecine Pierre-et-Marie-Curie, 75252 Paris, France*
[c] *UMRS INSERM-UPMC 1166 and Institute of Cardiometabolism and Nutrition (ICAN), 75013 Paris, France*
[d] *Department of Cardiology, AP—HP, Saint-Antoine Hospital, 75571 Paris, France*
[e] *Public Health Department, Hôpital Tenon, AP—HP, Institut Pierre-Louis de Santé Publique, Inserm, UPMC-Paris 6, UMRS 1136, 75970 Paris, France*
[f] *Department of Internal Medicine, Reference Centre for Adult Sickle Cell Disease, AP—HP, Tenon Hospital, 75970 Paris, France*

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Abbreviations: A, Late peak diastolic velocity of the mitral inflow; DD, Diastolic dysfunction; E, Early peak diastolic velocity of the mitral inflow; e′, Early diastolic tissue velocity at the septal mitral annulus level; LA, Left atrial/atrium; LAVi, Left atrial volume index; LV, Left ventricle/ventricular; LVMi, Left ventricular mass index; LVEF, Left ventricular ejection fraction; ROC, Receiver operating characteristic; SCA, Sickle cell anaemia.

* Corresponding author. Institut de cardiologie, groupe hospitalier Pitié-Salpêtrière, AP—HP, 47—83, boulevard de l'Hôpital, 75651 Paris cedex 13, France.
E-mail address: nadjib.hammoudi@psl.aphp.fr (N. Hammoudi).

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KEYWORDS
Left atrial volume;
Sickle cell disease;
Diastolic dysfunction;
LA remodelling;
Anaemia

Summary
Background. — Left ventricular diastolic dysfunction (LVDD) is common in sickle cell anaemia (SCA). Left atrial (LA) size is widely used as an index of LVDD; however, LA enlargement in SCA might also be due to chronic volume overload.
Aim. — To investigate whether LA size can be used to diagnose LVDD in SCA.
Methods. — One hundred and twenty-seven adults with stable SCA underwent echocardiographic assessment. LA volume was measured by the area—length method and indexed to body surface area (LAVi). Left ventricular (LV) filling pressures were assessed using the ratio of early peak diastolic velocities of mitral inflow and septal annular mitral plane (E/e′). Using mitral inflow profile and E/e′, LV diastolic function was classified as normal or abnormal. LAVi > 28 mL/m^2 was used as the threshold to define LA enlargement.
Results. — The mean age was 28.6 ± 8.5 years; there were 83 women. Mean LAVi was 48.3 ± 11.1 mL/m^2 and 124 (98%) patients had LA dilatation. In multivariable analysis, age, haemoglobin concentration and LV end-diastolic volume index were independent determinants of LAVi (R^2 = 0.51; P < 0.0001). E/e′ was not linked to LAVi (P = 0.43). Twenty patients had LVDD; when compared with patients without LVDD, they had a similar LAVi (52.2 ± 14.7 and 47.5 ± 10.2 mL/m^2, respectively; P = 0.29). Receiver operating characteristics curve analysis showed that LAVi could not be used to diagnose LVDD (area under curve = 0.58; P = 0.36).
Conclusion. — LA enlargement is common in SCA but appears not to be linked to LVDD. LAVi in this population is related to age, haemoglobin concentration and LV morphology.

MOTS CLÉS
Volume atrial gauche ;
Drépanocytose ;
Dysfonction diastolique ;
Remodelage OG ;
Anémie

