Left ventricular hypertrophy and diastolic dysfunction in children with sickle cell disease are related to asleep and waking oxygen desaturation

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Premature death and cardiac abnormalities are described in individuals with sickle cell disease (SCD), but the mechanisms are not well characterized. We tested the hypothesis that cardiac abnormalities in children with SCD are related to sleep-disordered breathing. We enrolled 44 children with SCD (mean age, 10.1 years; range, 4-18 years) in an observational study. Standard and tissue Doppler echocardiography, waking oxygen saturation averaged over 5 minutes, and overnight polysomnography were obtained in participants, each within 7 days. Eccentric left ventricular (LV) hypertrophy was present in 46% of our cohort. After multivariable adjustment, LV mass index was inversely related to average asleep and waking oxygen saturation. For every 1% drop in the average asleep oxygen saturation, there was a 2.1 g/m$^{2.7}$ increase in LV mass index. LV diastolic dysfunction, as measured by the E/E′ ratio, was present in our subjects and was also associated with low oxygen saturation (sleep or waking). Elevated tricuspid regurgitant velocity (≥ 2.5 m/sec), a measure of pulmonary hypertension, was not predicted by either oxygen saturation or sleep variables with multivariable logistic regression analysis. These data provide evidence that low asleep and waking oxygen saturations are associated with LV abnormalities in children with SCD. (*Blood*. 2010;116(1):16-21)

Introduction

Sickle cell disease (SCD) is associated with premature death,[1,2] which often occurs in the midst of an acute illness.[3,4] Elevated right ventricular (RV) pressure has been well documented as a risk factor for death in adults with SCD[5-7] and has been implicated in autopsy studies.[3,8] Adults with SCD and peak tricuspid regurgitant velocity greater than 2.5 m/sec have a 2-year mortality rate of near 50%.[9]

The prevalence of echocardiographically defined elevated RV pressure is 11% to 46% in adults and children with SCD.[5,10-15] Age is associated with elevated RV pressure in adults[5] but not children[14] with SCD. The pathophysiologic mechanism of pulmonary hypertension in individuals with SCD has not been well defined and is probably multifactorial. Potential etiologic factors include hemolysis interfering with nitric oxide-mediated vasodilatation, left ventricular (LV) dysfunction, pulmonary thromboembolism, airway hyperreactivity, and sleep-disordered breathing.[16-18] LV hypertrophy and diastolic dysfunction have been found in adults and children with SCD, and the latter has also been implicated as an independent risk factor for death.[17,19-22]

Sleep-disordered breathing is described in children with SCD,[16,18,23-25] and nocturnal desaturation is related to pain episodes.[16] The possibility that nocturnal desaturation or obstructive sleep apnea is related to cardiac function and mortality has not been thoroughly evaluated. Sleep-disordered breathing in adults is associated with LV hypertrophy, endothelial dysfunction, and a proinflammatory state leading to increased cardiovascular risk.[26-30] Based on the known association of sleep-disordered breathing with LV hypertrophy[26,30,31] and diastolic dysfunction[32-35] in adults and children, we tested the hypothesis that cardiac abnormalities in children with SCD are related to sleep abnormalities. In a prospective cohort, we undertook a cross-sectional study using 2-dimensional, Doppler and tissue Doppler echocardiography in parallel with overnight polysomnography.

Methods

Patients

The Sleep and Asthma Cohort (SAC) study protocol was approved by institutional review boards at all 3 centers (Washington University School of Medicine, St Louis, MO; Case Medical Center, Cleveland, OH; and the United Kingdom National Research Ethics Service for Great Ormond Street National Health Service Hospital Trust and the Institute of Child Health, with St Mary's Hospital and the North Middlesex [National Health Service] Hospital Trusts, London). The SAC study was designed to determine the epidemiology, physiologic basis, and sequelae of sleep disturbance and desaturation in unselected children with SCD.

