Myocardial injury and coronary microvascular disease in sickle cell disease

Myocardial infarction and microvascular ischemic damage in the heart are one of the least well-described entities in the sickle cell disease (SCD) spectrum.[1] Over the last few decades, some autopsy studies and case reports have described myocardial infarction without obstructive coronary artery disease suggesting microvascular ischemic injury in SCD patients.[2] Impaired myocardial perfusion reserve in SCD has been demonstrated using different modalities including contrast echocardiography, nuclear myocardial perfusion scans, single-photon emission computerized tomography (SPECT) as well as cardiac magnetic resonance imaging (MRI).[3] During a state of physiological stress or acute crisis, it can lead to myocardial injury which can be detected by serum troponin measurement. The role of troponin in microvascular disease in sickle cell disease has not been well defined. troponin-I was elevated (>0.4 ng/mL) in two of 32 patients 24 hours after the onset of acute crisis, with chest pain and electrocardiogram findings of sinus tachycardia and non-specific ST-T wave changes.[4] In another study of six patients, troponin-T was normal 24 hours after admission for a sickle cell crisis in all patients.[5]

Cardiac magnetic resonance (CMR) is a non-invasive diagnostic tool that can be used for myocardial tissue characterization and assessment of coronary microvascular disease (CMD).[6] Due to high spatial resolution with first-pass perfusion imaging, it can visualize diffuse subendocardial perfusion abnormality resulting from CMD during the administration of a vasodilating drug such as adenosine.[7] Late gadolinium enhancement (LGE) imaging visualizes decreased clearance of gadolinium-based contrast agents from the extracellular space in areas of damaged myocardium. LGE has become the *in vivo* gold standard for visualization of myocardial injury from a variety of causes;[8] subendocardial enhancement indicates an ischemic injury, whereas midwall enhancement indicates fibrosis of non-ischemic myocardial disease and epicardial enhancement is consistent with inflammatory damage.[9] Our study aims to estimate the prevalence of myocardial injury defined by elevated troponin-I levels. We will also define the prevalence of coronary microvascular disease and other myocardial abnormalities in an SCD cohort clinically referred for cardiac MRI.

We conducted a retrospective study of the SCD patients seen at The Ohio State University Wexner Medical Center over a period of 10 years from July 2005 to July 2015. Patients age 18 years or above, with troponin-I level elevation (level >0.11 ng/mL) and/or cardiac MRI were included in the initial cohort. Coronary microvascular disease (CMD) on CMR was defined by the presence of either subendocardial damage by LGE or impaired myocardial perfusion by adenosine stress perfusion imaging. All other abnormalities were categorized as non-CMD due to a lack of specificity. Clinical and laboratory variables closest to the peak troponin elevation and cardiac MRI were recorded, if available within 4 weeks. For all patients with troponin level measurement and cardiac MRI, the date of death confirmed by chart review by June 2019 was recorded.

Out of 373 SCD patients, 69 had either troponin level measurement or cardiac MRI, or both done. The median age was 34 years (range, 19-67 years) with 30% of patients over the age of 40 years. Thirty-four (49%) patients were female. Seventy-five percent of the patients were hemoglobin (Hb) SS, and the rest 25% were other genotypes (SC 15%, S-βthal 9%). Median baseline Hb (defined by Hb level at a steady-state within the preceding year) was 8.0 g/dL (range, 4.5-13 g/dL) and median current Hb at the time of the event (either troponin ele-
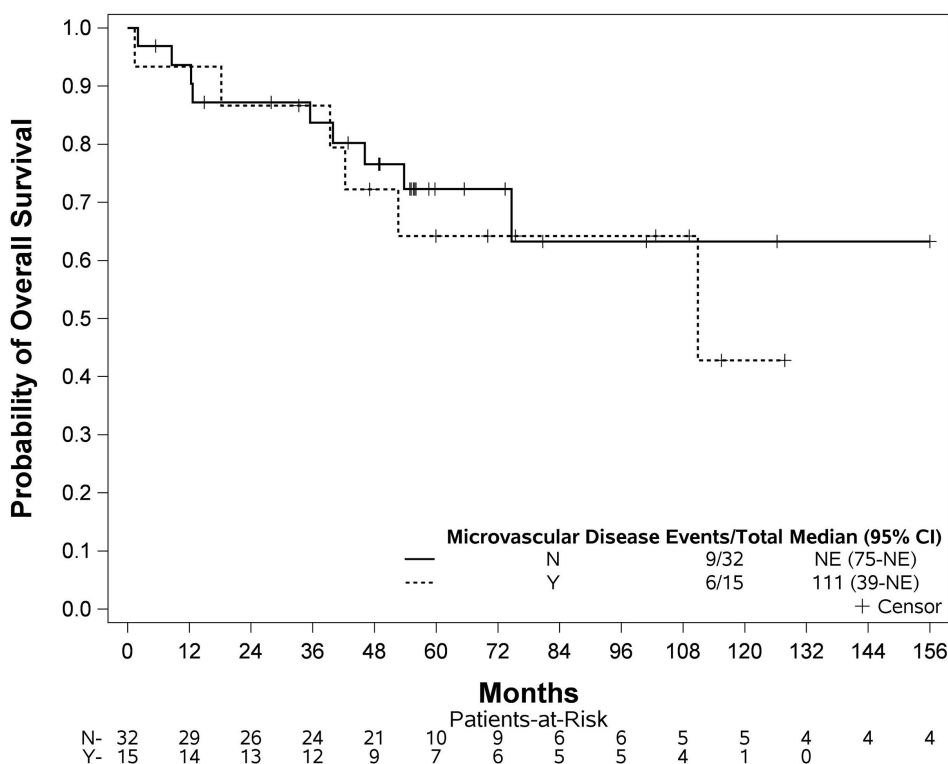

