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Abnormal submaximal cardiopulmonary exercise parameters predict impaired peak exercise performance in sickle cell anemia patients

Adam W. Powell^{1,2}, Tarek Alsaied^{1,2}, Omar Niss^{2,3}, Robert J. Fleck^{2,4}, Punam Malik^{2,3,4}, Charles T. Quinn^{2,3}, Wayne A. Mays^{1,2}, Michael D. Taylor^{1,2}, and Clifford Chin^{1,2}

¹Division of Cardiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

²Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio

³Division of Hematology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

⁴Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Abstract

Purpose: Sickle cell anemia (SCA) patients frequently have many comorbidities, including diastolic dysfunction (DD) and exercise intolerance. SCA patients often cannot reach maximal effort on exercise testing; little is known regarding whether submaximal exercise parameters can predict abnormal maximal exercise results in SCA patients and if there are any possible associations with DD.

Methods: A prospective longitudinal study was performed in SCA patients. All patients had a resting cardiac MRI (CMR), cardiopulmonary exercise test (CPET) with cycle ergometry using a ramp protocol, and an echocardiogram. Exercise data were compared with age-, gender-, and size-matched normal controls.

Results: Compared with normal controls, the SCA group ($n = 19$) had lower mean max oxygen consumption (VO_2 ; 1378 ± 412 mL/min vs 2237 ± 580 , $P < 0.01$) and workload (117 ± 37.6 watts vs 175 ± 50.5 watts, $P = 0.0003$). When evaluating the submaximal exercise parameters, there was lower VO_2 at the anaerobic threshold (AT; 950 ± 311.7 vs 1460 ± 409.9 , $P < 0.01$) and oxygen uptake efficiency slope (OUES) at AT (1512 ± 426.2 vs 2080 ± 339 , $P < 0.01$). The max VO_2 strongly correlated with VO_2 at AT ($r = 0.9$, $P < 0.01$) and OUES ($r = 0.83$, $P < 0.01$) at AT. The VO_2 at AT correlated with hematocrit ($r = 0.77$, $P < 0.05$). The OUES correlated with left ventricular ejection fraction by CMR ($r = 0.55$, $P = 0.01$), hematocrit ($r = 0.52$, $P = 0.02$), and lateral E/e' ($r = -0.54$, $P = 0.01$).

Conclusions: SCA patients have abnormal submaximal exercise measures compared with controls, which is strongly associated with abnormal maximal exercise results. The degree of

Correspondence: Adam W. Powell, Division of Cardiology, Cincinnati Children's Hospital Medical Center, 3333 Burnett Avenue, MLC 2003, Cincinnati, OH 45229-3026. Adam.Powell@cchmc.org.

CONFLICTS OF INTEREST

None.

submaximal abnormality correlates with DD abnormalities by echocardiography. These data expand the scope of functional cardiovascular abnormalities in SCA.

Keywords

cardiopulmonary exercise test; sickle cell disease; submaximal exercise

1 | INTRODUCTION

Sickle cell anemia (SCA) is common in the United States, with approximately 1 in 700 African Americans having a diagnosis of SCA and as many as 100 000 individuals being affected.¹ Cardiac complications are leading causes of mortality and morbidity in SCA patients.^{2,3} Diastolic dysfunction (DD) and pulmonary hypertension are known cardiac complications of SCA and have been shown to be independent risk factors for mortality in SCA patients.^{4–6} In addition, DD is associated with diffuse myocardial fibrosis by cardiac MRI (CMR) in patients with SCA.^{7,8} SCA patients are known to have exercise limitations that are often due to a combination of exercise avoidance secondary to fear of exercise precipitating a vasoocclusive episode or sequelae of the disease including painful avascular necrosis, pulmonary vascular disease, DD, congestive heart failure, or chronic lung disease.⁹