Children with SCD 4 to 18 years of age followed regularly in outpatient hematology clinics at the 3 centers were enrolled in the SAC study after informed consent and assent were obtained. A subset of the SAC study patients (convenience sample size) had echocardiograms obtained when the treating physician judged that screening for elevated pulmonary pressure was clinically indicated based on published adult data. This study sample was restricted to include only subjects with sleep study and echocardiogram

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performed within 7 days to eliminate time between evaluations as a confounding factor. Exclusion criteria were chronic blood transfusion therapy, continuous positive airway pressure or overnight oxygen therapy, noncompliance with clinic follow-up, participation in clinical trials of blood transfusion, oxygen or hydroxyurea, comorbidities known to predispose to sleep-disordered breathing (eg, Pierre-Robin sequence, craniosynostosis, neuromuscular disease), chronic lung disease, cardiac disease requiring surgical or catheter-based intervention, or HIV disease. Adenoidal or tonsillar hypertrophy was not an excluding condition.

Polysomnography

Baseline polysomnography was performed with the Embla N-7000 system. Sleep stages were measured using standard sensors (C_3/A_2, C_4/A_1, O_1/A_2, O_2/A_1 patient ground and common reference), electro-oculography from leads at ROC/A_2 and LOC/A_1, and submental electromyography with 3 lead placements. In addition, the following cardiorespiratory and other ancillary data were continuously recorded: chest and abdominal wall motion by inductive plethysmography with noncalibrated sum signal (Embla Xact-Trace bands), airflow by both nasal pressure cannula and oronasal thermocouple (Pro-Tech Services), pulse oximetry numeric and plethysmograph waveform using the 2 seconds averaging mode (Masimo Radical), heart rate by 1 ECG channel with a standard 3-lead precordial placement, right and left leg movements (by electromyography), snore microphone (Dymedix), and position sensor.

Sleep variables included (1) average oxygen saturation asleep; (2) percentage of sleep time with oxygen saturation less than 95%; (3) obstructive apnea hypopnea index (OAHI), that is, the count of all obstructive apneas regardless of associated desaturation plus the count of hypopneas associated with at least a 3% oxygen desaturation divided by the total sleep time expressed in hours; (4) arousal index (total number of EEG arousals that met recommended American Academy of Sleep Medicine scoring criteria[36] per hour of sleep); (5) sleep maintenance efficiency: percentage of time from sleep onset to morning waking that was spent sleeping, or the ratio of total sleep time to (total time in bed − sleep latency), expressed as a percentage; and (6) oxygen desaturation index: number of validated desaturations of at least 3% per hour of sleep. The waking oxygen saturation, estimated by the average saturation value collected during a standardized 5-minute period with the participant seated quietly before the sleep study, was included as a potential covariate.

The morning after the sleep study, data were electronically transmitted to the Case Sleep Reading Center (Cleveland, OH) for standardized scoring, blinded to personal identification data and clinical correlates.

Echocardiography

Echocardiograms were only available for study participants who had these measurements made as part of routine clinical care. Echocardiograms were obtained during scheduled, well visits to an outpatient clinic or at the time of sleep study, when participants were at their baseline health status, not reporting illness or increased pain. Although obtained for clinical care, all echocardiograms were performed following a standardized protocol, which incorporated standard 2-dimensional, M-mode, pulse Doppler, and color Doppler images. LV mass was determined from M-mode images and indexed to height raised to the 2.7th power and compared with sex- and age-based normal values.[37] Relative wall thickness was calculated by RWT = 2(LV posterior wall)/left ventricle end-diastolic dimension.[38] Transmitral flow Doppler tracing was obtained to measure rapid filling (E) and atrial contraction (A) velocities. In addition, spectral tissue Doppler imaging sampling was obtained from the basal LV wall and interventricular septum at the level of the mitral annulus. At both locations, measurements were obtained for peak systolic annular velocity (S′), peak early diastolic annular velocity (E′), and peak late diastolic annular velocity (A′). The basal LV wall E′ was used in the calculation of the E/E′ ratio (increased ratio is indicative of diastolic dysfunction). The myocardial performance (Tei) index was determined from tissue Doppler tracings calculated as $(a - b)/b$ where a is the sum of isovolumic contraction time plus ejection time plus isovolumic relaxation time and b is the LV ejection time. Three consecutive cardiac cycles were measured and averaged. For peak tricuspid regurgitant velocity, the highest value obtained with a good quality Doppler envelope from either apical 4-chamber or parasternal views was recorded. Heart rate was determined from ECG tracings obtained during echocardiographic studies.

