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ORIGINAL ARTICLE

Right ventricular functions in subphenotypes of sickle cell disease

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Abstract

Objectives: **Sickle cardiomyopathy is the most important cause of death in patients with sickle cell disease (SCD). Based on recent evidence, SCD can be divided into two subphenotypes, namely, the viscosity vaso-occlusion (VVO) subphenotype and the hemolysis endothelial dysfunction (HED) subphenotype. The aim of our series is to study right ventricular (RV) functions in both subphenotypes.**

Methods: **Echocardiography including conventional and tissue Doppler imaging as well as speckle tracking echocardiography was performed in 50 patients (23 from the VVO subgroup and 27 from the HED subgroup) based on a serum lactate dehydrogenase (LDH) level below or above 270 U/L, respectively, and in 50 controls. Reticulocyte count and hemoglobin levels were assessed in different groups of patients.**

Results: **The HED subgroup showed RV dysfunction. Patients in this subgroup also showed systolic and diastolic functions similar to those seen in the VVO subgroup and controls. In addition, a tight correlation exists between LDH and both RV global longitudinal strain (−0.68) and RV E/E′ ratio (0.9), defined as the ratio of early diastolic tricuspid inflow velocity to tricuspid annular early diastolic velocity.**

Conclusions: **Results reveal a marked discrepancy in RV functions between HED and VVO subphenotypes of SCD, with patients in the former subgroup being more prone to RV dysfunction. This warrants early screening of such patients in daily practice.**

Keywords: Hemolysis endothelial dysfunction, Lactate dehydrogenase, Right ventricular functions, Viscosity vaso-occlusion

1. Introduction

Cardiopulmonary complications are the leading cause of mortality in patients with sickle cell disease (SCD) [1].

In recent years, two distinct phenotypes have been identified in SCD: the viscosity-vaso-occlusion subphenotype [viscosity vaso-occlusion (VVO)], in which patients suffer mainly from severe vaso-occlusive crises with mildly elevated or non-elevated lactate dehydrogenase (LDH) levels, and the hemolysis endothelial dysfunction (HED) subphenotype, in which patients suffer mainly from stroke and pulmonary hypertension with markedly elevated LDH levels as a result of high rates of intravascular hemolysis depleting nitrous oxide levels, thus inducing microvascular dysfunction [2]. To our knowledge, few have studied the discrepancy in myocardial dysfunction, especially of the right ventricle (RV), between the VVO and HED subphenotypes. Besides being outdated, available studies only weighed the

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discrepancy of pulmonary hypertension and death risk rather than performing a true assessment of myocardial dysfunction across different phenotypes [3,4]. In addition, a wide disagreement exists about the state of systolic myocardial dysfunction in cases with SCD. Most series [5–7] claim that left ventricular strains are normal and comparable to matched controls in cases with SCD while fewer studies contradict such a finding and confirm the presence of subtle systolic dysfunction especially during vaso-occlusive crises [8]. Such contradictions may raise the need to re-examine systolic function of the myocardium across divergent phenotypes, in order to identify the existence of a potential difference that might be responsible for the varying findings reported in this regard.

The aim of this study is to review the RV systolic and diastolic functions in the two subphenotypes of SCD to be able to confirm or preclude if a certain subphenotype needs a more close follow-up of its myocardial functions than the other.

Abbreviations

BSA	Body surface area
Cm	Centimeter
dL	Deciliter
E	Early diastolic inflow velocity
E′	Early diastolic tissue velocity
ECG	Electrocardiogram
GE	General Electric
Kg	Kilogram
LDH	Lactate dehydrogenase
m^2	Square meter
MHz	Mega Hertz
mL	Milliliter
Mm	Millimeter
Msec	Millisecond
Ng	Nanogram
NO	Nitrous oxide
PAP	Pulmonary artery Pressure
SD	Standard deviation
SCD	Sickle cell disease
SPSS	Statistical package for social science
TDI	Tissue Doppler imaging
TRV	Tricuspid regurgitant velocity
2-D	Two dimensional
U	Unit
USA	United State of America

2. Patients and methods

2.1. Study population

This was a cross-sectional study conducted between June 2017 and July 2018, and included two groups: Group 1 and Group 2.