The cardiopulmonary exercise test (CPET) is a valuable tool to gain information on a patient's cardiac function and aerobic fitness and to determine how the heart, lungs, and peripheral musculature respond to the stress of exercise.¹⁰ In the cardiopulmonary exercise laboratory, the test is performed to assess functional capacity, aerobic fitness level, diagnose certain diseases, determine disease severity, and monitor the effects of treatment such as medication and exercise programs.¹¹ Measurements and calculations are made of the primary determinants of cardiac function, including maximal oxygen consumption (VO_2) and the peak oxygen pulse (O_2 pulse) among other outcome measures; however, these peak measures are only useful in patients who are able to complete a maximal exercise CPET.¹¹ Submaximal indicators of cardiac function may be useful in SCA patients because they may be deconditioned or impaired by their disease and may be unable to complete a maximal exercise CPET.^{8,9}

It is not known whether abnormal submaximal exercise parameters can predict maximal exercise parameters in patients with SCA. Our group recently determined an association between DD and functional capacity in SCA, but it is unknown whether there is a similar association between submaximal exercise performance and DD.⁸ The primary aim of this study was to determine if SCA patients have abnormal measures on submaximal exercise testing compared with normal healthy controls and if these submaximal measures can predict abnormal maximal exercise results. We also aimed to determine if there is an association between abnormal submaximal exercise parameters and DD.

2 | METHODS

Participants with SCA were enrolled in a prospective, longitudinal CMR study to characterize SCA-related cardiomyopathy ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02410811) NCT02410811). Participants who had a CMR and a resting echocardiogram during this study were approached to

participate in a voluntary CPET and exercise echocardiogram at their study exit visit. Exclusion criteria were current chronic transfusion therapy, glomerular filtration rate < 60 mL/min/1.73 m², and any contraindication to CMR or CPET. The study was approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center. Informed consent was obtained from adults or parents of minor participants. Participants were monitored for the development of adverse events in the 30 days following CPET.

2.1 | CPET

All patients underwent standardized exercise on the cycle ergometer using a ramp protocol and were compared with gender-, age-, and size-matched normal controls. The ramp protocol uses an upright cycle ergometer (Lode Corival) and consists of setting an initial work rate based on patient's body surface area (BSA) with linear increases every minute for a goal to reach peak exercise after 10 minutes. The expected work rate is calculated using prediction equations described by Wasserman et al and then adjusted depending on our clinical experience relative to the patient's degree of frailty and fitness.¹³ Expired gases were measured continuously using breath-by-breath gas analysis throughout the study utilizing a metabolic cart (Ultima CardiO2; Medgraphics MGC Diagnostics). In order to compare and determine if the submaximal exercise measures predict maximal exercise results, all patients underwent a maximal exercise test, which was judged to be successful when two of the following three criteria were met: respiratory exchange ratio (RER) greater than or equal to 1.1, maximal heart rate greater than or equal to 85% of the age predicted maximal heart rate ($220 - \text{age in years}$), and maximal rating of perceived exertion > 18 .^{12,13} The submaximal measurements were taken by recording the ventilatory efficiency (VE/VCO₂ slope) and oxygen uptake efficiency slope (OUES) at anaerobic threshold (AT) and the VO₂ at both AT and RER@1.0 on a maximal effort test. AT is often defined as the point when the amount of oxygen delivered to the cardiovascular system is insufficient to meet demands (i.e., aerobic metabolism stops and anaerobic metabolism begins).¹³ The VO₂@RER1.0 is defined as the VO₂ when the RER is consistently equal to or greater than 1.0. This submaximal measure may be more reliable to determine and reduce interobserver variability compared with AT. A VO₂@RER1.0 that falls more than two standard deviations below the regression line is considered abnormal and has been demonstrated to be sensitive and specific to predict a peak VO₂ $< 70\%$ of normal.¹⁴ The predicted peak VO₂ was calculated using the prediction equations described by Wasserman et al and Cooper et al.^{13,15} A VO₂ at AT $< 80\%$ of predicted normal was considered abnormal per the normative VO₂ values at AT described by Wasserman et al.¹³

