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Developing Cardiac Screening Guidelines for Children with Sickle Cell Disease

A. Study Purpose and Rationale

Sickle cell disease (SCD) is a genetic erythrocyte disorder that affects multiple organ systems[1]. It is well known that cardiac changes are common in patients with SCD. Multiple reports have documented increased left ventricular mass[2–5], increased left ventricular dimensions in both systole and diastole[6] and echocardiographic findings of elevated right sided pressures (pulmonary hypertension) as measured by elevated tricuspid regurgitant jet velocity (TRV))[2,7–11]. Although these changes are well documented, the clinical significance and prognosis of these findings in the pediatric population is unclear. In adults, increased right heart pressures and diastolic dysfunction[12] are of poor prognostic significance and associated with increased mortality[13]

Increased cardiac mass and dimensions are in large part attributed to the long standing anemia that is present in SCD patients and the resultant development of a high output cardiac state[3,6,14]. There is still a lot of debate about whether this state leads to abnormal systolic and/or diastolic function in pediatric patients with SCD. Several groups have reported abnormal systolic and diastolic function indexes[2,4,15], while others have shown normal ventricular function despite dilation[6,16,17].

The reported prevalence of elevated TRV in pediatric patients with SCD is variable. It ranges from less than 10%[2,18], to as high as 30%[5,7,15,19], almost the same prevalence as in the adult SCD population. The pathogenesis and clinical significance of an increased right heart pressures is also uncertain in the pediatric population. The definitive way to diagnose pulmonary hypertension is by cardiac catheterization showing an elevated pulmonary artery pressure. However, this measurement does not give an idea of ambulatory pressures as catheterization in children is performed under anesthesia and reflect the pressures in deep sleep. Since this is not routinely done in the pediatric population, many groups have started to use an elevated TRV by Doppler echocardiography as a marker of pulmonary hypertension. However, not all patients have tricuspid regurgitation,sufficient to measure a gradient, this measurement may not be possible in a good proportion of patients.

Many groups believe that the chronic hemolysis in SCD leads to scavenging of NO in the pulmonary vasculature, resulting in an increase in pulmonary vascular resistance[7,20], and eventually pulmonary hypertension. However, other groups disagree and argue the elevated RV pressures are caused by RV diastolic dysfunction secondary to the increased cardiac output[2,9] without the presence of increased pulmonary vascular resistance and, by extension, do not believe the elevated TRV is a marker of pulmonary hypertension. I would omit this paragraph

In addition, the reported prevalence of elevated TRV in pediatric patients with SCD is very variable. It ranges from less than 10%[2,18], to as high as 30%[5,7,15,19], almost the same prevalence as in the adult SCD population. The prevalence largely depends on the cutoff used to define an elevated TRV, and whether or not the patients were in a stable disease state at the time of their echocardiogram. I would omit this paragraph. Reports on prevalence were mostly consistently using a cut-off of at least 2.5 m/sec based on the landmark study in adults by Gladwin et al. and using echocardiogram performed at steady-state.

Although many of the published pediatric studies are conflicting in regards to the clinical and prognostic significance of the cardiac abnormalities in sickle cell disease, several prospective studies in adult patients with SCD have shown that the development of diastolic dysfunction and elevated TRV are both independent risk factors for increased mortality[12,13]. Since this is well known in adult patients, early detection of these cardiac abnormalities in pediatric patients may provide an opportunity for early treatment to prevent an increased mortality in adulthood. There are, however, currently no definitive guidelines for screening cardiac disease in pediatric patients with SCD, and the risk factors for the development of cardiac complications are not well defined.

One of the major limitations in the current literature describing cardiac abnormalities in children with SCD is the lack of longitudinal studies looking at cardiac changes over time. Most studies to date have only looked at echocardiogram findings at a single point in time across a range of patient ages. Hagar et al.[8] performed a retrospective chart review of pediatric SCD patients followed at Oakland's Children's Hospital. However, since annual screenings were not being performed, only 57% of their subjects had ever received an echocardiogram, and it was unclear whether they were screened during a disease exacerbation or at steady disease state. Covitz et al.[17] reported on the pediatric cardiac outcomes from the Cooperative Sickle Cell Disease Study, the largest comprehensive sickle cell trial to date. However, the mean age of the pediatric patients was 25.9±8.8 years, and only a single echocardiogram was performed on each patient. Finally, the largest and most recent prospective study, performed by Dham and colleagues[9], was NIH supported and multi-institutional, but investigated each child at only one point in time with a single echocardiogram. I am sending you an early paper by the Cooperative study of SCD that reported cardiac abnormalities by echo in SCD; it's a very well-designed study, but again done cross-sectionally, but analyzed the changes at different age groups and in a more homogeneous population – ie only SS patients.

