Left Ventricular Rotational Mechanics in Tanzanian Children with Sickle Cell Disease

Michael V. Di Maria, MD, Hao H. Hsu, MD, Ghassan Al-Naami, MD, Jeanine Gruenwald, RDCS, K. Scott Kirby, RDCS, Fenella J. Kirkham, MD, Sharon E. Cox, PhD, and Adel K. Younoszai, MD, *Aurora, Colorado; Omaha, Nebraska; Fort McMurray, Alberta, Canada; London, United Kingdom; and Dar es Salaam, Tanzania*

Background: Sickle cell disease (SCD) is a common inherited hemoglobinopathy. Adults with SCD manifest both systolic and diastolic cardiac dysfunction, though the age of onset of dysfunction has not been defined. Left ventricular (LV) rotational mechanics have not been studied in children with SCD. The aim of this study was to investigate whether cardiac rotational mechanics differed between children with SCD and age-matched controls.

Methods: Basal and apical LV short-axis images were acquired prospectively in 213 patients with SCD (mean age, 14.1 ± 2.6 years) and 49 controls (mean age, 13.3 ± 2.8 years) from the Muhimbili Sickle Cohort in Dar es Salaam, Tanzania. The magnitude of basal and apical rotation, net twist angle, torsion, and untwist rate were obtained by two-dimensional speckle-tracking. The timing of events was normalized to aortic valve closure.

Results: Mean basal rotation was significantly lower in patients with SCD compared with controls (P = .012), although no difference was observed in apical rotation (P = .37). No statistically significant differences in torsion or net twist angle were detected. Rotation rate at the apex (P = .001) and base (P = .0004) were significantly slower in subjects with SCD compared with controls. Mean peak untwisting rate was also significantly slower in patients with SCD (P = .006). No associations were found between hemoglobin concentration and apical rotation, basal rotation, net twist, and torsion.

Conclusion: This study demonstrates alterations in LV rotational mechanics in children with SCD, including lower basal rotation, peak differential twist, and untwist rate. These abnormalities denote subclinical changes in LV systolic and diastolic performance in children with SCD. Future work may reveal an association between rotational metrics and long-term patient outcomes. (J Am Soc Echocardiogr 2015;28:340-6.)

Keywords: Sickle cell disease, Sickle cell disease, Left ventricular torsion, Left ventricular torsion

From the University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, Colorado (M.V.D.-M., J.G., K.S.K., A.K.Y.); the Division of Pediatric Cardiology, Children's Hospital & Medical Center, University of Nebraska Medical Center, Omaha, Nebraska (H.H.H.); Fort McMurray, Alberta, Canada (G.A.); the Department of Neurosciences, UCL Institute of Child Health, London, United Kingdom (F.J.K.); Muhimbili Wellcome Programme, Muhimbili University of Health & Allied Sciences, Dar es Salaam, Tanzania (S.E.C.); and The London School of Hygiene and Tropical Medicine, London, United Kingdom (S.E.C.).

Drs Cox and Younoszai made equal contributions to this work and are co–senior authors.

This research was supported in Tanzania by the Wellcome Trust, United Kingdom: project grant 080025 and strategic award (085438) with support from the Jayden DeLuca Foundation, the Leah Bult Foundation, UL1 RR025780 Colorado Clinical Translational Science Institute, National Center for Research Resources, and National Institutes of Health to support staff time and travel to Tanzania.

Reprint requests: Michael V. Di Maria, MD, The Heart Institute at Children's Hospital Colorado, 13123 E 16th Avenue, Aurora, CO 80045 (E-mail: *michael.dimaria@childrenscolorado.org*).

0894-7317

http://dx.doi.org/10.1016/j.echo.2014.11.014

Sickle cell disease (SCD) is a common hemoglobinopathy, the sequelae of which can be life threatening.[1] Patients with SCD are at risk for left ventricular (LV) systolic dysfunction.[2-6] Previous studies have also demonstrated that this population is also susceptible to diastolic dysfunction,[7-9] and some suggest that this diastolic dysfunction plays a role in the development of pulmonary hypertension.[2,10] One proposed mechanism for the development of cardiac dysfunction is microvascular occlusion in the coronary circulation as a result of red blood cell sickling, resulting in chronic, indolent myocardial ischemia.[11] In addition, chronic anemia leads to a high cardiac output state and LV volume overload. Over time, this may cause LV dilation, which may also adversely affect LV function.

Conventional echocardiographic measures of LV function, such as shortening fraction and ejection fraction, have not been demonstrably different when patients with SCD and unaffected individuals have been compared[7,10]; however, decreased LV peak systolic strain in subjects with SCD suggests that conventional methods of evaluating LV function by measuring chamber size, such as shortening fraction, are not precise enough to detect early dysfunction.[10] LV rotation, net twist angle (twist), and torsion, a means of quantifying the rotational movement of the myocardium during systole,[12] have been studied in other disease states and have

Abbreviations
Hb = Hemoglobin
LV = Left ventricular
MSC = Muhimbili Sickle Cohort
SCD = Sickle cell disease

demonstrated an early decline in LV systolic performance.[13-15] LV torsion has not been previously studied in pediatric patients with SCD. We hypothesized that there would be significant differences in rotational metrics between individuals with SCD and healthy age-matched controls. The aim of this study was to evaluate cardiac rotational mechanics in patients with SCD, compared with age-matched, unaffected control subjects.