Echocardiograms were sent for central review and measurement on digital media by a single echocardiographer blinded to clinical data and sleep study results.

Blood pressure

To minimize observer variability, an automated oscillometric (Dinamap) method was used for seated systolic and diastolic blood pressures that were obtained either at initial enrollment or on the day of the sleep study. After 5 minutes of rest, 3 blood pressure measurements were obtained with 5 minutes between each measurement. The mean of these 3 measures was used to generate relative age-, sex-, and height-adjusted systolic and diastolic percentiles based on auscultatory normative data.[39] Blood pressure percentiles, as continuous linear variables, were included as potential confounding variables in the multivariable analysis.

Laboratory variables

Hemoglobin, reticulocytes, lactate dehydrogenase (LDH), and plasma arginine-ornithine ratio were obtained. Hemoglobin levels were extracted from clinical records, using data obtained on the day of sleep study or at steady state close to it. Plasma was obtained at the time of the sleep study and sent to the Washington University laboratory for determination of LDH, arginine, and ornithine levels. A chemistry analyzer scanned all samples at 540 nm to detect hemoglobin in the plasma. None of the samples were flagged for evidence of hemolysis.

Statistical analysis

Continuous measurements are summarized as mean plus or minus SD. To describe differences between subjects with echocardiograms and those without echocardiograms, χ^2 test or the Wilcoxon 2-sample tests were used to compare categorical and continuous variables, respectively. Exact one-sample binomial tests (for single proportion) and one-sample t tests (for single mean) were used to compare echocardiographic and sleep study data to published normal values,[37,40,41] which were used as the null hypotheses values. LV mass indexed values were tested against age- and sex-specific normal values.[37] Echocardiographic values significantly different from expected values ($P < .05$), as well as peak tricuspid regurgitant velocity, were defined as dependent variables representing cardiac dysfunction. Spearman univariable coefficients were used to measure the correlation of these dependent cardiac variables with 6 selected sleep variables. The inflated type I error resulting from multiple testing was controlled by the Bonferroni method with the raw P value multiplied by relevant number of tests for the variable of interest. Backward stepwise elimination multivariable analysis was performed using echocardiographic measurements as dependent variables with statistically significant sleep variables as independent variables of main interest. LV E/E′ ratio was a dependent variable of interest because of the link between diastolic dysfunction and mortality in individuals with SCD.[17] Elevated tricuspid regurgitation velocity was treated as a nominal dependent variable for backward stepwise logistic regression analysis with a cutoff value of greater than or equal to 2.5 m/sec. If the tricuspid regurgitation velocity was not measurable, it was considered normal for this logistic regression analysis.[5] In addition to sleep variables, other covariates considered in the multivariable analysis were: hemoglobin, LDH, arginine-ornithine ratio, waking oxygen saturation, age, heart rate during the echocardiogram, systolic and diastolic blood pressure percentiles, and body mass index percentile.[42] Oxygen saturation while waking was included as a covariate because prior studies have demonstrated a relationship between waking and nocturnal saturations.[23,25] The arginine-ornithine ratio was a covariate because this ratio is related to elevated tricuspid regurgitant velocity and mortality in adults with SCD.[43] To avoid multicollinearity, separate models were fitted for the 3 independent variables with very high correlation (oxygen saturation waking vs average

oxygen saturation asleep or percentage of sleep time with oxygen saturation < 95%, average oxygen saturation asleep vs percentage of sleep time with oxygen saturation < 95%, r values 0.93, −0.88, and −0.88, respectively). A correlation coefficient of greater than 0.8 was used as a cutoff for separate models. The final models were chosen based on the maximum r^2. The significance level for variable retention in multivariable models was set at 10%. The distributional assumptions for the final models (conditional normality and constant variance) were checked by residual plots. The linearity assumption was examined by the added variable plots.[44]