Figure 1. Overall survival comparison between coronary microvascular disease and non-CMD group. CI: Confidence Interval; Y: CMD present; N: no CMD; NE: not estimable.

vation or cardiac MRI) was 7.6 g/dL (2.9-12.6 g/dL). Only 5 (7.2%) patients had a history of diabetes mellitus and (8.6%) patients had a family history of myocardial infarction. A majority of these patients (n=57, 83%) had a history of acute chest syndrome (ACS) (Table 1).

Median initial troponin level was 0.14 ng/dL (range, 0.01-38.09) and peak troponin of 0.44 ng/dL (range, 0.01-19.97). Patients with troponin elevation were more likely to have acute chest syndrome (40% *vs.* 10%; *P*=0.02) and acute kidney injury (0% *vs.* 18%; *P*=0.0002). There was no difference in median Hb in both groups; however, the troponin elevation group tended to have lower platelet count (272 *vs.* 165 K/uL, *P*=0.007), higher lactate dehydrogenase (LDH) level (392 *vs.* 498 U/L, *P*=0.37) (Table 2). In an expanded cohort of 239 patients with troponin measurement, 42 (18%) had elevated troponin-I at one or multiple instances. Troponin elevation significantly increased the likelihood of death with a hazard ratio of 2.6 (95% Confidence Interval [CI]: 1.4-4.9; *P*=0.0003).

There were 47 patients with cardiac MRI performed over the 10-year period for various indications, most common being chest pain and/or troponin elevation (n=26) and iron overload. CMD was present in 15 patients (32%), only five patients had normal CMR and the rest of them had other non-ischemic findings. There was no statistically significant difference between the CMD and non-CMD groups in terms of baseline characteristics, clinical or laboratory variables (Table 2). Cardiac catheterization showed no epicardial vessel obstruction in eight patients, one patient had triple vessel disease. Overall survival was similar in both groups (*P*=0.42; Figure 1). Patients were treated with the following medications either alone or in combination: low dose aspirin (n=9), long-acting nitrate (n=5), beta-blockers (n=4), or angiotensin-converting enzyme inhibitors (ACEI) (n=3), clopidogrel (n=1). One patient, a 33-year-old male, presented with ST-elevation MI with a peak troponin-I level of 38.09 ng/dL, cardiac catheterization with clean coronaries and microvascular disease on MRI was started on aspirin, clopidogrel, beta-blockers, and ACEI. Two patients received a simple transfusion, exchange transfusion was recommended in one patient but was deferred later due to clinical improvement.

In 22 patients with troponin level measurement within 30 days before cardiac MRI, troponin elevation predicted the presence of CMD with a sensitivity of 87.5% (95% CI: 47-100) and specificity of 57% (95% CI: 29-82). There was no correlation between the degree of troponin elevation and CMD, the difference between median baseline and peak troponin was similar in both groups (0.08 ng/mL, range, 0-25.92 in CMD *vs.* 0.07 ng/mL, range, 0-1.04 in non-CMD; *P*=0.31). After restricting the analysis to troponin elevation within 14 days prior, the proportion of CMD was higher in elevated troponin group in patients without ACS (n=14, 100% *vs.* 43%, *P*=0.07) or AKI (n=19, 73% *vs.* 50%, *P*=0.38).