As part of the exercise test, all patients underwent pulmonary function testing (PFT) using a metabolic cart (TrueMax 2400; Parvo Medics or Ultima CardiO2; Medgraphics). Each patient performed three tests with the best result used for analysis. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁) were measured prior to exercise in a standing position. Predicted FVC and FEV₁ were based on gender, age, and height.¹⁶ Restrictive lung disease was defined as having an FVC and FEV₁ $< 80\%$ of predicted normal. Obstructive lung disease was defined as having an FEV₁ and FEV₁/FVC $< 80\%$ of predicted normal.¹⁶ The percentage of exercise breathing reserve was defined as follows: $[(\text{maximal voluntary ventilation (MVV)} - \text{maximum exercise ventilation/MVV}) \times 100]$.¹⁴

2.2 | Transthoracic echocardiogram

Transthoracic echocardiography was performed with a Philips iE-33 system (Philips Electronics; Andover, MA). Measurements were analyzed using Syngo Dynamics (Siemens Healthcare, Germany). Pulsed-wave Doppler was used to measure mitral and tricuspid inflow peak velocity at early (E) and late filling (A). Tissue Doppler imaging was used to determine mitral and tricuspid valve annular velocities in early (e') and late diastole (a') at both the septal and lateral annulus. Continuous-wave Doppler sampling of the peak tricuspid regurgitation velocity (TRV) was used.

DD was diagnosed according to the published American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines.¹⁷ The criteria were modified to account for potential anemia-related changes or changes that may not be exclusively attributed to DD in SCA as previously described.⁷ Briefly, patients with abnormalities in all of the following parameters (left atrial [LA] enlargement plus abnormal e' and E/e' ratio) were considered to have DD. Patients with LA enlargement and only one additional abnormality out of three (abnormal e' , E/e' ratio, or $TRV \geq 2.8$ m/s) were considered to have inconclusive results. Patients with inconclusive results were further classified based on exercise echocardiography. For the patients with inconclusive results, exercise stress echocardiogram was used according to the guidelines and was considered positive for DD if mitral annular e' velocity < 2 SD below, and $E/e' > 2$ SD above the mean for age, gender, and body size. Patients with inconclusive classification who had exercise mitral annular e' velocity < 7 cm/s and $E/e' > 14$ were considered to have DD.¹⁷ Patients with inconclusive resting echocardiogram who did not meet these criteria on exercise echocardiogram were classified as having no DD. Age, body size, and sex-corrected z-scores were used to adjust for echocardiographic variables for DD when available.^{17–19}

All patients underwent an exercise echocardiogram immediately after maximum exercise according to the American Society of Echocardiography guidelines.¹⁷ Similar to the echocardiographic evaluation at rest, we evaluated systolic and diastolic function while the patients were in the supine position immediately after peak exercise. In case of fusion of early and late diastolic Doppler waves (E and A and/or e' and a') at high heart rates, imaging was delayed until separation of these waves. Patients with inconclusive classification who had exercise mitral annular e' velocity < 7 cm/s, and $E/e' > 14$ were considered to have DD¹⁸ whereas those who did not meet these criteria were classified as having no DD. The correlations between measures of diastolic function using resting echocardiogram and exercise parameters on CPET were studied.

2.3 | Cardiac MRI

CMR was performed on a 1.5 T scanner (Philips Ingenia, Best, the Netherlands). Vectorcardiographic gated sequences were performed in the ventricular long- and short-axis planes for chamber sizes, ejection fraction, and ventricular mass. The normal values for the volumetric data are based on previous published data.²⁰

2.4 | Statistical methods

Data are presented as mean $\pm$ standard deviation. Differences between study and control participants were assessed using the two-sided, unpaired Student *t* test. The correlations between measures of diastolic function using resting echocardiogram and exercise parameters on CPET were determined using the Pearson correlation coefficient test. A *P* value < 0.05 was considered significant. Analysis was performed using JMP, Version 12 from SAS Institute Inc., Cary, NC.