2.1.1. Group 1

The group included 50 children of both sexes with SCD. Children were between 6 and 9 years of age (mean: 7.28 ± 1.48 years). A total of 25 patients were females (50%) and 25 were males (50%), with positive consanguinity in 30/50 (60%) patients. The frequency of blood transfusion per year ranged between one and 24 times/yr (mean: 5.57 ± 4.99 times/yr). Patients with symptoms or signs suggesting pulmonary or cardiac abnormalities were excluded from the study. The group was subdivided into two based on subphenotype: Group 1A, including patients with the VVO subphenotype ($n = 23$); and Group 1B, including patients with the HED subphenotype. The discrimination was performed based on an LDH cutoff of 270. Patients with an LDH level <270 U/L were included in the VVO subphenotype and those with an LDH level ≥270 U/L were included in the HED subphenotype [9].

2.1.2. Group 2

Fifty healthy children matched for age, sex, and body surface area were set as the control group. Both groups were enrolled in the study after obtaining consent from the patients or their legal guardians and obtaining the approval of the ethical committee of Cairo University, Cairo, Egypt.

2.2. Methods

Patients were subjected to full clinical assessment and clinical definitions, echocardiography, and laboratory investigations.

2.2.1. Clinical assessment and clinical definitions

All included patients were subjected to (1) full history taking and (2) clinical examination (complete general and systemic examination) with special attention to anthropometric measurements including body weight (kg), height (cm), and heart rate. Data were collected on SCD complications in the two defined subgroups following the methodology recommended by Van Der Land et al. [10]. Vaso-occlusive pain episodes were expressed as number of episodes per patient per year (in the past 3 years). Stroke was defined as a focal neurological deficit at the time of the study with evidence on neuroimaging of a cerebral infarct corresponding to the focal deficit (expressed as number of patients with evidence on neuroimaging per affected patients) at the time of the study. Acute chest syndrome was defined as a new infiltrate on chest radiograph in the presence of pulmonary symptoms and expressed as number of patients having more than one episode per year. Leg

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ulcers were defined as painful skin defects on lower legs and expressed as number of affected patients at the time of examination.

2.2.2. Echocardiography

Echocardiography was performed according to the protocol recommended by DiLorenzo et al. [11] for assessment of RV functions (but with some modifications for the purpose of this study rather than for routine assessment). The procedure was performed using a GE ultrasound system (GE Vivid 7 Dimension; GE Healthcare, Horten, Norway) with probe frequencies appropriate for patient size according to the guidelines for performing echocardiogram published by the American Society of Echocardiography [12]. The motion-mode (M-mode) was used to calculate tricuspid annular plane systolic excursion.

2.2.2.1. Continuous wave Doppler. This is one of the first tools used to estimate the presence of pulmonary hypertension in any group, which involves measuring the pulmonary artery pressure. In this study, the tricuspid gradient was estimated from peak tricuspid regurgitation velocity (TRV), with TRV >2.5 m/s considered significant for pulmonary hypertension [13].

2.2.2.2. Conventional and tissue Doppler method. RV diastolic function was assessed using the RV E/E′ ratio, which is defined as the ratio of early diastolic tricuspid inflow velocity to the early diastolic tricuspid annular velocity. An E/E′ ratio >15 was considered suggestive of RV diastolic dysfunction [14].

2.2.2.3. 2D speckle tracking echocardiography. Digital loop ECG recording was obtained for the RV in four-chamber view and analyzed by the EchoPAC (General Electric, Horten, Norway) offline analysis software for calculation of global longitudinal strain of RV using the average of the three segments of RV free wall.

Echocardiography was performed by two senior cardiologists who were blinded for the phenotype of SCD, including laboratory data, and subsequent kappa analysis for intra- and interobserver variability was performed.

