The effects of cardio-selective β blockade on diastolic dysfunction in children with sickle cell disease

Among individuals living with sickle cell disease (SCD), diastolic dysfunction (DD) is common (up to 77% of patients) and is associated with exercise intolerance and premature death.[1,2] Increase in the left ventricular filing pressure, a marker of DD, leads to left atrial dilation. This maladaptation progresses to pulmonary venous hypertension and the associated increased tricuspid regurgitant jet velocity (TRV), consistent with the phenotype of restrictive cardiomyopathy. Pulmonary hypertension and TRV elevation are predictors of early mortality in adults with SCD.[3,4] Several mechanisms have been proposed in the development of DD, including microcirculatory dysfunction, myocardial fibrosis, and siderosis.[5,6] There is insufficient evidence to guide the treatment of DD in SCD. β blockers are routinely used in non-SCD patients with heart failure with reduced ejection fraction (HFrEF) and, in some centers, for heart failure with preserved ejection fraction (HFpEF) and DD, a phenotype akin to sickle cardiomyopathy.[7] The primary objective of the present study was to test if diastolic parameters improved after initiation of metoprolol, in children with SCD

This is a parallel cohort study, where all subjects were participants of two prospective cohorts: the Sickle Cell Clinical Research and Intervention Program (SCCRIP) (*clinicaltrials gov. Identifier: NCT02098863*) or the Long-Term Effects of Erythrocyte Lysis (ELYSIS) (*clinicaltrials gov. Identifier: NCT00842621*).[8,9] SCCRIP is a multicenter cohort study, initiated in 2014, that covers ~99% of the actively treated SCD population and evaluates the progression of organ injury over the lifespan of the participating individual.[8] ELYSIS was an observational surveillance study of cardiac abnormalities in SCD, conducted from 2009-2016, which enrolled unbiased patients from the same population as in SCCRIP, excluding those with a history of cardiac surgery, structural heart defects or left ventricular systolic dysfunction.[9] For the current analysis, children enrolled in SCCRIP, ages 5-18 years with presence of any finding of DD on clinically indicated echocardiograms (performed at the discretion of the clinician for presence of cardiopulmonary symptoms or hypertension) were started on the cardiac-selective β blocker metoprolol and included in the metoprolol treatment group. Metoprolol was started orally at a dose of 0.1 mg/kg twice daily and titrated up to a maximum of 2 mg/kg/day or 200 mg/day (mean final dose achieved 0.3 mg/kg twice daily) for chronotropic effect. Because ELYSIS occurred prior to the institutional clinical practice of metoprolol treatment, they served as controls from the same institution population.

For this analysis, age-, and sex-matched untreated controls with echocardiographic findings of DD were selected among the ELYSIS participants and frequency-matched at a 1:1 ratio. As there were no *a priori* sample size calculations based on a specific primary endpoint, these analyses are exploratory. SCCRIP and ELYSIS cohorts are Institutional Review Board-approved, and participants (or their legal guardians) signed informed consent for study participation. This study was in accordance with Declaration of Helsinki.

Complete two-dimensional transthoracic echocardiography was obtained using a Vivid 7 echocardiogram machine with the Echopac picture archive software (GE Medical Systems, Milwaukee, Wisconsin). Measures included early diastolic mitral annulus velocity (e') and the ratio between early mitral inflow velocity and early diastolic mitral annular velocity (E/e') obtained at both the septal and lateral annulus. Left atrial end systolic volume index (LAVi) and left ventricular end diastolic volume (LVIDd) were measured. All measurements were performed according to the American Society of Echocardiography guidelines.[10] A septal or lateral e' velocity <2 standard deviations (SD) for that age range, lateral *or* septal E/e' >2 SD for that age range, or LAVi of >30 mL/m^2 were all considered indicative of DD.[11,12] Laboratory measures (hemoglobin, absolute reticulocyte count, lactate dehydrogenase), and spirometry studies were collected. Among treated participants, vaso-occlusive events (VOE) were collected for the 24 months before and after initiation of metoprolol. Among controls, VOE were collected for the 24 months prior to and after the initial echocardiogram. All study evaluations were obtained at steady state (at least 30 days from an acute illness, hospitalization, or emergent blood transfusion). All laboratory tests were obtained within 7 days of echocardiograms. Individuals on monthly transfusions had all the laboratory and echocardiogram evaluations performed on the same day, but prior to the scheduled blood transfusion.

