Elevated transpulmonary gradient and cardiac magnetic resonance-derived right ventricular remodeling predict poor outcomes in sickle cell disease

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Online Supplementary Appendix

Supplemental Methods

Patient Recruitment

Detailed patient enrollment criteria of the Bethesda Sickle Cell Cohort (ClinicalTrials.gov identifiers NCT00011648, NCT00081523, NCT00023296, and NCT00352430) have been previously described[1]. Briefly, consecutive patients (age ≥18 years) with suspected SCD were prospectively recruited from 2002-2010 from the National Institutes of Health (NIH) and Howard University and were screened using echocardiography. SCD was confirmed in 524 subjects using high performance liquid chromatography. A right heart catheterization (RHC) was offered if the patient returned to clinic after the initial screening echocardiogram, agreed to see an NIH pulmonologist, and (1) had a tricuspid regurgitant (TR) jet ≥2.8 m/s and a 6-minute walk distance (6-MWD) <500 meters or (2) a TR jet ≥2.5 m/s with unexplained symptoms of dyspnea or oxygen desaturation. Of those who agreed to undergo RHC, a CMR study was offered (Supplemental Figure 1). The investigation conforms with the principles outlined in the Declaration of Helsinki and was approved by the NIH Institutional Review Board. All patients provided written informed consent.

Right Heart Catheterization

Cardiac output (CO), right atrial, RV, pulmonary artery, and pulmonary wedge pressures (PAWP) were measured under local anesthesia. Supplemental

inspired oxygen was not used except in cases of desaturation during RHC measurements. All other hemodynamic parameters were calculated using standard formulas.[2] Specifically, the TPG, PVR, left ventricular (LV) stroke work index (SWI), RV SWI were calculated according to the following formulas: *TPG (mmHg) = mPAP-PAWP*; $PVR = \frac{mPAP-PAWP}{CO}$; *LV SWI = (MAP-PAWP) x SVI x 0.0136; RV SWI = (mPAP-CVP) x SVI x 0.0136* where CVP=central venous pressure, dPAP=diastolic pulmonary artery pressure, SVI=stroke volume index, and MAP=mean arterial pressure. Pulmonary vascular capacitance, which reflects the ability of the pulmonary vasculature to dilate and recoil during systole and diastole, respectively, was calculated as the ratio of stroke volume to pulmonary pulse pressure.[3]

Image Acquisition

CMR was performed using a 1.5 Tesla imaging system (General Electric (GE) Health (n=24), New York, USA, or Siemens Medical Solution (n=17), Erlangen, Germany). Cine images were acquired using a steady-state free precession sequence (typical parameters GE: TR 3.6ms, TE 1.6ms, flip angle 40-50º, voxel size FOV 280 x 280mm, slice thickness 8mm, acquisition matrix 160 x 192, bandwidth 977Hz/pixel; Siemens: TR 4.38ms, TE 1.4ms, flip angle 50º, FOV 270 x 360mm, slice thickness 6mm, acquisition matrix 144 x 256, iPAT 2-3, bandwidth 930Hz/pixel). In those who gave consent for contrast administration (n=20), gadopentetate dimeglumine (Magnevist, Bayer HealthCare, Wayne, NJ) 0.2 mmol/kg body weight was given at 5mL/sec 10 minutes prior to

acquisition of late gadolinium enhancement images. A phase sensitive inversion recovery spoiled gradient recalled echo sequence was used for late gadolinium enhancement imaging (typical parameters GE: TR 6.5ms, TE 3.2ms, TI nulled for individual myocardium, flip angle 20º, FOV 360 x 360mm, slice thickness 8mm, acquisition matrix 128 x 256, bandwidth 244Hz/pixel; Siemens: TR 700ms, TE 4.2ms, TI nulled for individual myocardium, flip angle 25º, FOV 270 x 360mm, slice thickness 6mm, acquisition matrix 125 x 256, iPAT 2-3, bandwidth 140Hz/pixel).

Image Analysis

Investigators blinded to the hemodynamic data analyzed the images using a commercial workstation (Siemens, Erlangen, Germany). End-systolic and end-diastolic LV and RV volumes, masses, and ejection fraction were calculated using cine short axis slices.[4, 5] Markers suggestive of RV remodeling including eccentricity index,[6] septal-to-LV free wall curvature ratio,[7] septomarginal trabecular (SMT) mass index,[8] and ventricular mass index (ratio of RV mass to LV mass at end-diastole)[8] were measured as previously described. Ventricular mass was calculated by multiplying myocardial tissue density (1.05 gm/cm^3) by the myocardial volume. Late gadolinium enhancement (LGE) at the right ventricular insertion point (RVIP) of the interventricular septum was considered to be present if the signal intensity at the RVIP was equal to or greater than the ventricular blood pool on two consecutive short axis slices.