METHODS

A nested case-control study was undertaken, including study participants with SCD and unaffected control patients from the Muhimbili Sickle Cohort (MSC) in Dar es Salaam, Tanzania.

Study Population

Cases were recruited prospectively from patients enrolled in the MSC and controls from children who had attended the clinic for sickle screening and were determined not to have SCD. Inclusion criteria included age between 9 and 19 years and, for patients with SCD, sickle status confirmed by hemoglobin (Hb) electrophoresis and high-performance liquid chromatography, while controls without SCD had the HbAS or HbAA phenotype by electrophoresis. Blood pressure was measured twice after 5 min of rest using an automated digital device (PRO 400 V2 Dinamap; GE Healthcare, Little Chalfont, United Kingdom) and the mean calculated. Axial temperature, height, and weight were recorded, and a clinical examination was performed to exclude acute complications. Exclusion criteria included history of blood transfusion within the previous 2 months, symptoms of sickle crisis within the previous 2 weeks, febrile illness within the 7 days before echocardiography, fever or signs of acute illness on the day of echocardiography, and known or echocardiographically identified hemodynamically significant congenital heart disease.

The study was approved in the institutional review board of Children's Hospital Colorado (Reference No. COMIRB protocol #10-0030) and by the Muhimbili University of Health & Allied Sciences Research and Publications Committee (Reference No. MU/RP/AEC/Vol.XIIV/01). Written informed consent was obtained from all study participants.

Definitions

Rotation was defined as circumferential myocardial motion around the centroid, or long axis, of the ventricle.[12] By convention, rotation is said to be positive in the counterclockwise direction when viewed from the apex of the left ventricle and vice versa. As depicted in Figure 1, a basal short-axis plane used to determine twist was obtained just below the mitral valve annulus, where muscle appears in the plane of insonation throughout the cardiac cycle. The apical short-axis plane used was defined as a short-axis plane just above the apex, where the LV lumen can be seen throughout the cardiac cycle. Net twist angle was defined as the instantaneous difference in rotation between the apex and the base at the time of aortic valve closure, or end-systole.[12] Peak differential twist is the maximum difference in rotation between the apex and base, independent of time. Torsion was defined as net twist divided by the length of the left ventricle at end-diastole to account for heart size. Untwisting is defined as the difference between apical recoil and basal recoil. The timing of these events is described both in milliseconds and as a percentage of systole, with the onset of systole defined as the initial deflection of the Q wave on the surface electrocardiogram and end-systole defined as aortic valve closure.

Echocardiography

For each patient, measurements of LV chamber size and fractional shortening were made from short-axis basal images. From the apical window, LV peak systolic mitral annular velocity (LV S′), LV peak early diastolic mitral annular velocity (LV E′), early diastolic mitral inflow (LV E), duration of late diastolic mitral inflow (mitral valve a-wave duration), and duration of the late diastolic a wave in pulmonary vein inflow (pulmonary vein a-wave duration) were made. The LV myocardial performance index was also calculated from mitral inflow and aortic outflow spectral Doppler patterns.[16]

Short-axis images of the base and apex of the left ventricle were obtained using the VividQ platform (GE Healthcare) and an M4S, 5S, or 7S probe, depending on patient characteristics and image quality. Frame rates of >75 and <125 frames/sec were accepted. An acquisition of five consecutive beats was obtained. An apical view was also obtained for the purposes of measuring end-diastolic LV length and performing spectral Doppler measurement of mitral inflow and aortic outflow. End-diastolic LV length was measured from the apical four-chamber view as the distance from the mitral valve to the apex of the left ventricle.

Commercially available software (EchoPAC version 113, revision 0.4; GE Healthcare) was used to perform speckle-tracking analysis. A single cardiac cycle was isolated for the base, and a region of interest was identified. The magnitude and timing of basal rotation was calculated. The process was repeated for the short-axis apical image. Net twist was calculated as the difference between apical and basal rotation. Torsion was calculated by dividing the net twist by LV end-diastolic length. This process was repeated two additional times and an average over three cardiac cycles was calculated.

Laboratory Data

Hb phenotype was determined by alkaline Hb electrophoresis (Helena; Sunderland, United Kingdom) and by quantification of Hb fractions, including HbF, by high-performance liquid chromatography (β-Thalassemia Short Program, VARIANT analyzer; BioRad, Hercules, CA). In subjects with SCD, the most recent steady-state Hb, total bilirubin, conjugated bilirubin, and lactate dehydrogenase levels were obtained from MSC records (steady state defined as absence of pain or fever, malaria rapid test negative, and with no recorded hospital admission or blood transfusion within 30 days). Full blood counts were performed using an automated cell counter (Pentra 60; Horiba ABX, Kyoto, Japan). Biochemical tests were performed using an automated chemistry analyzer (Cobas Mira [Roche, New York, NY] or Abbott Architect [Abbott Diagnostics, New York, NY]).

Statistical Analysis

SAS version 9.2 (SAS Institute Inc, Cary, NC) was used to perform statistical analyses. Continuous variables are presented as mean ± SD or median (interquartile range), and categorical variables are presented as proportions. The Student independent two-sample *t* test was used to compare mean values between two patient groups. Simple linear regression was used to evaluate associations between independent variables and a continuous, dependent variable. Pearson