Chi-squared or Fisher's exact tests compared differences in the distribution of genotype, sex, and disease-modifying therapy between metoprolol users and controls. Two-sample *t*-tests and Wilcoxon rank sum tests compared differences in age, spirometry and VOE. For participants on metoprolol, the baseline values were calculated by averaging all measurements (hematological and echocardiogram) within 6 months prior to starting metoprolol. Duration of metoprolol use for each patient was defined as the period between starting metoprolol and the date

of the last echocardiogram while on metoprolol. Change in all study evaluations from baseline to endpoint were measured using one-sample *t*-tests (for normally distributed variables) and Wilcoxon signed rank (for non-normally distributed variables). Two-sample *t*-tests or Wilcoxon rank sum tests were used to compare changes between metoprolol users and the control group. Linear mixed-effect models were used to assess the associations between metoprolol use and diastolic parameters after adjusting for age, sex, hydroxyurea, and transfusions. For all analyses, false discovery rate (FDR) adjusted *P* values were produced.

This analysis included 42 children with SCD; 21 treated with metoprolol for the presence of any abnormal diastolic parameter (86% with LAVi >30 mL/m^2, 21% with septal E/e' >2 SD, 15% with septal e' <2 SD and 5.2% with lateral E/e' >2 SD) and followed for a mean duration of 14.7±4.8 months. The control group included 21 age- and sex-matched participants, with abnormal diastolic parameters (100% with LAVi >30 mL/m^2, 21% with septal E/e' >2 SD and 5.3% with lateral E/e' >2 SD), who were followed for 24 months.

Most participants were of HbSS genotype and on concomitant disease-modifying therapy (Table 1). Between the two groups, participants in the metoprolol treatment group had a higher number of VOE in the 2 years prior to starting metoprolol compared to controls; however, this was not significant at pFDR 0.35. Furthermore, their

Table 1. Patient characteristics.

	Metoprolol-treatment N=21	Control N=21	pFDR
Baseline age in years (range)	15.33 (6.5-17.83)	14.53 (6.65-17.88)	0.41
Sex, N (%) Male Female	 10 (47.62) 11 (52.38)	 10 (47.62) 11 (52.38)	 >0.99
Genotype, N (%) Hb SS Hb Sβ^{0}thalassemia Hb SC Hb Sβ$^+$thalassemia	 18 (85.71) 1 (4.76) 1 (4.76) 1 (4.76)	 21 (100) 0 (0) 0 (0) 0 (0)	 0.41
History of disease-modifying therapy, N (%) Hydroxyurea Monthly transfusions Both None	 12 (57.14) 4 (19.05) 3 (14.29) 2 (9.52)	 15 (71.43) 5 (23.81) 0 (0) 1 (4.76)	 0.53
Echocardiogram parameters Lateral e', m/s Septal e', m/s Lateral E/e' Septal E/e' LVIDd z score LAVi, mL/m^2 TRV, m/s	 0.19 (0.03) 0.14 (0.03) 6.02 (1.39) 8.37 (1.95) 1.01 (1.58) 39.83 (8.60) 2.30 (0.33)	 0.21 (0.02) 0.15 (0.02) 5.88 (1.19) 8.29 (1.67) 1.97 (1.47) 37.75 (6.52) 2.43 (0.23)	 0.19 0.35 0.91 0.58 0.21 0.48 0.21
Hematological parameters Hemoglobin, g/dL ARC, x10^3/mm^3 LDH, units/L	 8.61 (1.03) 279.87 (105.00) 519.29 (144.23)	 8.87 (1.16) 210.13 (111.13) 587.55 (150.30)	 0.55 0.19 0.41
Spirometry Baseline FEV_1 (% predicted) Baseline FVC (% predicted) Baseline FEV_1/FVC (% predicted)	 95.07 (12.21) 98.00 (10.39) 0.97 (0.04)	 73.33 (4.04) 79.00 (10.54) 0.93 (0.07)	 0.19 0.19 0.53
Number of VOE (pain crisis + ACS)*	1 (0, 13)	0 (0, 5)	0.35