Our study highlights the fact that myocardial injury and coronary microvascular disease is indeed prevalent in SCD. The presence of troponin elevation in 18% of the SCD patients suggests that they suffer some degree of myocardial injury when presenting with chest pain or in an acute crisis. This number differs from a previous report by Aslam *et al.*, in which 6.2% patients had troponin elevation. However, the sample size was smaller and a higher troponin cutoff (0.4 ng/mL *vs.* 0.11 ng/mL) was used.[4] Since troponin-I is well-established to be a very sensitive and specific marker of ongoing myocardial injury,[10] lower sensitivity and specificity in our cohort might be explained by the timing of the troponin testing.

Table 1. Patient characteristics.

Variable	Number, out of total 69 patients (%)
Age (years)	
Median (range)	34 (19-67)
≤ 20	3 (4)
≤40	45 (65)
>40	21 (30)
Sex	
Male	35 (51)
Female	34 (49)
Genotype	
SS	51 (75)
SC	11 (16)
Sβ-thal	6 (9)
History of SCD related complications	
ACS	57 (83)
AVN	25 (36)
Stroke	17 (25)
Retinopathy	10 (14)
Leg ulcer	5 (7)
PHT	22 (33)
Body Mass Index (kg/m^2) Median (range)	23.9 (12.3-46.2)
Coronary artery disease related factors	
Diabetes mellitus	5 (7)
Chronic kidney disease	14 (20)
History of aspirin use	19 (28)
Family history of myocardial infarction	6 (9)
Indications for cardiac MRI	
Chest pain and/or troponin elevation	26
Iron overload	11
Cardiomyopathy	2
Arrhythmias[†]	3
Right atrial mass	1
Pulmonary stenosis	1
Right to left shunt	1
Unknown	1

SS: homozygous sickle cell with hemoglobin SS; SC: homozygous sickle cell with hemoglobin SC; Sβ-thal: sickle cell β thalassemia; SCD: sickle cell disease; ACS: acute chest syndrome; AVN: avascular necrosis; PHT: pulmonary hypertension. [†]included ventricular tachycardia and AV-nodal re-entrant tachycardia.

As it is not a provocative test, troponin-I will not capture chronic ischemic changes, infarct scaring, and impaired myocardial perfusion reserve unless there is acute ischemia leading to myocardial damage at the time of testing. These findings can be elicited by CMR with contrast and stress testing with great precision and accuracy. Patients with CMD will have impaired perfusion reserve at rest and ischemia on stress testing, it may or may not translate into myocardial injury to cause troponin elevation.

To our knowledge, this is the first study to assess the effect of myocardial injury and CMD on mortality for SCD patients. Myocardial injury was associated with a 2.6-fold increase in all-cause mortality and there was a statistically insignificant trend towards lower survival in the CMD group. These findings can be a potential explanation of the high frequency of sudden death, especially of cardiac cause, in otherwise healthy patients presenting in acute crisis.[11] Myocardium in distress with underlying ischemia can act as an arrhythmogenic substrate leading to fatal arrhythmias.[12]

There is no randomized controlled data on coronary

Table 2. Association between troponin elevation and other variables, and between coronary microvascular disease on cardiac magnetic resonance imaging and other variables.

	Troponin data (N=63)[†]			Cardiac MRI data (N=47)[†]		
	Normal Troponin (n=21)	Elevated Troponin (n=42)	P*	CMD (n=15)	Non-CMD (n=32)	P*
Clinical variables, number (%)						
ACS at time of event						
No	19 (90)	25 (60)	0.02	12 (80)	26 (81)	1.00
Yes	2 (10)	17 (40)		3 (20)	6 (19)	
AKI at the time event						
No	21 (100)	24 (57)	0.0002	NA	NA	
Yes	0 (0)	18 (43)				
EKG changes						
No	5 (100)	27(73)	0.31	7 (78)	11 (85)	1.00
Yes	0 (0)	10(27)		2 (22)	2 (15)	
missing	16	5		6	19	
OME use 24 hour prior to peak troponin elevation, median (range)	75 (75-75)	64 (0-1524)	1.00	NA	NA	
missing	20	19				
OME use 24 hour after peak troponin elevation, median (range)	NA	119 (0-3200)	NA	NA	NA	
Lab variables, median (range)						
WBC count (×10⁹/L)	12.2 (5.2-61)	13.7 (4.5-34.7)	0.39	11.9 (8-61)	13.6 (5.2-26.8)	0.35
Hemoglobin (g/dL)	7.7 (5.6-12)	7.7 (2.9-12.6)	0.93	7.8 (5.6-11.9)	7.6 (2.9-12)	0.34
Platelet count (×10⁹/L)	272 (127-633)	165.5 (41-824)	0.007	282 (140-664)	259 (119-633)	0.30
Serum creatinine (mg/dL)	0.7 (0.1-1.4)	1.4 (0.4-7.6)	0.0002	0.8 (0.5-1.6)	0.7 (0.1-7.6)	0.41
LDH (U/L)	391.5 (210-1584)	498 (142-18500)	0.37	375 (142-1066)	486.5 (210-2647)	0.29