Résumé
Contexte. — Chez les patients drépanocytaires homozygotes (DH), la dysfonction diastolique (DD) ventriculaire gauche (VG) est fréquente. La taille de l'oreillette gauche (OG) est couramment utilisée pour le diagnostic de DDVG, cependant, chez les DH la dilatation OG peut également être liée à la surcharge volumique secondaire à l'anémie.
Objectif. — Évaluer le volume OG indexé (VOGi) comme indice de DDVG chez les DH.
Méthodes. — Cent vingt-sept DH en état stable (28,6 ± 8,5 années, 83 femmes) ont bénéficié d'une échocardiographie. Le VOGi a été mesuré par la méthode de surface—longueur. Les pressions de remplissages VG ont été évaluées par le ratio des pics des vélocités proto-diastoliques du flux transmitral et de la portion septale de l'anneau mitral (E/e′). La fonction diastolique VG a été catégorisée comme normale ou anormale en utilisant le profil transmitral et E/e′. Un VOGi > 28 mL/m^2 définissait une OG dilatée.
Résultats. — Le VOGi moyen était de 48,3 ± 11,1 mL/m^2 ; 124 (98 %) patients avaient une dilatation de l'OG. En analyse multivariée, l'âge, le taux d'hémoglobine et le volume VG télédiastolique indexé étaient les déterminants du VOGi (R^2 = 0,51 ; p < 0,0001) ; E/e′ n'était pas corrélé au VOGi (p = 0,43). Le VOGi des patients avec DDVG (n = 20) était comparable à celui des patients sans DDVG (respectivement, 52,2 ± 14,7 et 47,5 ± 10,2 mL/m^2 ; p = 0,29). Le VOGi n'avait pas de valeur pour le diagnostic de DDVG (aire sous la courbe = 0,58 ; p = 0,36).
Conclusion. — La dilatation OG observée chez les DH ne semble pas être un indice diagnostic de DDVG. Dans cette population, le VOGi est lié à l'âge, au taux d'hémoglobine et à la morphologie VG.

Background

Sickle cell disease is one of the most common inherited blood disorders worldwide [1]. Besides chronic anaemia, many pathophysiological processes contribute to the complexity of the disease, including haemolysis and repeated vaso-occlusive events, with ischaemia-reperfusion injury leading to endothelial cell dysfunction [1,2].

In patients with homozygous sickle cell disease — also called sickle cell anaemia (SCA) — cardiac remodelling includes left heart chamber enlargement due to volume overload induced by anaemia [3]. In addition to morphological remodelling, left ventricular (LV) functional impairment is common in these patients. Two recent studies in invasive right heart catheterization have shown that post-capillary pulmonary hypertension is the most frequent cause of pulmonary hypertension in SCA [4,5]. LV diastolic dysfunction (LVDD) diagnosed by echocardiography is common and is an independent risk factor for mortality [6,7]. In addition, concomitant to the improvement in life expectancy

observed over recent years, the prevalence of heart disease in adult patients has also increased, and now represents up to one-fourth of all deaths [8]. LV ejection fraction (LVEF) is usually preserved in SCA [9].

Left atrial (LA) volume indexed for body surface area (LAVi) is the most accurate measure of LA size by standard echocardiography [10,11]. It has been widely proved that LA enlargement is linked to LV function [12]; thus, the use of LAVi is currently encouraged for the diagnosis and evaluation of patients with heart failure, particularly those with normal LVEF [13,14]. To the best of our knowledge, determinants of LA size have not been investigated in detail in SCA. In this population at high risk of LVDD, LA size could be linked to LV functional impairment and may be helpful in diagnosing this condition. However, LA remodelling induced by haematological disorders may modify the usual relationship between LA size and LV diastolic function [14]. The objectives of this study were therefore to characterize the determinants of LA morphological remodelling in a large population of patients with SCA and to investigate in particular whether LAVi is related to LVDD and if it could be used to diagnose this condition.

Methods

Study population

From 1 March 2007 to 31 May 2011, all patients with SCA referred from the Reference Centre for Adult Sickle Cell Disease of Tenon Hospital to our echocardiography laboratory were eligible for inclusion. Patients who had developed acute chest syndrome, vaso-occlusive crisis or an acute complication within the previous 6 weeks (including fever, surgery, blood transfusion or hospital admission, whatever the reason) were excluded in order to focus on a group of stable patients free of confounding factors that could be linked to LA size. Other exclusion criteria were: more than mild mitral regurgitation, more than mild aortic stenosis, more than mild aortic insufficiency, any degree of mitral stenosis, valvular prosthesis, pregnancy, arteriovenous fistula and history of atrial arrhythmia (including atrial fibrillation, atrial flutter and other documented and/or treated atrial rhythm abnormality).