Note: values presented as mean (standard deviation), median (range), or frequency (%) unless otherwise noted. Tests between-group differences were performed using Chi-square or Fishers Exact test for categorical variables and two-sample *t*-tests or Wilcoxon rank sum for continuous variables. e': early annular diastolic velocity; E: early diastolic velocity; LVIDd: left ventricular end-diastolic diameter; LAVi: left atrial volume index; TRV: tricuspid regurgitant velocity; ARC: absolute reticulocyte count; LDH: lactate dehydrogenase; PFT: pulmonary function test; FEV_1: forced expiratory volume at 1 second; FVC: forced vital capacity; VOE: vaso-occlusive episodes; ACS: acute chest syndrome; pFDR: false discovery rate (FDR) adjusted *P* values. *Number of VOE during the 24 months prior to initiation of metoprolol (metoprolol-treatment group) and before baseline echocardiogram (control group). Median and range are reported for the number of VOE.

echocardiographic diastolic parameters, degree of anemia and hemolysis before initiating metoprolol were like the control group (Table 1).

We then compared the change in diastolic and hematological parameters over the study period, between the two groups (metoprolol-treatment *vs.* control) (Table 2). While metoprolol treatment improved LAVi, septal and lateral E/e', this did not maintain at pFDR <0.05. Next, we evaluated the change in these parameters within each group (Table 2). Metoprolol use resulted in significant decrease in mean LAVi (difference =-4.59±6.86, pFDR =0.04), septal E/e' (difference =-1.14±1.43, pFDR=0.02), and lateral E/e' (difference =-0.89±1.22, pFDR =0.04), with no change in hemoglobin or hemolysis markers. However, after adjusting for age, sex, hydroxyurea, and transfusions, the effect of metoprolol on septal E/e', lateral E/e' and LVIDd z-score did not maintain at pFDR <0.05 (*Online Supplementary Table S1*). The decreasing trends in the prevalence of abnormal diastolic parameters with metoprolol treatment are promising but not statistically significant (*Online Supplementary Table S2*). On the other hand, participants in the control group did not see any change in diastolic function or hematological parameters over the observation period.

The safety of metoprolol therapy was evaluated by measuring change in forced expiratory volume (FEV1), FEV1/forced vital capacity (FVC) and frequency of VOE (pain crisis or acute chest syndrome) over the observation period. Metoprolol was well tolerated and was not associated with worsening of FEV1 (mean difference =-0.64±6.39, pFDR =0.8) and FEV1/FVC (mean difference =-0.02±0.03, pFDR =0.28) or increase in VOE (median difference =0; range, -5 to 2, pFDR 0.77) (*Online Supplementary Table S3*).

SCD patients have a unique cardiomyopathy that is predominately characterized by DD but with preserved systolic function. Currently, the literature does not support any definitive treatment strategy for DD in patients with SCD. The non-selective β blocker propranolol has been explored as a potential anti-adhesion agent in SCD and found to reduce sickle red cell adhesion when measured *in vitro*.[13] β blockers are widely used for HFrEF and have been shown to reduce hospitalization and improve survival. Most patients with HFpEF have evidence of DD and

Table 2. Change in diastolic echocardiogram variables and laboratory markers over study period.