3 | RESULTS

3.1 | Patient characteristics

A total of 21 patients with SCA (homozygous HbSS) participated in the study (age, 24 ± 9.23 years; age range, 13–44 years). Two patients were unable to complete a maximal effort CPET and were not included in the final analysis. The remaining 19 patients had their CPET results compared with gender-, age-, and size-matched normal controls. Due to a lack of African-American controls, the groups were not matched by ethnicity (SCA group 19 African-American patients vs control group 4 African-American patients and 15 Caucasian patients). There were no statistically significant differences in the baseline demographics between SCA patients and controls (Table 1). Hematologic parameters of the SCA group were all consistent with their underlying diagnosis (Table 1). SCA patients had abnormal resting FVC and forced expiration in one second (FEV1) compared with the controls in keeping with their SCA diagnosis with 8 of 19 patients having a restrictive pattern and no patients having an obstructive pattern (Table 1). Fifteen of 19 patients (78%) were prescribed hydroxyurea at the time of testing.

3.2 | Cardiac imaging

All patients in the SCA group ($n = 19$) had an echocardiogram performed at rest and peak exercise. All patients had normal systolic function and 6 of 19 patients were found to have DD.⁷ The data from the resting echocardiogram are summarized in Table 2.

All patients in the SCA group ($n = 19$) had a CMR performed and results are summarized in Table 2.

3.3 | CPET

Compared with normal controls, the SCA group ($n = 19$) had lower functional capacity indicated by lower maximum VO_2 (1378 ± 412 mL/min vs 2237 ± 580 mL/min, $P < 0.00001$) and percentage of predicted maximum VO_2 ($61\% \pm 14.5\%$ vs $87\% \pm 12.3\%$, $P < 0.00001$) (Figure 1A). In addition, SCA patients had a lower stroke volume at maximum exercise as evidenced by a lower percentage of predicted maximal oxygen pulse (O_2 pulse) ($67\% \pm 15.9\%$ vs $95\% \pm 8.3\%$, $P < 0.01$) (Figure 1A). SCA patients were likely deconditioned compared with the healthy controls based on the lower maximum workload (117 ± 37.6 watts vs 175 ± 50.5 watts, $P = 0.0003$). There were no significant differences between the peak heart rate (179 ± 14.7 bpm vs 182 ± 14.2 bpm, $P = 0.62$), the peak systolic blood pressure (SBP) (173 ± 16.1 mmHg vs 174 ± 19.9 mmHg, $P = 0.88$), or the VE/VCO_2 slope (ventilatory efficiency) (31.7 ± 7 vs 27 ± 4.3 , $P = 0.05$) (Table 2). Additionally, the

breathing reserve percentage was normal ($46\% \pm 13.6\%$), indicating that whereas SCA patients have increased risk of restrictive lung disease, in this cohort there were no pulmonary limitations to exercise.

Considering the submaximal exercise parameters, patients with SCA had significantly lower VO_2 at AT (950 ± 311.7 mL/min vs 1460 ± 409.9 mL/min, $P = 0.0002$), percentage of predicted VO_2 at AT ($42\% \pm 12.5\%$ vs $59\% \pm 18.4\%$, $P = 0.004$) and OUES at AT (1512 ± 426.2 vs 2080 ± 339 , $P = 0.00006$) compared with normal controls (Figure 1B). There was no significant difference between groups in the VE/VCO₂ slope at AT (24 ± 6.6 vs 21 ± 3.1 , $P = 0.06$) (Table 2; Figure 1B). Twelve of 19 patients had a VO_2 @RER1.0 < 2 standard deviations below the mean compared with 2 of 19 among controls ($P = 0.0008$) (Figure 2). All 12 SCA patients with a VO_2 @RER1.0 less than 2 SD had a peak VO_2 less than 70% compared with the two of seven SCA patients with a VO_2 @RER1.0 greater than 2 SD ($P = 0.006$). The maximum VO_2 strongly correlated with VO_2 at AT ($r = 0.9$, $P < 0.00001$), VO_2 @RER1.0 ($r = 0.79$, $P < 0.00001$), and OUES at AT ($r = 0.83$, $P < 0.00001$). The VE/VCO₂ slope at maximal exercise also strongly correlated with VE/VCO₂ slope at AT ($r = 0.88$, $P < 0.00001$).