A total of 187 patients were considered for eligibility, of whom 60 did not meet the inclusion criteria. The remaining 127 patients constituted the study population. All of these patients were referred for routine evaluation of cardiac function and/or systematic screening for pulmonary artery hypertension.

Clinical data were obtained from a comprehensive review of each patient's medical record. The diagnosis of SCA was based on molecular genetic techniques. All enrolled patients gave their consent to participate. The study was approved by the institutional committee on human research.

Echocardiography

Transthoracic echocardiography was performed by two experienced operators (N. Hammoudi, M. Djebbar) using the Vivid 7 system (GE Healthcare, Horten, Norway) or the iE33 system (Phillips Medical Systems, Andover, MA, USA). Images were transferred to a workstation equipped with Echopac PC software (GE Vingmed Ultrasound, Horten, Norway) for offline analysis. All examinations were analysed offline by two senior cardiologists (N. Hammoudi, M. Charbonnier) who were blinded to the clinical data. All projections were obtained according to the recommendations of the American Society of Echocardiography [10,15] and measurements were averaged over three cardiac cycles.

From the M-mode, the following measurements were made at end-diastole: LV internal diameter and interventricular septal and posterior wall thicknesses. LV mass was derived and indexed to body surface area (LVMi); relative wall thickness was also calculated and LV remodelling was categorized as recommended [10]. LV hypertrophy was defined as LVMi > 95 g/m^2 in women and > 115 g/m^2 in men. Further classification as either concentric hypertrophy (relative wall thickness > 0.42) or eccentric hypertrophy (relative wall thickness $\leq$ 0.42) was made [10].

From the two-dimensional mode, LA maximal volume was measured in all patients at the end of ventricular systole, just before opening of the mitral valve, using the area—length method from the apical four-chamber view, and indexed to body surface area [10,16]. Since 2011, the LA apical two-chamber view has been acquired systematically and therefore biplane LA volume measurement was feasible in 24 patients. LA enlargement was defined as LAVi > 28 mL/m^2, and severe enlargement as LAVi > 40 mL/m^2 [10]. LV volumes and LVEF were measured using Simpson's biplane method [10].

Using the pulsed-wave Doppler mode, LV outflow tract time—velocity integral, early and late peak diastolic velocities of the mitral (E and A) inflow and E-wave deceleration time were measured. LV output was calculated and indexed to body surface area as recommended [15]. The peak e′ velocity was used to calculate the E/e′ ratio using pulsed tissue Doppler imaging of the septal mitral annulus [14].

Blinded to the LA volume measurements, the LV diastolic function profile was independently interpreted and categorized as normal or abnormal. DD was defined as an E/A ratio < 1 and/or deceleration time > 240 ms; E/A ratio $\geq$ 1 and E/e′ ratio > 10; E/A ratio > 95th percentile for age; or deceleration time < 140 ms and E/e′ > 10. This classification of LV diastolic function has a prognostic value for mortality in SCA [7]. From continuous-wave Doppler, peak tricuspid regurgitation was recorded in multiple views and the highest level of velocity was selected.

Statistical analysis

All quantitative data are expressed as means $\pm$ standard deviations; qualitative data are expressed as counts and percentages. Comparisons between continuous patient data were made using the Mann—Whitney *U* test. The Chi-square test or Fisher's exact test were used to compare categorical data, as appropriate. Pearson's correlation test was used to analyse the univariate relations between variables. Stepwise multiple linear regression analysis was used to explore the independent predictors of LAVi; the variables included in the analysis were those associated with LAVi in univariate analysis, with a *P* value < 0.20.