2.2.2.4. Laboratory investigations. Hemoglobin, platelet, and LDH levels were measured after collection of samples in dry tubes. Serum LDH assays were performed with a spectrophotometer at 340 nm. The LDH assay kit was provided by Cypress Diagnostics (Hulshout, Belgium) [15] with a reference range between 160 and 320 U/L. Reticulocyte counts and fetal hemoglobin (percentage) were measured in the studied cases only.

2.3. Statistical analysis

Data were statistically described in terms of mean ± standard deviation. A comparison of numerical variables between the study groups was performed using a paired *t*-test (normal distribution). For comparisons of multiple groups, the Turkey–Kramer test was applied, with individual *p* values listed in Table 1. Correlation between various variables was done using the Pearson moment correlation equation. All *p* values <0.05 were considered statistically significant. All statistical calculations were done using SPSS for Microsoft Windows (version 15; SPSS Inc., Chicago, IL, USA).

Table 1. Demographic and clinical criteria of the three study groups.

Variables	Group 1A ($n = 30$)	Group 1B ($n = 30$)	Control, Group 2 ($n = 25$)	*p* value[a,*]	*p* value[b,*]	*p* value[c,*]
Age (yr)	12 ± 3	12 ± 4	12 ± 3	NS	NS	NS
HR (BPM)	86 ± 8	85 ± 5	84 ± 10.4	NS	NS	NS
BSA (m^2)	1.2 ± 0.02	1.3 ± 0.01	1.2 ± 0.02	NS	NS	NS
Frequency of blood transfusion (mL/kg/yr)	152 ± 15	240 ± 22	–	–	–	<0.01
Hb (g/dL)	10 ± 3.1	8.5 ± 1.9	–	–	–	<0.01
Platelets ($\times 10^9$/L)	301 ± 120	421 ± 77				<0.01
Reticulocyte count	4	8				
Serum LDH (U/L)	457 ± 51	125 ± 10	–	–	–	<0.01

Data are presented as mean ± standard deviation or %.
BPM = beats per minute; BSA = body surface area; HR = heart rate; LDH = lactate dehydrogenase; SD = standard deviation; NS = non-significant.
[a] Between Groups 1A and 2.
[b] Between Groups 1B and 2.
[c] Between Groups 1A and 1B.
[*] A *p* value <0.05 was considered statistically significant.

3. Results

Clinical characteristics of the studied population (Groups 1A and 1B) were matched for age, heart rate, and body surface area, and compared with controls (Group 2; Table 1). Group 1B showed higher hemolysis indices as confirmed by the greater need for blood transfusion, higher LDH, and lower hemoglobin.

Table 2 summarizes the discrepancy of clinical manifestations between the two subphenotypes of SCD. Data show that vaso-occlusion is higher in the VVO subgroup, whereas more leg ulcers and higher evidence of cerebral infarcts were noted in the HED subgroup.

As can be seen in Table 3, parameters suggesting RV dysfunction are obvious in Group 1B. However, the RV functions showed no statistically significant difference between Group 1A and controls (Group 2).

Figs. 1 and 2 present two regression curves demonstrating tight correlation between RV global longitudinal strain and RV E/E′ ratio on the one hand and LDH on the other.

The intraobserver variability was low for each cardiologist; for Cardiologist 1 kappa coefficient was 0.91, whereas for Cardiologist 2 it was 0.89. The interobserver variability was also very trivial with a kappa coefficient of 0.87.

4. Discussion

Sickle cell is more than just a hemolytic anemia. Some patients with sickle cell anemia do not present with hemolysis or anemia. Instead, these patients may initially encounter severe pain from vaso-occlusion or right-sided heart failure as a result of myocardial involvement [10].

The wide spectrum of manifestations seen in SCD and the weight exerted by SCD cardiomyopathy on mortality and morbidity make it mandatory to detect SCD cardiomyopathy early and to elucidate the risk factors and at-risk groups to stratify the patients according to the presence or absence of such risks.