When comparing the results of maximal exercise testing between the patients with DD ($n = 6$) and without DD ($n = 13$), there were significant differences in the VE/VCO₂ slope (36 ± 8.6 vs 29 ± 4.8 , $P = 0.02$) but not in the percentage of predicted maximum VO_2 ($53\% \pm 4.7\%$ vs $65\% \pm 16.1\%$, $P = 0.1$), percentage of predicted maximum O₂ pulse ($61\% \pm 6.8\%$ vs $70\% \pm 18.1\%$, $P = 0.22$) and percentage of predicted peak workload ($47\% \pm 11.5$ vs $59\% \pm 14.5\%$, $P = 0.1$) (Figure 3A). There were significant differences in multiple submaximal parameters, notably the VE/VCO₂ slope at AT (29 ± 9.3 vs 22 ± 3.7 , $P = 0.04$), the VO_2 @RER1.0 (705 ± 147.2 vs 1023 ± 188 , $P = 0.002$) and the OUES (1205 ± 365 vs 1653 ± 384.9 , $P = 0.03$) (Figure 3B). Although there was no difference between patients with and without DD in the percentage of predicted VO_2 at AT ($39\% \pm 6.8\%$ vs $44\% \pm 14.8\%$, $P = 0.45$), both groups were abnormal (normal percentage of predicted VO_2 at AT 55%–60%).

Significant associations are summarized in Table 3.

Two patients were unable to reach maximal exercise and the test concluded around ventilatory anaerobic threshold. They were an eight-year-old female with mild restrictive lung disease and DD on echocardiogram and a 17-year-old female with mild restrictive lung disease and no DD apparent on echocardiogram. Although their data are not included in the final analysis, their submaximal data at test conclusion were similar to those of the SCA patients who completed maximal effort tests and were considered abnormal (VE/VCO₂ slope 44 and 37; OUES 804 and 1394; VO_2 @RER1.0 520 and 630 mL/min; VO_2 at AT 690 and 840 mL/min).

4 | DISCUSSION

Our data show that SCA patients have significant abnormalities in submaximal exercise parameters when compared with healthy normal controls. Submaximal exercise testing parameters have been minimally studied in SCA patients.²¹ Each of the submaximal

measures we studied has different advantages in identifying potential reasons for exercise intolerance in the SCA population. This is important when considering the multifactorial nature of exercise intolerance.⁹ The fact that few of the submaximal exercise test results strongly correlated with CMR functional data or echocardiographic measures of DD speaks to this likely multifactorial nature of exercise intolerance with a strong interplay between the musculoskeletal, pulmonary, and cardiovascular performance in SCA patients.

The VO_2 at AT is often used in normal populations as an effort-independent measure to predict the maximum VO_2 . This value is often low in patients who fail to augment cardiac output, have impaired tissue oxygen delivery during exercise, or have peripheral vascular disease.¹³ In the SCA patients studied, the percentage of predicted VO_2 at AT was significantly less than both the 55%–60% normal values described by Wasserman et al and the normal controls.¹³ Thus, the SCA patients shift to anaerobic metabolism sooner and have a worse adaptation response to early exercise as opposed to the healthy controls. SCA patients have multiple possible etiologies for this, including diastolic heart failure, restrictive lung disease, and physical deconditioning, all of which was demonstrated in our cohort. Although the comparison between patients with and without DD did not yield a difference between groups in VO_2 at AT, both groups were markedly below expected normal, again highlighting that multiple factors are involved in functional capacity in SCA patients.