Receiver operating characteristic (ROC) curves were plotted to determine the relevance of LAVi for predicting LVDD. In addition, using the Bland–Altman method, agreement between single-plane and biplane measurement of LAVi was assessed in the subgroup of patients in whom both apical four- and two-chamber views were acquired.

MedCalc Statistical Software, version 12.7.7 (MedCalc Software, Ostend, Belgium) was used for calculation. A P value < 0.05 indicated statistical significance.

Results

The clinical characteristics of the population are summarized in Table 1. The mean age of the patients was 28.6 ± 8.5 years and 83 of 127 (65%) patients were women. The mean haemoglobin concentration was 8.9 ± 1.3 g/dL and in 36 (28%) cases, it was ≤ 8 g/dL. The echocardiographic characteristics of the patients are summarized in Table 2. One patient had an LVEF ≤ 50%, 53 (42%) patients had eccentric LV hypertrophy and two (2%) patients had LV concentric remodelling.

The left atrium (LA) was markedly dilated, with a mean LAVi of 48.3 ± 11.1 mL/m^2 (Fig. 1); 124 (98%) patients had LA enlargement and 94 (74%) had severe enlargement.

Univariate relationships between LAVi and clinical and echocardiographic variables are shown in Table 3. The LAVi was not related to the E/e′ ratio (Fig. 2). In multivariable analysis, age, haemoglobin concentration and LV end-diastolic volume index were independent determinants of LAVi (R^2 = 0.51; P < 0.0001).

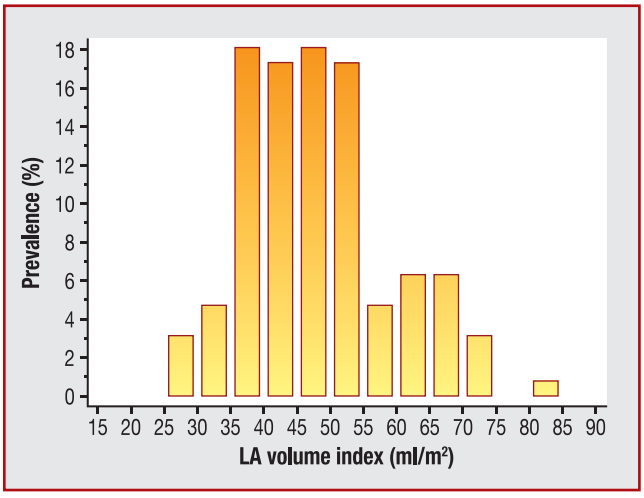

Figure 1. Distribution of left atrial (LA) volume index in the population (n = 127).

Diastolic function was fully characterized in 123 patients (the e′ value was missing in four patients). Twenty (16%) patients had LVDD and 103 (84%) patients had normal LV diastolic function (Tables 1 and 2). There was no difference in LAVi between subgroups (52.2 ± 14.7 and 47.5 ± 10.2 mL/m^2, respectively; P = 0.29). ROC curve analysis showed that LAVi was not useful for prediction of LVDD (area under curve = 0.58, 95% confidence interval 0.48–0.66; P = 0.36) (Fig. 3).

Table 1 Clinical and biological characteristics of the population.