Results

Subject characteristics

Of a total of 149 children of African origin with SCD enrolled in the entire SAC cohort between June 2006 and February 2008, 44 (mean age, 10.1 years; range, 4-8 years) were included in this analysis. The remaining patients were excluded because an echocardiogram was not ordered (n = 70), not completed within 7 days of the sleep study (n = 30), the child had overnight oxygen supplementation prescribed during the study (n = 3), or there were technical problems with the polysomnography data collection (n = 2). A potential selection bias toward obtaining echocardiograms was assessed based on variables shown in supplemental Table 1 (available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). The group with echocardiograms compared with those without echocardiograms varied by center, had fewer males, had decreased history of acute chest syndrome, and had lower diastolic blood pressure. The 44 subjects in the final study group were composed of 100% HgbSS sickle cell phenotype; those without echocardiograms included 86% HgbSS and 14% HgbS β (0)-thalassemia phenotypes. There was no difference in the sleep variables or waking oxygen saturation between the 69 study subjects with echocardiograms and 70 subjects excluded because an echocardiogram was not ordered (data not shown).

Among the study participants, systolic and diastolic blood pressures were greater than the 90th percentile of the general population in 27% and 0%, respectively.

Sleep measures and waking saturation

Sleep-disordered breathing and reduced oxygen saturation values during wakefulness were common among children with SCD. Lower average oxygen saturation during sleep, increased sleep time less than 95% oxygen saturation, and increased obstructive apnea hypopnea indices during sleep were found in 33%, 47%, and 19% of the final study group, respectively, compared with expected normal thresholds.[45] The mean oxygen saturation asleep was 97% plus or minus 3% (range, 86%-100%). The mean saturation during wakefulness was 97% plus or minus 4% (range, 82%-100%), and 26% of the participants had mean values less than 96%. There were no relationships between sleep variables and blood pressure percentiles (data not shown).

Echocardiographic measures

Echocardiographic abnormalities were common among children with SCD (Table 1). Specifically, 46% had LV hypertrophy with LV mass index greater than 95th percentile for age and sex. Among the patients with LV hypertrophy, all had eccentric hypertrophy as defined by a normal relative wall thickness less than 0.41.[38] Dilated LV with diastolic dimension Z-score greater than 2 was present in 59% of the cohort. Tricuspid regurgitant velocity was greater than or equal to 2.5 m/sec in 9% of the sample. Four subjects (9%) had nonmeasurable tricuspid regurgitant velocity. Both LV and septal myocardial performance indices were above normal thresholds in 16% of the sample. Compared with expected values, subjects also had increased estimated LV filling pressure (E/E′) and altered LV diastolic function. LV systolic function was normal as measured by shortening fraction but abnormal based on decreased LV tissue Doppler S′. Mean heart rate during the echocardiogram was 86 beats/min.

Table 1. Echocardiographic measures

Category/variable	Mean (SD)	Expected normal values	*P*
LV size and mass			
LV diastolic dimension Z-score	2.5 (1.3)	0 (−2 to 2)	< .001
LV mass index, g/m$^{2.7}$	44.9 (10.7)	26-39*	< .001
Relative wall thickness	0.27 (0.04)	< 0.41	.7
LV systolic function			
Shortening fraction	0.37 (0.04)	≥ 0.28	.7
LV tissue Doppler			
E′	15.7 (3.4)	16.5 (5.3)	.1
A′	4.8 (1.2)	6.4 (1.9)	< .001
S′	8.0 (2.1)	9.3 (3.4)	< .001
E/E′	7.2 (2.2)	6.1 (2.4)	.002
MPI index	0.45 (0.09)	0.35 (0.09)	< .001
Septal tissue Doppler			
E′	11.7 (2.0)	12.6 (3.4)	.004
A′	5.6 (1.9)	6.1 (1.6)	.1
S′	7.6 (1.1)	7.6 (1.9)	.8
MPI index	0.47 (0.08)	0.35 (0.09)	< .001

Mean (SD) values for echocardiographic variables in 44 study subjects with *P* values based on comparison with expected normal values.[37,40,41] Tissue Doppler values E′, A′, and S′ are given as centimeters per second.

MPI indicates myocardial performance index (a measure of combined systolic and diastolic function).