		Metoprolol-treatment		Control		Metoprolol-treatment *vs.* control
		Mean change (SD)	pFDR	Mean change (SD)	pFDR	pFDR
Hematological parameters	Hemoglobin, g/dL	0.20 (0.79)	0.40	0.34 (0.77)	0.20	0.86
	ARC, x10^3/mm^3	-21.75 (113.53)	0.49	-6.61 (65.16)	0.80	0.86
	LDH, units/L	-34.63 (124.27)	0.20	-46.95 (124.13)	0.24	0.97
Echocardiographic measurements	Heart Rate, beats/min	-6.85 (14.33)	0.16	-7.00 (13.63)	0.20	0.97
	TRV, m/s	0.05 (0.26)	0.49	-0.11 (0.25)	0.20	0.17
	LVIDd z-score	-0.24 (0.88)	0.18	-0.21 (0.74)	0.38	0.86
	Septal E/e'	-1.14 (1.43)	0.02	-0.01 (1.98)	0.99	0.17
	Lateral E/e'	-0.89 (1.22)	0.03	0.40 (1.57)	0.42	0.08
	LAVi, mL/m^2	-4.59 (6.86)	0.03	1.68 (11.13)	0.68	0.17
	Septal e', m/s	0.00 (0.03)	0.67	-0.16 (2.16)	0.81	0.90
	Lateral e', m/s	0.01 (0.03)	0.40	-1.36 (3.17)	0.20	0.17

Note: values presented as mean (standard deviation). Change in values tested using one-sample *t*-tests or Wilcoxon signed rank tests. ǂTwo-sample *t*-tests or Wilcoxon rank sum tests were used to compare changes between metoprolol-treated and control groups. ARC: absolute reticulocyte count; LDH: lactate dehydrogenase; HR: heart rate; TRV: tricuspid regurgitant velocity; LVIDd: left ventricular end-diastolic diameter; e': early annular diastolic velocity; E: early diastolic velocity; LAVi: left atrial volume index. PFDR: *P* value adjusted by false discovery rate (FDR).

β blockers have been found to be beneficial in this population.[7] One proposed theory is that tachycardia is poorly tolerated in patients with DD as the reduced filling time further increases diastolic filling pressures. β blockers modulate the sympathetic nervous system in the heart by reducing the heart rate and allowing for longer filling times.[7] Additionally, the preventive effect of metoprolol on myocardial fibrosis may contribute to halting the progression of DD.[14]

Our study shows that patients with SCD who were treated with metoprolol, a cardio-selective β blocker, had an improvement in diastolic function with a decrease in LA volume and E/e' (an echocardiographic surrogate for left ventricle filling pressure). Additionally, the hemoglobin level in those treated with metoprolol did not change, indicating that the improvement in diastolic parameters was likely independent from the degree of anemia. Although underpowered to see a change in heart rate, a reduction was observed, but not significant, pointing to additional mechanisms of DD improvement in addition or independent of heart rate modulation. Airway hyperreactivity is prevalent in patients with SCD irrespective of asthma comorbidity.[15] Even though metoprolol is considered cardioselective, as a precaution, none of the patients who were given metoprolol had an asthma diagnosis. Furthermore, treatment with metoprolol did not lead to obstructive respiratory symptoms or increase in VOE. The interpretation of our results is limited by the small sample size, lack of randomization (which did not correct for differences between groups like disease severity and possible mediation of disease-modifying therapies), and a short follow-up period. Our findings are preliminary but indicate potential cardiac benefit of β blocker therapy in SCD to improve DD. Future long-term prospective studies are warranted to confirm our preliminary findings.

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Contributions

PR, JSH, GB wrote the manuscript. GK and VO analyzed the data. NK and JAT critically reviewed the data and edited the manuscript.

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Data-sharing statement

All data generated or analyzed during this study are included in the article and the *Online Supplementary Appendix*. Further inquiries can be directed to the corresponding author.

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