Characteristic	All patients (n = 127)[a]	Patients without DD (n = 103)	Patients with DD (n = 20)	P value
Age (years)	28.6 ± 8.5	27.0 ± 7.6	36.7 ± 9.1	< 0.0001
Women	83 (65)	65 (63)	15 (75)	0.44
Body mass index (kg/m^2)	21.1 ± 3.2	21.0 ± 3.2	21.6 ± 3.1	0.37
Hydroxyurease therapy	43 (34)	33 (32)	7 (35)	0.91
History of SCA complications				
Acute chest syndrome	53 (42)	45 (44)	7 (35)	0.88
Cerebral vasculopathy	10 (7)	7 (7)	3 (15)	0.18
Priapism	8 (18)[b]	7/38 (18)	1/5 (20)	1
Leg ulcer	14 (11)	10 (10)	4 (20)	0.22
Retinopathy	35 (28)	29 (28)	5 (25)	0.81
Osteonecrosis	31 (25)	27 (26)	3 (15)	0.55
Laboratory data				
Haemoglobin (g/dL)	8.9 ± 1.3[c]	9.0 ± 1.3	8.6 ± 1.4	0.28
Lactate dehydrogenase (U/L)	433 ± 316[c]	433 ± 340	434 ± 193	0.86
Bilirubin total (μmol/L)	50.6 ± 36.1[d]	50.8 ± 36.0[e]	49.4 ± 38.1[f]	0.92
Ferritin (μg/L)	533 ± 899[c]	532± 949	455 ± 335	0.50
Creatinine (μmol/L)	58.0 ± 15.0	56.3 ± 14.8	63.2 ± 15.0	0.03

Data are expressed as mean ± standard deviation or number (%); DD: diastolic dysfunction; SCA: sickle cell anaemia.
[a] Diastolic function was fully characterized in 123 patients.
[b] n = 44 men.
[c] n = 126.
[d] n = 122.
[e] n = 100.
[f] n = 19.

Table 2 Echocardiographic characteristics.

Characteristic	All patients ($n=127$)[a]	Patients without DD ($n=103$)	Patients with DD ($n=20$)	*P* value
Systolic blood pressure (mmHg)	114.1 ± 14.1	113.4 ± 13.6	117.2 ± 14.8	0.28
Diastolic blood pressure (mmHg)	66.5 ± 9.0	66.1 ± 9.1	68.4 ± 9.2	0.32
Heart rate (beats/min)	70.8 ± 12.0	71.8 ± 11.2	69.1 ± 14.6	0.16
LV end-diastolic volume index (mL/m^2)	89.3 ± 18.6	88.6 ± 18.1	90.6 ± 21.4	0.90
LVEF (%)	60.3 ± 4.5	61.0 ± 4.5	59.6 ± 3.1	0.37
Cardiac index (L/min/m^2)	4.0 ± 0.9	4.0 ± 0.8	4.2 ± 1.2	0.66
LVMi (g/m^2)	99.9 ± 24.0	98.5 ± 22.1	104.1 ± 33.5	0.77
LV hypertrophy	53 (42)	40 (39)	9 (45)	0.79
E (cm/s)	93.6 ± 19.6	91.9 ± 17.5	104.1 ± 26.3	0.02
E-wave deceleration time (ms)	167.6 ± 34.0	166.4 ± 30.2	175.2 ± 50.4	0.63
A (cm/s)	51.4 ± 14.2[b]	49.3 ± 11.0	63.0 ± 22.4	0.01
E/A	1.9 ± 0.6[b]	1.9 ± 0.5	1.9 ± 1.0	0.50
e′ (cm/s)	12.1 ± 2.5[c]	12.4 ± 2.4	10.9 ± 2.2	0.02
E/e′	8.0 ± 2.1[c]	7.7 ± 1.8	9.7 ± 2.4	0.0005
LAVi (mL/m^2)	48.3 ± 11.1	47.5 ± 10.2	52.2 ± 14.7	0.29
Tricuspid regurgitation maximal velocity (m/s)	2.5 ± 0.3[d]	2.4 ± 0.2[e]	2.6 ± 0.3[f]	0.004

Data are expressed as mean ± standard deviation or number (%); A: late peak diastolic velocity of the mitral inflow; DD: diastolic dysfunction; E: early peak diastolic velocity of the mitral inflow; e′: early diastolic tissue velocity at the septal mitral annulus level; LAVi: left atrial volume index; LV: left ventricular; LVEF: left ventricular ejection fraction; LVMi: left ventricular mass index.

[a] Diastolic function was fully characterized in 123 patients.

[b] $n=126$.

[c] $n=123$.

[d] $n=121$.

[e] $n=98$.

[f] $n=19$.

Table 3 Univariate correlations of left atrial volume index.