CMD: coronary microvascular disease; MRI: magnetic resonance imaging; CMR: cardiac MRI; ACS: acute chest syndrome; AKI: acute kidney injury; EKG: electrocardiography; OME: oral morphine equivalents; WBC: white blood cell; LDH: lactate dehydrogenase; NA: not applicable; n: number. *Fisher's exact test for categorical variables; Wilcoxon rank sum test for continuous variables. The number in parenthesis represents percentage of total patients for categorical variables and range for continuous variables, which are reported as median. [†]Troponin level was not available for six of 69 patients and CMR was not available for 22 of 69 patients.

microvascular disease management in SCD patients. Patients are usually managed with standard acute coronary syndrome management with anticoagulation and antiplatelet agents. In patients with microvascular ischemia in general, aspirin, nitrate, beta-blockers, statins, and other coronary artery disease management interventions have been used but specific data for SCD is not available.[13] Exchange transfusion with a goal HbS <30% has been reported to be effective in a patient with recurrent myocardial infarction.[14] In a recent study evaluating the effect of hydroxyurea on skeletal and cardiac muscles, SCD patients treated with hydroxyurea had higher resting myocardial perfusion as compared to those without hydroxyurea.[15] Newer therapies that target Hb modification could also have a role in the management, but prospective trials are needed to assess the effectiveness of various treatment strategies. We suggest that cardiac MRI with stress testing can be considered as a screening tool for patients with evidence of myocardial damage and recurrent chest pain. This could potentially identify patients who need to be started on medical therapy or considered for exchange transfusions. Improving access to cardiac MRI will be essential since a lack of its universal availability would be a hurdle in adopting this practice widely.

Kiranveer Kaur,[1] Ying Huang,[2] Subha V. Raman,[3] Eric Kraut[2] and Payal Desai[2]

[1]Division of Medical Oncology, The Ohio State University Wexner Medical Center, Columbus, OH; [2]Division of Hematology, The Ohio State University Wexner Medical Center, Columbus, OH and [3]Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, IN, USA

References

1. Gladwin MT, Sachdev V. Cardiovascular abnormalities in sickle cell disease. J Am Coll Cardiol. 2012;59(13):1123-1133.
2. Martin CR, Johnson CS, Cobb C, et al. Myocardial infarction in sickle cell disease. J Natl Med Assoc. 1996;88(7):428-432.
3. Raman SV, Simonetti OP, Cataland SR, et al. Myocardial ischemia and right ventricular dysfunction in adult patients with sickle cell disease. Haematologica. 2006;91(10):1329-1335.
4. Aslam AK, Rodriguez C, Aslam AF, et al. Cardiac troponin I in sickle cell crisis. Int J Cardiol. 2009;133(1):138-139.
5. Lippi G, De Franceschi L, Salvagno GL, et al. Cardiac troponin T during sickle cell crisis. Int J Cardiol. 2009;136(3):357-358.

6. West AM, Kramer CM. Comprehensive cardiac magnetic resonance imaging. J Invasive Cardiol. 2009;21(7):339-345.
7. Gerber BL, Raman SV, Nayak K, et al. Myocardial first-pass perfusion cardiovascular magnetic resonance: history, theory, and current state of the art. J Cardiovasc Mag Reson. 2008;10(1):18.
8. Niss O, Taylor MD. Applications of cardiac magnetic resonance imaging in sickle cell disease. Blood Cells Mol Dis. 2017;67:126-134.
9. Hunold P, Schlosser T, Vogt FM, et al. Myocardial late enhancement in contrast-enhanced cardiac MRI: distinction between infarction scar and non-infarction-related disease. AJR Am J Roentgenol. 2005; 184(5):1420-1426.
10. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. J Am Coll Cardiol. 2018;72(18):2231-2264.
11. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639-1644.
12. James TN, Riddick L, Massing GK. Sickle cells and sudden death: morphologic abnormalities of the cardiac conduction system. J Lab Clin Med. 1994;124(4):507-520.
13. Samim A, Nugent L, Mehta PK, et al. Treatment of angina and microvascular coronary dysfunction. Curr Treat Options Cardiovasc Med. 2010;12(4):355-364.
14. Khalique Z, Pavlu J, Lefroy D, et al. Erythrocytapheresis in the prevention of recurrent myocardial infarction in sickle cell disease. Am J Hematol. 2010;85(1):91-91.
15. Sachdev V, Sidenko S, Wu MD, et al. Skeletal and myocardial microvascular blood flow in hydroxycarbamide-treated patients with sickle cell disease. Br J Haematol. 2017;179(4):648-656.