Cardiac Fibrosis in Sickle Cell Anemia Using MRI T1 Cardiac Mapping

A Thesis

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بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

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Amany Bedier El Sayed Ismail

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List of Abbreviations

Abbr.	Full-term
4 CH	**:** Four chamber
99Tc-MDP	**:** Technetium 99m-methyl diphosphonate
ACEI	**:** Angiotensin-converting enzyme inhibitors
ACS	: Acute chest syndrome
AHA	: American Heart Association
ALP	**:** Alkaline phosphatase
ASS	**:** Acute splenic sequestration
AUB	**:** Abnormal uterine bleeding
AVN	**:** Avascular necrosis
BB	**:** Black blood
CE	**:** Contrast enhanced
CMR	**:** Cardiac magnatic resonance
CVD	**:** Coronary vascular disease
CVF	**:** Collagen volume fraction
DM	**:** Diabetes mellitus
DNMT	**:** DNA methyltransferase
ECG	**:** Electrocardiogram
ECV	**:** Extracellular volume
eDAMPs	**:** Erythrocyte damage-associated molecular patterns.
EMB	**:** Endomyocardial biopsy
FA	**:** Flip angle

Fast SSh : Fast Single shot scan
FFE : Fast field echo
FOV : Field of view
FSE : Fast spin echo
GBCA : Gadolinium-based contrast agents
GRE : Gradient echo
HB A : Hemoglobin A
HB A_2 : Hemoglobin A_2
HB F : Hemoglobin F
HB S : Hemoglobin S
HBV : Hepatitis B virus
HCV : Hepatitis C virus
HJB : Howell-Jolly bodies
HPLC : High performance liquid chromatography
HRCT : High resolution CT scan
HS : Hyperhemolysis syndrome
HSCT : Hematopoietic stem cell transplantation
HU : Hydroxyurea
ICAM-4 : Intercellular-adhesion-molecule-4
IEF : Isoelectric focusing
Ip : Isoelectric points
LDH : Lactic dehydrogenase
LGE : Late Gadolinium Enhancement
LL : Look-Locker
LV : Left ventricle

MI : Myocardial infarction
MIC : Myocardial iron concentration
MOLLI : Modified Look-Locker
MRI : Myocardial iron
MTEF : Multiecho turbo field echo
NO : Nitric oxide
NSAIDs : Non-steroidal anti-inflammatory drugs.
PAH : Pulmonary arterial hypertension
PAP : Pulmonary artery pressure
PASP : Pulmonary artery systolic pressure
Pcv : Packed cell volume
PCWP : Pulmonary capillary wedge pressure
PH : Pulmonary hypertension
PS : Phosphatidyl serine
PVH : Pulmonary venous hypertension
RBC : Red blood cell
ROI : Region of interest
ROS : Reactive oxygen species
RR : Ribonucleotide reductase
SA : Short axis
SCA : Sickle cell anemia
SCD : Sickle cell disease
SCMR : Society for Cardiovascular Magnetic Resonance
Sh-MOLLI : Shortened-MOLLI
SSFP : Steady-state free precession

ST **:** Section thickness

TCD **:** Transcranial Doppler

TI **:** Invertion time

TR **:** Repetition time

TRV : Tricuspid regurgetant jet velocity

VLA **:** Vertical long axis

WBCs **:** White blood cell

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Abstract

Background: Several studies conducted in the last two decades have identified cardiac risk factors for early mortality in sickle cell anemia (SCA) including diastolic dysfunction and pulmonary hypertension. Most of these studies are echocardiographic studies and have focused primarily on pulmonary hypertension and pulmonary vascular pathology. The use of cardiac magnetic resonance (CMR) has been limited to quantifying myocardial iron in transfusion dependent SCA patients. More recently, CMR studies in SCA have shed new light on myocardial tissue characteristics that could be reflect cardiac pathology in SCA.

Aims: Our aim was to use of MRI T1 cardiac mapping to detect diffuse myocardial fibrosis by measuring Extracellular volume fraction (ECV) in patients with SCA.

Methods: Participants with SCA were enrolled in cross sectional CMR study to characterize SCA-related cardiac fibrosis.

Results: Twenty patients with SCA (9 HbSS and 11 HbSβ0-thalassemia) were enrolled, their age ranging from 7 to 29 years; 55% were male and median (IQR) of Hg S (%) was 63.5 (50.7-87.2). ECV and native T1 values were increased in 14 (70%) patients with SCA indicating the presence of diffuse myocardial fibrosis with equal distribution between patients with HbSS and HbSβ0- thalassemia. Significantly older age in patients with diffuse myocardial fibrosis was observed (p=0.013) with no gender predilection. There was no significant difference between patients who had cardiac fibrosis and those who had not regarding median (IQR) of serum ferritin (ng/ml) (1080 (107.3-1540), 1489 (950-1994) respectively) (P=0.375).Cardiac LV quantitative iron assessment (T2* value) was less than 20 ms in 6 (30%) patients indicating the presence of cardiac iron overload. ECV was significantly associated with the number of acute transfusions (r = 0.618 and P =.04) but no correlation was detected between ECV and Hg S %, serum ferritin or cardiac MRI T2*values.

Conclusion: In this cohort of SCA patients, we found that diffuse myocardial fibrosis was a common feature that appears to predate the development of diastolic dysfunction. The inherent features of the cardiomyopathy of SCD make CMR an excellent tool to study cardiac disease in SCD due to its ability to detect and quantify myocardial tissue characteristics, without the need for tissue biopsy, including T2* for iron deposition, T1 mapping for myocardial fibrosis which allow for a better assessment of intrinsic myocardial changes that may have functional and prognostic implications in SCD.

Keywords: Sickle anemia, Children, Cardiac CMR, Myocardial fibrosis

Introduction

Sickle cell anemia (SCA) results from a point mutation in theβ globin gene and affects millions world-wide. It is characterized- by production of the mutant hemoglobin S (HbS), which polymerizes upon deoxygenation and distorts the shape of RBCs, increasing their propensity to hemolysis and microvascular occlusion. Recurrent cycles of HbS polymerization result in a host of acute and chronic complications, including vaso-occlusive pain crisis, chronic hemolytic anemia, and organ damage ***(Quinn et al., 2004).***

All body organs can be affected in sickle cell disease. Mortality from cardiopulmonary causes has become the most prevalent cause of death. While the specific etiology of cardiac death remains unclear ***(Bakeer et al., 2016)***.

We recently demonstrated that diffuse myocardial fibrosis is a common and novel mechanism of heart disease in sickle cell anemia (SCA) that is strongly associated with diastolic dysfunction. Diffuse myocardial fibrosis can be detected noninvasively by cardiac magnetic resonance imaging ***(Quinn et al., 2017)***.

Several studies conducted in the last two decades have identified cardiac risk factors for early mortality in SCD including diastolic dysfunction and pulmonary hypertension.