Although VO_2 at AT is generally used to differentiate normal from abnormal exercise capacity on a submaximal test, a major limitation is in the difficulty to reliably and consistently identify the AT, which may lead to significant interobserver variability.¹⁴ The advantage of using the VO_2 @RER1.0 is easy to consistently determine.¹⁴ Additionally, it has been shown to predict abnormal maximal VO_2 in both an anatomically normal population and pediatric cancer survivors and patients with Fabry disease.^{14,22,23} We demonstrated a novel finding that the VO_2 @RER1.0 is abnormal in the majority of individuals with SCA and that it can predict abnormal maximal VO_2 . This reflects an additional potentially useful submaximal exercise test parameter for SCA patients.

SCA patients can also have chronic parenchymal and restrictive lung disease, which has been shown to limit their maximal effort exercise.⁸ In addition to evaluating PFT at rest, the CPET is helpful in assessing the ventilatory efficiency by utilizing the VE/VCO_2 slope. The VE/VCO_2 slope has previously been used as a measure in heart failure and pulmonary hypertension patients with higher slopes (> 32), indicating heightened ventilation associated with reduced cardiac output and poor pulmonary perfusion.^{24,25} The VE/VCO_2 slope is often calculated as a maximal effort result with values from rest to peak exercise as opposed to reporting as a submaximal measure (calculating from rest to AT). In the heart failure population, the VE/VCO_2 slope at maximum exercise has been shown to be higher than VE/VCO_2 at AT, with both values showing prognostic significance.²⁶ The examination of the relationship between VE/VCO_2 values at both maximum exercise and AT is a novel finding in the SCA population. Although in this study the mean VE/VCO_2 slope was not abnormal nor significantly different from the controls, it did trend toward statistical significance, and the strong correlation between the VE/VCO_2 slope at both maximum exercise and AT shows that this could be an additional submaximal variable to consider, specifically in light of the significant lung disease this patient population can manifest.

Lastly, the OUES, which is a variable that indicates how effectively oxygen is extracted and taken into the body, has been shown to correlate with the maximal VO_2 in both a normal population and patients with congenital heart disease.^{27,28} As this is an effort-independent measure, it is not dependent on the final stages of exercise such as the maximum VO_2 .²⁷ This measure is primarily determined by the relationship between minute ventilation and oxygen consumption, and it is worsened by both heart failure and pulmonary disease leading to high physiologic dead space and increased carbon dioxide production.²⁸ As SCA patients can have both restrictive lung disease and diastolic heart failure, this is a potentially useful variable to consider with these patients and not surprisingly abnormal in our cohort. This is further supported in that this measure was more abnormal in SCA patients with DD as opposed to those SCA patients without DD.

This work did have several limitations. First, this is a relatively small observational study with 19 participants who were on the healthier end of the SCA spectrum with the ability to complete a maximal effort CPET and with few vasoocclusive crises. Second, due to a limited availability of African-American patients for the control group, the groups were not ethnically matched (SCA group, 19 African-American patients vs control group, 4 African-American patients), but they were matched by age, gender, and size. Third, the submaximal exercise parameters outside of VO_2 at AT have been minimally studied, and the clinical utility and impact of using these measures is unknown, although they can potentially be very helpful in individuals who cannot reach maximum exercise, which is the case in many patients with SCA. Fourth, classification of DD is challenging in children. In this study, we used contemporary consensus criteria for DD in adults, because pediatric guidelines are lacking.¹⁸ When available, we compared results to normal values for age, size, and sex. We also used exercise stress echocardiogram to aid in diagnosis, which is a new emerging tool used for inconclusive cases, but there are insufficient data in the pediatric population.

Lastly, the SCA patients as a whole had anemia in keeping with their pathology, whereas the normal controls had unknown hemoglobin levels. The effects of anemia on maximum VO_2 are well established in multiple different patient populations,^{29–31} and if the normal controls have normal hemoglobin, then that would be another confounder when comparing the groups. Ideally, future study should be performed comparing SCA patients with anemia with normal controls with anemia in order to reduce this confounder.