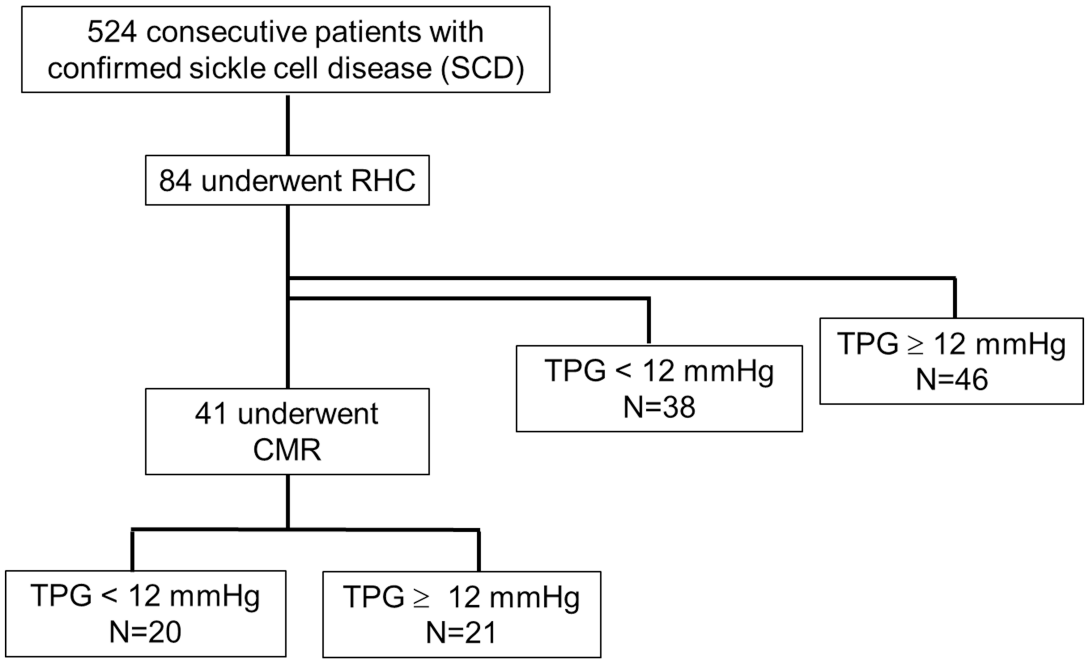
Statistical analysis

A Cox proportional hazard analysis was performed to assess the association between CMR measurements and mortality. Logistic regression analyses were performed to examine the association between CMR measurements and World Health Organization / New York Heart Association (WHO/NYHA) class III-IV symptoms, mPAP ≥25mmHg, and 6-MWD < 400 meters. Although we recruited subjects with a 6-MWD < 500 meters, a 6-MWD value of <400 meters was chosen because the normal range has been reported to be between 400-700 meters[9]. Performance of logistic regression and Cox regression models was assessed using the area under the receiver operating characteristics curve (AUC)[10] and the c-statistic,[11] respectively. Event-free survival curves were obtained using the Kaplan-Meier method and compared by means of the log-rank test. A two-tailed p value <0.05 was considered significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Supplemental Table 1. Composition of Sickle Cell Patients with Normal vs Elevated Transpulmonary Gradient.

		Number of patients
TPG < 12 mmHg (n= 38)	mPAP ≥ 25	13
	mPAP ≥ 25, PAWP ≤ 15 mmHg	4
	mPAP ≥ 25, PAWP > 15 mmHg	9
	mPAP ≥ 25, PAWP ≤ 15 mmHg, PVR ≥ 3 Woods unit	0
	mPAP < 25	25
	mPAP < 25, PAWP ≤ 15 mmHg	22
	mPAP < 25, PAWP > 15 mmHg	3
	20 < mPAP < 25 mmHg	12
	mPAP ≤ 20 mmHg	13
TPG ≥ 12 mmHg (n=46)	mPAP ≥ 25	42
	mPAP ≥ 25, PAWP ≤ 15 mmHg	27
	mPAP ≥ 25, PAWP > 15 mmHg	15
	mPAP ≥ 25, PVR ≥ 3 Woods unit	21
	mPAP ≥ 25, PAWP ≤ 15 mmHg, PVR ≥ 3 Woods unit	16
	mPAP < 25	4
	mPAP < 25, PAWP ≤ 15 mmHg	4
	mPAP < 25, PAWP > 15 mmHg	0
	20 < mPAP < 25 mmHg	3
	mPAP ≤ 20 mmHg	1
*mPAP=mean pulmonary artery pressure; PAWP=pulmonary artery wedge pressure; PVR=pulmonary vascular resistance; TPG=transpulmonary gradient		

Supplemental Figure 1. Recruitment and Categorization of Patients with Sickle Cell Disease. CMR=cardiac magnetic resonance imaging; RHC=right heart catheterization; SCD=sickle cell disease; TPG=transpulmonary gradient



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