Since participation in the Cooperative Study of Sickle Cell Disease (CSSCD) in the early 1990's , our institution has begun performing annual to bi-annual echocardiograms on our pediatric sickle cell population beginning at the age of five years. This puts our institution at a unique advantage to perform an analysis of serially performed echocardiograms in a single patient population over several

years. By performing a retrospective, longitudinal chart review we are hoping to be able to better characterize the cardiac changes that are seen in pediatric sickle cell patients. We plan to retrospectively look at serial changes in left and right heart parameters in a cohort of SCD patients that have been followed in our clinic, and to correlate these findings with changes in treatment modalities, specifically chronic transfusion and hydroxyurea theray, and patient characteristics over time. This will yield information about the prevalence of the various cardiac abnormalities that are seen at different ages, and the incidence of progression of cardiac changes over time in a single patient population.

Our long-term goal is to be able to develop screening guidelines for cardiac abnormalities in sickle cell disease. We expect to be able to determine whether annual cardiac screening beginning at age 5 is adequate to capture most children before they begin to develop cardiac abnormalities, or if screenings should begin earlier. We also hope to better define risk factors for the development of cardiac abnormalities among pediatric sickle cell disease patients, which would allow practitioners to risk-categorize patients who may require early echocardiograms.

Specific Aims:
The long-term outcome of this study is to establish cardiac screening guidelines for pediatric SCD patients. This will be accomplished with the following aims:

AIM 1: To describe the prevalence of cardiac abnormalities (increased left and right ventricular mass, ventricular dilation, systolic dysfunction, diastolic dysfunction, and elevated right sided pressures) in the cohort of SCD patients followed in our clinics in an age-stratified manner.

AIM 2: To describe the serial changes in left and right-sided heart parameters in the cohort of pediatric SCD patients with multiple echocardiograms followed in our clinics.

AIM 3: To identify risk factors for the development of cardiac abnormalities by correlating our findings with changes in treatment modality and clinical variables.

Hypothesis:
Serial changes over-time will be detected in the left and right heart parameters in children with sickle cell disease, and that these changes will be correlated with clinical variables. We hypothesize that there will be progression of cardiac abnormalities, in both right and left parameters, in children with sickle cell disease, and that these will be associated with severity and duration of the disease.

B. Study Design and Statistical Analysis

This will be a single center retrospective chart review of children cared for at the Comprehensive Sickle Cell Center at the CUMC. We will conduct a chart review of all patients aged 1-21 who have had at least one lifetime echocardiogram performed at steady disease state at our medical center dating back to 1997.

For each patient identified, we will collect the following data: demographics (age, gender, sickle cell type), parameters of hemolysis (hemoglobin and reticulocyte count, LDH, transfusion history, bilirubin levels, oxygen saturation at rest), treatment parameters (Hgb F levels, timing and length of treatment with hydroxyurea, if any, whether or not the patient is on a chronic transfusion protocol), disease history (lifetime admissions for ACS, pain crises, sepsis, stroke), presence of co-morbid disease (asthma, obstructive sleep apnea etc).

Each patient's echocardiogram report(s) will be reviewed in the EMR. In addition, the recorded echocardiogram studies will be reviewed independently by two cardiologists. The cardiologists will be blinded to the patient characteristics when performing the echocardiogram analysis. We will look at both left and right sided parameters, such as ventricular dimensions and mass. All parameters will be corrected for body surface area when appropriate. LV hypertrophy will be defined as LV mass/volume index > 1.15g/ml. We will calculate Z scores (LV dilation will be defined as z-value > 2), stroke volume, and cardiac output and we will assess the TRV (elevated TRV will be defined as > 2.5m/s). We will assess LV systolic function by calculating the shortening fraction (considered abnormal if < 30%) and ejection fraction and we will assess diastolic function by measuring the mitral inflow velocities and calculating the E/A ratio.

Results will be expressed as mean ± SD and will be compared between groups using ANOVA. In a multivariate analysis, a logistic regression will be used to assess the relationship between the echocardiogram parameters and clinical variables. A p-value less than 0.05 will be considered significant.

C. Study Procedure.
Not applicable.

D. Study Drugs.
Not applicable.

E. Medical Device.
Not applicable

F. Study Questionnaires.
Not applicable

G. Study Subjects.
Children followed at our Comprehensive Sickle Cell Center whom have had at least one echocardiogram performed.

H. Recruitment of Subjects.
Not applicable.

I. Confidentiality of Study Data.
The patient data will be stored on encrypted, password-protected computers that may only be accessed by the study investigators.

J.Potential Conflict of Interest.
None.

K. Location of the Study.
Not applicable.

L. Potential Risks.
Since this study is a retrospective chart review there is minimal potential risk to the patient. The only foreseeable risk is the loss of confidentiality of patient data. This risk is being minimized by the previously described measures.

M. Potential Benefits
The potential benefit from this study is the development of screening parameters for cardiac abnormalities in pediatric sickle cell disease patients. This study will help to identify risk factors for developing cardiac abnormalities and will help guide practitioners about the timing and frequency of cardiac screening.

N. Alternative Therapies
None.

O. Compensation to Subjects.
None

P. Costs to Subjects.
None.

Q. Minors as Research Subjects.
Not applicable.

R. Radiation or Radioactive Substances.
Not applicable.

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