*LV mass index normal values vary by age and sex; 27% of the reference population was African American.[37]

Relationship of sleep and echocardiographic measures to markers of hemolysis

A series of regression analyses were used to examine the relationship of the laboratory variables, including markers of hemolysis (hemoglobin, LDH, and arginine-ornithine ratio) with sleep and abnormal echocardiographic variables. Peak tricuspid regurgitant velocity was associated with LDH levels (age-adjusted r = 0.50, *P* = .002, multiple comparison-adjusted *P* = .006). The oxygen desaturation index was inversely related to hemoglobin (age-adjusted r = −0.47, *P* = .004, multiple comparison-adjusted *P* = .01). LV diastolic dimension had an inverse relationship with hemoglobin that was not retained with adjustment for multiple comparisons (age-adjusted r = −0.39, *P* = .01, multiple comparison-adjusted *P* = .05), whereas LV mass had no relationship with hemoglobin (age-adjusted r = −0.26, *P* = .1, multiple comparison-adjusted *P* = .3).

Relationship of sleep measures and echocardiographic abnormalities

Lower average oxygen saturation waking and during sleep were predictors of LV mass. In both the Bonferroni-adjusted univariable (supplemental Table 2) and multivariable analyses (Tables 2-3), a lower average oxygen saturation predicted LV mass index. The multivariable model with percentage of sleep time with oxygen saturation less than 95% (not shown) revealed similar relationships. The best model for LV mass used sleeping oxygen saturation.

Table 2. Multivariable models with oxygen saturation asleep

Dependent variable/independent covariates	Parameter estimate	Standardized coefficient	*P*
LV mass index, g/m$^{2.7}$ (R^2 = 0.66, *P* < .001)			
Oxygen saturation asleep, percentage	−2.1	−0.60	< .001
Age, y	−0.73	−0.26	.02
Systolic blood pressure percentile	0.10	0.24	.03
Arousal index	0.48	0.18	.09
LV diastolic dimension Z-score (R^2 = 0.74, *P* < .001)			
Oxygen saturation asleep, percentage	−0.18	−0.43	< .001
Sleep maintenance efficiency, percentage	−0.06	−0.48	< .001
Systolic blood pressure percentile	0.02	0.42	.001
Heart rate	−0.04	−0.38	.006
Oxygen desaturation index	0.03	0.32	.007
Body mass index percentile	−0.01	−0.25	.02
Arginine-ornithine ratio	0.22	0.22	.05
LV E/E′ (R^2 = 0.4, *P* < .001)			
Oxygen saturation asleep, percentage	−0.46	−0.63	< .001
Oxygen desaturation index	−0.04	−0.31	.03

Multivariable models of LV mass index, LV diastolic dimension Z-score, and LV E/E′ with oxygen saturation asleep, other sleep variables, and confounding independent variables for 44 study subjects. Sleep variables as potential independent variables: arousal index, sleep maintenance efficiency, OAHI at 3% desaturation, average oxygen saturation asleep, and oxygen desaturation index. Potential confounding variables evaluated: hemoglobin, LDH, arginine-ornithine ratio, age, heart rate, systolic and diastolic blood pressure percentiles, and body mass index percentile.

Specifically, for every 1% drop in the mean oxygen saturation during sleep, there is a 2.1 g/m$^{2.7}$ increase in the LV mass index. In this model, younger age predicted increased LV mass. OAHI had a univariable relationship with LV mass (r = 0.47, *P* = .001; adjustment for multiple comparisons *P* = .01) that was not retained in the multivariable analysis.

Given the observation that, in a normal pediatric population, LV mass indexed to height is inversely related to age,[37] we elected to further investigate a potential age effect on LV mass. Specifically, we generated a model with the same covariates as in Table 2 (arousal index, sleep maintenance efficiency, OAHI, average oxygen saturation asleep, oxygen desaturation index, hemoglobin, LDH, arginine-ornithine ratio, age, heart rate, systolic and diastolic blood pressure percentiles, and body mass index percentile), but modeled LV mass indexed to body surface area[46] as an alternative dependent variable. Lower oxygen saturation asleep and systolic blood pressure percentile remained associated (*P* < .001 and *P* = .04, respectively, model R^2 = 0.49) with LV mass, but age dropped (*P* = .66) from this model.