Variable	*n*	*r*	*P* value
Age	127	0.29	0.009
Body mass index	127	−0.006	0.95
Systolic blood pressure	127	0.07	0.44
Diastolic blood pressure	127	0.06	0.51
Haemoglobin	126	−0.35	0.0001
Ferritin	126	0.14	0.12
Lactate dehydrogenase	126	0.13	0.14
Bilirubin total	122	0.03	0.75
Creatinine	127	0.12	0.19
LV end-diastolic volume index	127	0.59	< 0.0001
LVEF	127	−0.11	0.24
Cardiac index	127	0.26	0.003
LVMi	127	0.39	< 0.0001
E	127	−0.04	0.67
E-wave deceleration time	127	0.16	0.10
A	126	0.10	0.25
E/A	126	−0.14	0.13
e′	123	−0.1	0.28
E/e′	123	0.07	0.43
DD	123	0.15	0.09
Tricuspid regurgitation maximal velocity	121	0.28	0.002

A: late peak diastolic velocity of the mitral inflow; DD: diastolic dysfunction; E: early peak diastolic velocity of the mitral inflow; e′: early diastolic tissue velocity at the septal mitral annulus level; LV: left ventricular; LVEF: left ventricular ejection fraction; LVMi: left ventricular mass index.

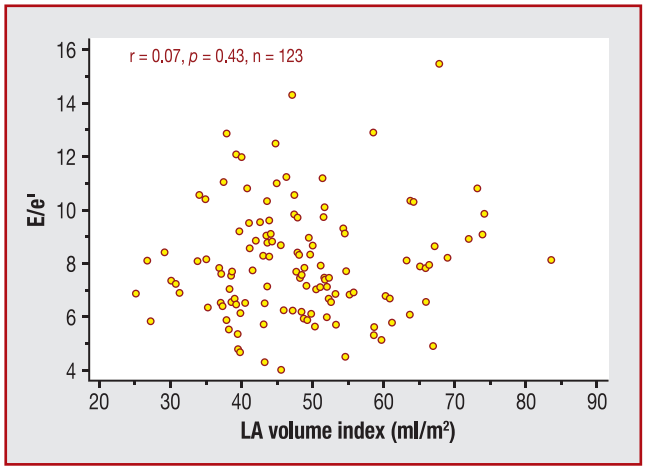

Figure 2. Lack of correlation between left atrial (LA) volume index and left ventricular filling pressures assessed by E/e′ (the ratio between early peak diastolic velocities of mitral inflow [E] and septal annular mitral plane [e′]).

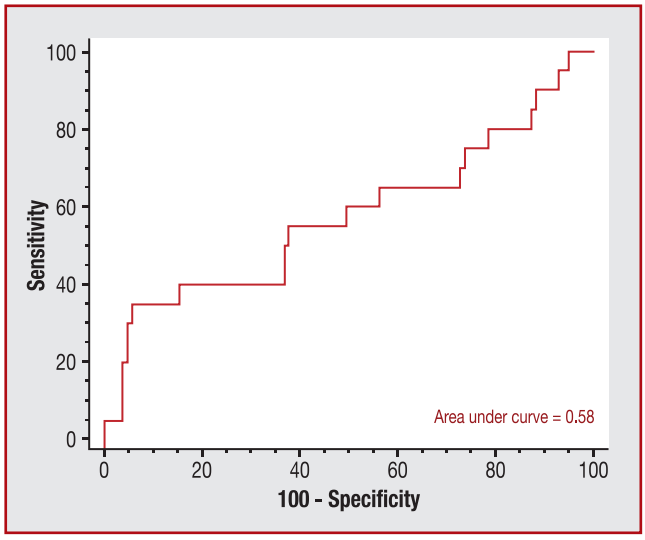

Figure 3. Receiver operating characteristic curve analysis, showing that left atrial volume index is not useful for prediction of patients with abnormal left ventricular diastolic function.