As mentioned earlier, SCD can be subdivided into two main subphenotypes: VVO and HED. These two phenotypes differ in their severity of manifestations, but few series have underlined the discrepancy in cardiac dysfunction across these subphenotypes [9].

In this series, we compared hematologic clinical data and laboratory data as well as RV myocardial functions between the two subphenotypes. The major study findings were the lower rate of hemoglobin, the higher need for blood transfusion, and the higher LDH levels (initial discriminating factor) in the HED phenotype, which were all expected in this subgroup [2].

Table 2. Clinical manifestations among the subgroups of the disease.

Variables	Group 1A ($n = 30$)	Group 1B ($n = 30$)	p value[a,*]
Vaso-occlusive events (number of events per patient/yr)	2.4	1.1	0.04
Cerebral infarcts (affected patients/patients with available imaging)	0/0	1/2	0.04
Acute chest syndrome (number of patients with ≥1 episode)	6	2	<0.01
Leg ulcers (affected patients)	2	7	<0.01

[a] Between Groups 1A and 1B.
[*] A p value <0.05 was considered statistically significant.

Table 3. Echocardiographic parameters of systolic and diastolic function of RV in the three study groups.

Variables	Group 1A ($n = 30$)	Group 1B ($n = 30$)	Controls Group 2 ($n = 25$)	p value[a,*]	p value[b,*]	p value[c,*]
TAPSE (mm)	22 ± 2	21 ± 3	20 ± 2	NS	NS	NS
TR velocity (m/s)	1.4 ± 0.42	1.5 ± 0.41	1.4 ± 0.32	NS	NS	NS
RV E/E′ ratio	6.5 ± 1.4	14 ± 2	6.2 ± 1.1	NS	<0.01	<0.01
RV GLS (%)	−22 ± 2	−15 ± 1.2	−21 ± 3	NS	<0.01	<0.01

Data are presented as mean ± standard deviation.
GLS = global longitudinal strain; RV = right ventricle; RV E/E′ = ratio of early diastolic tricuspid inflow velocity to the early diastolic tricuspid annular velocity; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitant velocity; SD = standard deviation; NS = Non significant.
[a] Between Groups 1A and 2.
[b] Between Groups 1B and 2.
[c] Between Groups 1A and 1B.
[*] A p value <0.05 was considered statistically significant.

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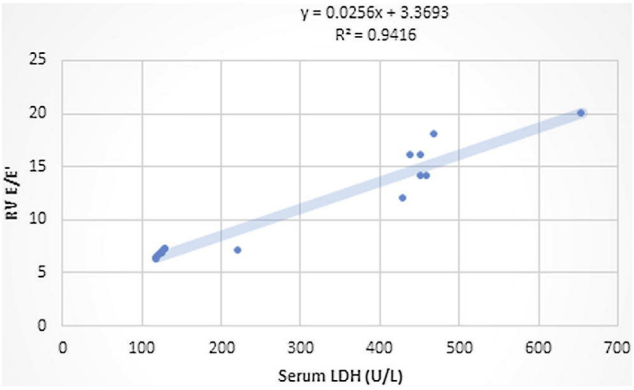

Fig. 1. Correlation of LDH with RV E/E′ ratio. LDH = lactate dehydrogenase serum level; R^2 = correlation coefficient of regression analysis; RV = right ventricle; RV E/E′ = ratio of early diastolic tricuspid inflow velocity to early diastolic tricuspid annular velocity.

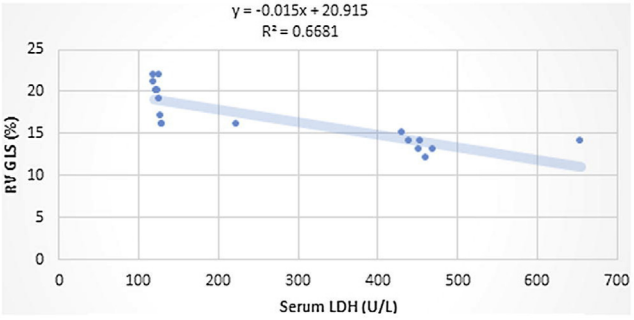

Fig. 2. Correlation of LDH with RV GLS. LDH = lactate dehydrogenase serum level; R^2 = correlation coefficient of regression analysis; RV = right ventricle; RV GLS = right ventricular global longitudinal strain.