In summary, we showed that SCA patients have impaired submaximal exercise capacity that was strongly associated with maximal effort exercise test results and can potentially be used to predict maximal CPET measures in the event of an SCA patient being unable to complete a maximal effort test. Additionally, abnormal submaximal exercise results were associated with concomitant DD.

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Abbreviations:

AT	anaerobic threshold
BSA	body surface area
CMR	cardiac MRI
CPET	cardiopulmonary exercise test
DD	diastolic dysfunction
FEV1	forced expiration in one second
FVC	forced vital capacity
HCT	hematocrit
MVV	maximal voluntary ventilation
O2Pulse	oxygen pulse
OUES	oxygen uptake efficiency slope
RER	respiratory exchange ratio
SCA	sickle cell anemia
TRV	tricuspid regurgitation velocity
VE/VCO₂ slope	ventilatory efficiency
VO₂	oxygen consumption

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FIGURE 1.

Comparison data between the SCA (blue) and control (red) patients at peak exercise (A) and submaximal exercise.² SCA, sickle cell anemia; % Pred, percentage of predicted; VO₂, oxygen consumption; O₂ pulse, oxygen pulse; VE/VCO₂ slope, ventilatory efficiency; AT, anaerobic Threshold

FIGURE 2.

Data from SCA and control groups plotted on a graph. Solid line is less than 2 standard deviations from the mean derived by the regression equation for calculating the VO_2 @ RER 1.0 described by Chin et al, 2009. SCA, sickle cell anemia; VO_2 , oxygen consumption; RER, respiratory exchange ratio

FIGURE 3.

Comparison data between the SCA patients with (purple) and without (orange) diastolic dysfunction at peak exercise (A) and submaximal exercise.² SCA, sickle cell anemia; % Pred, percentage of predicted; VO₂, oxygen consumption; O₂Pulse, oxygen pulse; VE/VCO₂ slope, ventilatory efficiency; AT, anaerobic threshold

TABLE 1

Baseline demographics

	Sickle cell	Control	<i>P</i> value
Number	19	19	
Sex	F10, M9	F10, M9	1
Age (years)	24 ± 9.2	23 ± 8.6	0.57
Height (cm)	169 ± 13.4	168 ± 10.2	0.76
Weight (kg)	67 ± 19.1	70 ± 16.9	0.53
BSA	2 ± 0.3	2 ± 0.2	0.69
FVC (%)	86 ± 14.3	100 ± 15.3	0.007
FEV1 (%)	80 ± 14.5	97 ± 15.1	0.002
FEV1/FVC	93 ± 7.9	97 ± 5.6	0.11
Hematocrit (%)	29 ± 2.3		
Reticulocyte count (%)	8 ± 5.7		
Platelets (1000/ μ L)	340 ± 97.1		
LDH (units/L)	572 ± 280		
Receiving hydroxyurea	15 (79%)		

BSA, body surface area; cm, centimeters; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; kg, kilograms; LDH, lactate dehydrogenase.