In the 24 patients in whom the apical two-chamber view was acquired, the Bland–Altman analysis demonstrated good agreement between the LAVi measurements from the apical four-chamber view and by Simpson's biplane method (mean difference −0.2 mL/m^2, 95% confidence interval of mean difference −1.7 to 1.2 mL/m^2). Measurements obtained using both methods were strongly correlated ($r = 0.95$; $P < 0.0001$).

Discussion

In a large population of young adults with SCA in a stable condition, we found that the LA was dilated in almost all of the patients and that three-quarters of patients had a severe dilation. Three factors were independently linked with LA size: age, haemoglobin concentration and LV morphological remodelling. In this population, LAVi was not independently linked to LVDD and could not be used to diagnose this condition.

LA enlargement in patients with SCA has been reported previously [17,18]; however, to the best of our knowledge, this is the first study to investigate the determinants and the potential contribution of LVDD to LA remodelling in SCA. As expected, we found a link between LA size and haemoglobin concentration. Indeed, reduced blood oxygen-carrying capacity induces increased cardiac output [3]. During acute anaemia, the rise in cardiac output is due mainly to tachycardia; however, chronic anaemia induces progressive cardiovascular remodelling, leading to an increase in stroke volume and cardiac output with only a mild rise in heart rate [18]. Volume overload contributes to increased cardiac output by inducing an increase in preload and a substantial enlargement in the cardiac chambers [19].

Conflicting results have been reported for the relationship between age and LAVi in normal subjects [20,21]. However, in addition to the effects of aging itself, age reflects disease duration in patients with SCA; therefore, the LA remodelling is, not surprisingly, linked to the chronic exposure of these patients to haematological disorders related to SCA. As previously reported in subjects without SCA [20], we found that LV end-diastolic volume was an independent determinant of LA size. This relationship is in favour of a proportional enlargement of the left ventricle (LV) and the LA in patients with SCA. A similar link between LV and LA volumes has been reported in healthy endurance-sport athletes [22]; this fact offers further support to the hypothesis of a physiological relationship between the size of both cavities.

Consistent with previous studies [3,6,7], we found that LV hypertrophy and LVDD are common in SCA. However, LA enlargement was not independently linked to LV mass index or to Doppler characterization of diastolic impairment. Recently, in a smaller population including 38 patients with sickle cell disease, another research group reported a major LA enlargement. However, in patients with and without DD there was no difference in LAVi [23].

In normal subjects, as well as in various pathological conditions, LV diastolic function is one of the most important determinants of LA size [12,20,22,24]. During diastole, the LA is directly exposed to pressures in the LV. With increased stiffness or non-compliance of the LV, the LA pressure rises to maintain adequate LV filling; hence, the increased atrial wall tension leads to chamber dilatation and stretch of the atrial myocardium [25]. Therefore, dilation of the LA usually reflects elevated LV filling pressures and constitutes a simple and reproducible diagnostic tool for LVDD and heart failure [13,24,26]. In patients with SCA, the magnitude of the LA enlargement, related to the severity and duration of the haematological condition, overshadows the additional contribution of LVDD. LA size should not therefore be used as an index of LVDD in this population.

Study limitations

Several limitations of our study need to be acknowledged. Our single-centre population of patients with SCA was subject to strict inclusion criteria to reduce bias from confounding factors linked to LA enlargement. Our results should not be applied to patients with the non-homozygous

SS variant of the disease, who were not included in the study; the haemoglobin sickle cell patients (SC variant) have different clinical and biological characteristics [27]. We did not use Simpson's biplane method for assessing LA volume in all of the patients. However, in the subgroup in whom the LA two-chamber view was acquired, we found good agreement between the biplane and single-plane methods. Volume overload in patients with SCA seems to induce a relatively homogenous LA dilatation.