Lower oxygen saturation during sleep was the primary predictor of increased LV diastolic dimension. In the model using waking oxygen saturation, lower sleep maintenance efficiency was the strongest predictor of LV dimension. Higher systolic blood pressure measurements were associated with increased LV dimension in both models.

LV E/E′, a measure of diastolic dysfunction, was also associated with asleep and waking oxygen saturations. In these models (Tables 2, 3), oxygen desaturation index asleep had a paradoxical, albeit weak, inverse relationship with diastolic dysfunction (fewer oxygen desaturation events per hour associated with higher LV E/E′, *P* = .03 and .04, respectively).

Peak tricuspid regurgitant velocity had no univariable relationships with sleep variables or waking oxygen saturation (supplemental Table 2). With logistic multivariable analysis that included the same covariates used in models for LV mass and diastolic dimension, the odds ratio for relationship of elevated tricuspid regurgitant velocity to mean oxygen saturation during sleep was 0.51 (95% confidence interval, 0.20-1.34, *P* = .17) and with daytime oxygen saturation 0.74 (95% confidence interval 0.44-1.25, *P* = .27). These odds ratios remain nonsignificant if the 4 patients with nonmeasurable tricuspid regurgitant velocities are excluded (data not shown).

Discussion

The etiology of abnormal cardiac function among children with SCD is not well defined. We present the first combined sleep and echocardiographic study in children with SCD. The major significant relationships observed were that lower sleeping and waking oxygen saturations are associated with LV mass and diastolic dysfunction. These data provide strong evidence that low oxygen saturation measurements are associated with cardiac structural and functional changes. Relationships of LV dimension to sleep maintenance efficiency, the oxygen desaturation index, and the apnea hypopnea index lend some support to the hypothesis that sleep abnormalities contribute to cardiac abnormalities in children with SCD. All children with LV hypertrophy had eccentric geometry with increased LV mass index and normal relative wall thickness. The relationship of eccentric hypertrophy and oxygen saturation asleep parallels findings in a large community-based adult cohort not selected for symptoms of sleep-disordered breathing.[26] The potential clinical impact of hypoxia is highlighted in a study of adult patients with congestive heart failure in which nighttime hypoxia, rather than apnea or arousals, predicted hemo dynamic stress as measured by brain natriuretic peptide levels.[47] The relative importance of asleep versus waking oxygen saturation as predictors of LV hypertrophy remains unclear because of the high collinear relationship of these measures.[23,25] Studies in the general population and in subjects with sleep-disordered breathing

Table 3. Multivariable models with waking oxygen saturation

Dependent variable/independent and confounding variables	Parameter estimate	Standardized coefficient	*P*
LV mass index, g/m$^{2.7}$ (R^2 = 0.62, *P* < .001)			
Waking oxygen saturation, percentage	−1.6	−0.57	< .001
Age, y	−0.78	−0.28	.02
Arousal index	0.65	0.24	.04
Systolic blood pressure percentile	0.1	0.23	.05
LV diastolic dimension Z-score (R^2 = 0.72, *P* < .001)			
Sleep maintenance efficiency, percentage	−0.07	−0.58	< .001
Waking oxygen saturation, percentage	−0.13	−0.42	< .001
Heart rate	−0.04	−0.4	.006
Arousal index	0.09	0.28	.02
Systolic blood pressure percentile	0.02	0.31	.02
Hemoglobin, g/dL	−0.3	−0.28	.03
LV E/E′ (R^2 = 0.31, *P* = .002)			
Waking oxygen saturation, percentage	−0.31	−0.56	< .001
Oxygen desaturation index	−0.05	−0.32	.04

Multivariable models of LV diastolic dimension Z-score and LV mass index with waking oxygen saturation, sleep variables, and confounding independent variables for 44 study subjects. Sleep variables as potential independent variables: arousal index, sleep maintenance efficiency, OAHI at 3% desaturation, and oxygen desaturation index. Potential confounding variables evaluated: hemoglobin, LDH, arginine-ornithine ratio, age, heart rate, systolic and diastolic blood pressure percentiles, and body mass index percentile.

have not investigated waking oxygen saturation as a potential covariate.