Besides, the other findings that confirm the role of LDH as a discriminating factor between these two clinical subphenotypes are the higher rate of vaso-occlusion and its surrogate manifestations such as the acute chest syndrome in the VVO subgroup and the presence of ischemic manifestations such as cerebral infarcts and skin ulcers in the HED subgroup. This result agrees with those reviewed by Habara et al. [2] regarding the frequency of manifestations in each group.

A relatively striking finding in this study is the lack of a statistically significant elevation in pulmonary artery pressure in both groups of patients compared with controls. This finding, however, disagrees with the review by Habara et al. [2], who noted that the HED group is susceptible to pulmonary hypertension. Based on recent evidence as well as reports of over-diagnosis of pulmonary hypertension in patients with SCD, Mushemi-Blake et al. reported that pulmonary hypertension in SCD is rather a state of overflow due to hyperdynamic circulation and that pulmonary hypertension is unrelated to RV dysfunction in this patient group [17,17].

Several studies, such as those by Barbosa et al. and Ahmad et al. [6,7], have concluded that ventricular strains are not reduced but might be increased in cases with SCD. A recent study by AbdelMassih et al. [18] showed that left ventricular strains are reduced in patients with SCD mainly in the subendocardium with overall preserved left ventricular global longitudinal strain. AbdelMassih et al. [18] compared the pattern of left ventricular dysfunction in thalassemia with SCD and proved that the patients with SCD experience early subendocardial involvement. The latter finding raises the suspicion of possible lack of vascular relaxibility in SCD as an underlying pathogenesis for the observed dysfunction. However, none of the studies has compared the ventricular strains in different phenotypes. Our study shows a normal strain in the VVO group; by contrast, the HED group has a markedly reduced RV strain compared with controls. This contradicts the fixed cliché about non-reduced strains in patients with SCD and underlines the neglected discrepancy between different phenotypes. This might also explain the observed ventricular dysfunction in the study by AbdelMassih et al. [18], whereby the HED phenotypes develop vascular stiffness due to intravascular hemolysis that can impair the subendocardial function of both ventricles. Moreover, RV dysfunction was marked in the HED group and no data are available that can be compared with our series. The observed difference between the two phenotypes and the tight correlation between measures of RV function and LDH might be explained by the fact that microvascular dysfunction characteristic of the HED group may induce subendocardial ischemia, with the latter inducing impaired functions in patients with SCD. This is in agreement with Sengupta et al. [8] who reported reduced subendocardial strain in patients with SCD.

5. Conclusion

SCD subphenotypes do not show uniform manifestations across different subphenotypes. The HED subphenotype clearly displays more ventricular dysfunction compared with the VVO group. Thus, LDH can be used as a stratifying factor to screen patients for RV dysfunction.

5.1. Limitations and future projects

Larger sample sizes are needed to generalize the results of this study. Because of financial reasons, a correlation analysis between genetic variabilities in

SCD and the observed RV dysfunction, and exploration of the relationship between SCD subphenotypes and SCD-causing mutations could not be performed.

In addition, the latter findings should serve as a basis for further research to underline the pathogenesis of ventricular dysfunction in the HED group. We aim in our next study to compare LV functions across the two subphenotypes.

Acknowledgments[1]

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Conflicts of interests

None declared.

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[1] Quote by Antoine Fakhry abdelMassih (the 3rd author): Each formerly discovered illness seemed at a time a single entity. There is an increasing body of evidence that points to the fact that each disease has multiple variable copies. Every person might end up with a different version of the same disease. The increasing understanding of such hypothesis is part of an enlarging branch in medicine, which is "personalized medicine." We no longer should treat a disease but we should rather treat "the patient with that disease." We seem to have been born not only with a predefined copy of our characters and shape but also our fate.