Conclusion

In adult patients with SCA, LA enlargement is very common and pronounced. LA size is related to age, haemoglobin concentration and LV morphology. However, LAVi appears not to be linked to LVDD and cannot be used to diagnose this condition.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

[1] Weatherall D, Hofman K, Rodgers G, Ruffin J, Hrynkow S. A case for developing North-South partnerships for research in sickle cell disease. Blood 2005;105:921—3.
[2] Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet 2010;376:2018—31.
[3] Gladwin MT, Sachdev V. Cardiovascular abnormalities in sickle cell disease. J Am Coll Cardiol 2012;59:1123—33.
[4] Fonseca GH, Souza R, Salemi VM, Jardim CV, Gualandro SF. Pulmonary hypertension diagnosed by right heart catheterisation in sickle cell disease. Eur Respir J 2012;39:112—8.
[5] Parent F, Bachir D, Inamo J, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. N Engl J Med 2011;365:44—53.
[6] Eddine AC, Alvarez O, Lipshultz SE, Kardon R, Arheart K, Swaminathan S. Ventricular structure and function in children with sickle cell disease using conventional and tissue Doppler echocardiography. Am J Cardiol 2012;109:1358—64.
[7] Sachdev V, Machado RF, Shizukuda Y, et al. Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. J Am Coll Cardiol 2007;49:472—9.
[8] Fitzhugh CD, Lauder N, Jonassaint JC, et al. Cardiopulmonary complications leading to premature deaths in adult patients with sickle cell disease. Am J Hematol 2010;85:36—40.
[9] Hammoudi N, Arangalage D, Djebbar M, et al. Subclinical left ventricular systolic impairment in steady state young adult patients with sickle-cell anemia. Int J Cardiovasc Imaging 2014; 30:1297—304.
[10] Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440—63.
[11] Tsang TS, Abhayaratna WP, Barnes ME, et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol 2006;47:1018—23.
[12] Abhayaratna WP, Seward JB, Appleton CP, et al. Left atrial size: physiologic determinants and clinical applications. J Am Coll Cardiol 2006;47:2357—63.
[13] McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787—847.
[14] Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009;10:165—93.
[15] Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002; 15:167—84.
[16] Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. Am J Cardiol 1999;84:829—32.
[17] Ahmed S, Siddiqui AK, Sadiq A, Shahid RK, Patel DV, Russo LA. Echocardiographic abnormalities in sickle cell disease. Am J Hematol 2004;76:195—8.
[18] Covitz W, Espeland M, Gallagher D, Hellenbrand W, Leff S, Talner N. The heart in sickle cell anemia. The Cooperative Study of Sickle Cell Disease (CSSCD). Chest 1995;108:1214—9.
[19] Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. Am Heart J 1972;83:415—26.
[20] D'Andrea A, Riegler L, Rucco MA, et al. Left atrial volume index in healthy subjects: clinical and echocardiographic correlates. Echocardiography 2013;30:1001—7.
[21] Thomas L, Levett K, Boyd A, Leung DY, Schiller NB, Ross DL. Compensatory changes in atrial volumes with normal aging: is atrial enlargement inevitable? J Am Coll Cardiol 2002;40: 1630—5.
[22] Nistri S, Galderisi M, Ballo P, et al. Determinants of echocardiographic left atrial volume: implications for normalcy. Eur J Echocardiogr 2011;12:826—33.
[23] Desai AA, Patel AR, Ahmad H, et al. Mechanistic insights and characterization of sickle cell disease-associated cardiomyopathy. Circ Cardiovasc Imaging 2014;7:430—7.
[24] Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002;90:1284—9.
[25] Greenberg B, Chatterjee K, Parmley WW, Werner JA, Holly AN. The influence of left ventricular filling pressure on atrial contribution to cardiac output. Am Heart J 1979;98:742—51.
[26] Douglas PS. The left atrium: a biomarker of chronic diastolic dysfunction and cardiovascular disease risk. J Am Coll Cardiol 2003;42:1206—7.
[27] Lionnet F, Hammoudi N, Stojanovic KS, et al. Hemoglobin sickle cell disease complications: a clinical study of 179 cases. Haematologica 2012;97:1136—41.