Previous pediatric studies in SCD describe an unadjusted inverse univariable relationship of LV diastolic dimension and hemoglobin.[21,22] In our subjects, hemoglobin was not a covariate in our multivariable models of LV mass and size with asleep oxygen saturation. These findings suggest that altered LV structure in children with SCD is not primarily from low hemoglobin levels, but rather oxygen desaturation.

Investigation of causes of elevated tricuspid regurgitation velocity, a surrogate measure for pulmonary hypertension, is of intense interest in adults with SCD because this velocity is an independent predictor of death.[5,6,9] However, mortality has not been linked to elevated pulmonary pressure in children with SCD.[7] The prevalence of peak tricuspid regurgitation velocity more than 2.5 m/sec in our study is comparable with other pediatric studies of SCD.[10,12,14,15,22] Other investigators have demonstrated a relationship between oxygen saturation and tricuspid regurgitation velocity.[14,15] In our study, after adjustment for other covariates in a multivariable analysis, no relationship existed between tricuspid regurgitation velocity and sleep or waking oxygen saturation. Our findings are similar to those in studies of sleep-disordered breathing in children without SCD where LV and not RV abnormalities have been demonstrated.[30,34,48]

We and others[22] found a higher than expected prevalence of diastolic dysfunction in children with SCD, as measured by the LV E/E′ ratio. Among our participants, this ratio was related to asleep and waking oxygen saturation. Diastolic dysfunction is an independent predictor of mortality in adults with SCD.[17] Given the cross-sectional study design, we can only postulate, but cannot confirm, that children with SCD are at an earlier stage of cardiac dysfunction in which lower oxygen saturations alter LV structure, but this is not yet associated with elevated tricuspid regurgitant velocity because LV filling pressure is minimally increased. Adults with SCD and elevated pulmonary pressures have elevated LV filling pressure as determined by cardiac catheterization.[9] Additional support for this line of reasoning is provided by Hagar et al, who described a lower prevalence of elevated RV pressure among children compared with adults with SCD (25% and 54%, respectively).[7]

Potential pathophysiologic mechanisms for the link between oxygen desaturation and LV hypertrophy have become more evident. Endothelial dysfunction, mediated in part by hemolysis, may account for cardiac dysfunction in individuals with SCD.[17,43,49,50] Increased sympathetic tone, elevated blood pressure, and lack of nighttime blood pressure dipping from disordered sleep are other possible mechanisms for LV hypertrophy.[48,51,52] In our study, the waking systolic blood pressure was an additional predictor of LV mass. However, we did not have 24-hour ambulatory monitoring to investigate the nuances of blood pressure regulation. A cause-and-effect relationship between low oxygen saturation and LV hypertrophy cannot be determined based on our cross-sectional study design. However, the potential clinical implications of our findings are highlighted by the well-documented association of LV hypertrophy with cardiovascular mortality and more specifically sudden death in adult populations.[53,54]

As is inherent in an observational study, the interpretations of our results are tempered by our inability to completely adjust for potential confounders. Our sample size of 44 participants did not permit a complete interrogation of subgroup analyses. However, despite the small sample size, we did find evidence to support our primary hypothesis, lending weight to the strength of the relationship. Further, our results are consistent with a previously published study demonstrating the relationship between nocturnal oxygen saturation and cardiac architecture in the non-SCD population.[26] Larger longitudinal sleep and cardiac studies are needed to confirm the association of LV abnormalities with oxygen desaturation. Further studies are required to elucidate the role of hemolysis and to determine the relative importance of waking versus sleeping oxygen desaturation on cardiac architecture. The ultimate goal of our future work is to investigate a potential age-related association between oxygen desaturation, LV hypertrophy with diastolic dysfunction, pulmonary hypertension, and SCD-related morbidity, as this may be a target for therapy.[55]

In conclusion, our data provide significant evidence to support the relationship of both asleep and waking oxygen desaturation with increased LV mass and LV diastolic dysfunction in SCD. In addition, we found a link between LV dimension and sleep abnormalities.

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Authorship

Contribution: M.C.J. analyzed the data and wrote the paper; M.R.D. designed the research and wrote the paper; Y.Y. performed the statistical analysis and edited the paper; and C.L.R., S.R., J.G., I.R., J.M., and F.J.K. designed the research, analyzed the data, and edited the paper.

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