TABLE 2

Results of imaging data and exercise testing

cMRI data (normal values)	SCA patients	Control	P value
RVEF (%) (64% ± 7%)	58 ± 7.13		
RVEF z score	-0.4 ± 0.9		
Indexed RVEDV(mL/m ²) (83 ± 11)	98 ± 19.4		
RVEDV z score	1.2 ± 1.8		
LVEF(%) (66 ± 4.5)	59 ± 2.98		
LVEF z score	-1.2 ± 0.7		
Indexed LVEDV(mL/m ²) (80 ± 9)	100 ± 17.33		
LVEDV z score	1.2 ± 2.5		
Indexed LA Volume (mL/m ²) (39 ± 6.7)	60 ± 13.81		
LA volume z score	1.3 ± 1.4		
Resting ECHO data (normal values)			
Mitral valve lateral E' z score	-1.34 ± 1.15		
Lateral E/e' z score	1.98 ± 1.7		
Septal e z score	-1.39 ± 0.6		
Septal E/e' z score	1.96 ± 0.95		
TR velocity (m/s) (< 2.8)	2.48 ± 0.4		
CPET data (normal values)			
RER (> 1.1)	1.4 ± 0.1	1.2 ± 0.1	0.00002
Total load (watts)	117 ± 37.6	175 ± 50.5	0.0003
% of predicted breathing reserve (> 20)	46 ± 13.6	51 ± 10.6	0.24
Max VO ₂ (mL/min)	1378 ± 412	2237 ± 580	<0.00001
% of predicted peak VO ₂ (> 80)	61 ± 14.5	87 ± 12.3	<0.00001
Max SBP (mmHg)	173 ± 16.1	179 ± 23.1	0.35
Max heart rate (bpm)	179 ± 14.7	182 ± 14.9	0.56
VE/VECO ₂ slope (< 32)	31 ± 7	27 ± 4.3	0.05
O ₂ Pulse	8 ± 2.7	12 ± 3.1	<0.00001
% of predicted O ₂ pulse (> 80%)	67 ± 15.9	95 ± 8.3	<0.00001
VO ₂ at AT (mL/min)	950 ± 311.7	1460 ± 409.9	0.0002
% of Predicted VO ₂ at AT (55%–60%)	42 ± 12.5%	59 ± 18.4%	0.004
VO ₂ @RER1.0 (mL/min)	923 ± 229.7	1535 ± 469.6	0.00001
VE/VCO ₂ slope at AT	24 ± 6.6	21 ± 3.1	0.06
OUES at AT (1790 ± 310)	1512 ± 426	2080 ± 339	0.00006

Abbreviations: AT, anaerobic threshold; EDV, end diastolic volume; EF, ejection fraction; LA, left atrium; LV, left ventricle; O₂ pulse, oxygen pulse; OUES, oxygen uptake efficiency slope; RER, respiratory exchange ratio; RV, right ventricle; SBP, systolic blood pressure; SCA, sickle cell anemia; TR, tricuspid regurgitation; VE/VCO₂ slope, ventilatory efficiency; VO₂, maximum oxygen consumption.

TABLE 3

Analysis of correlation using Pearson correlation coefficient (*R*) and a *P* value of < 0.05 as statistically significant. Values in bold represent statistically significant correlations

Correlations	VO ₂ @AT		VE/VCO ₂ @AT		OUES@AT		VO ₂ @RER1.0	
	<i>R</i> value	<i>P</i> value	<i>R</i> value	<i>P</i> value	<i>R</i> value	<i>P</i> value	<i>R</i> value	<i>P</i> value
RVEF	-0.18	0.45	-0.15	0.53	-0.16	0.51	-0.15	0.53
RVEDV	-0.36	0.12	-0.15	0.53	0.45	0.05	-0.32	0.18
LVEF	0.46	0.04	-0.13	0.59	0.55	0.01	0.28	0.24
LVEDV	0.48	0.04	-0.25	0.3	0.43	0.07	-0.31	0.19
Hematocrit	0.77	0.0001	-0.22	0.36	0.52	0.02	-0.001	0.99
Lateral E z score	0.27	0.25	-0.45	0.05	0.45	0.06	0.35	0.14
Lateral E/e' z score	-0.32	0.18	0.49	0.03	-0.55	0.01	-0.51	0.02
Septal E z score	0.36	0.15	-0.10	0.67	-0.04	0.86	0.46	0.04
Septal E/e' z score	-0.38	0.1	0.51	0.02	-0.42	0.07	-0.46	0.05
Echo LA volume	-0.09	0.9	0.12	0.63	-0.1	0.69	0.16	0.51
TR velocity	-0.22	0.37	0.11	0.66	0.11	0.64	-0.08	0.73

Abbreviations: AT, anaerobic threshold; EDV, end-diastolic volume; EF, ejection fraction; LA, left atrium; LV, left ventricle; OUES, oxygen uptake efficiency slope; RER, respiratory exchange ratio; RV, right ventricle; TR, tricuspid regurgitation; VE/VCO₂ slope, ventilatory efficiency; VO₂, oxygen consumption.