Letters to the Editor

Diastolic Dysfunction
Is an Independent Risk
Factor for Death in Patients
With Sickle Cell Disease

We read with interest the study by Sachdev et al. (1) that identified diastolic dysfunction as a poor prognostic factor in patients with sickle cell disease. Absolute serum creatinine in the study cohort may have underestimated the severity of kidney disease. The incidence of renal insufficiency in a cohort of sickle cell patients has been found to be 4% to 7% (2,3). Chronic kidney disease is known to be a prognostic factor for worse cardiovascular outcomes (4). The American Kidney Foundation has proposed creatinine clearance as a better assessment of kidney function (5).

In addition, methadone use for sickle cell-related chronic pain increases the risk of QT prolongation and torsades de pointes-related arrhythmic events (6,7).

Abnormal diastolic function may result from myocardial iron overload (8). Myocardial iron overload has been reported in an autopsy study of sickle cell patients (9). The use of validated cardiovascular T2* magnetic resonance for early diagnosis of myocardial iron overload demonstrated that myocardial iron content cannot be predicted from serum ferritin or liver iron (10).

Creatinine clearance, narcotic use, and myocardial iron overload should therefore be included in studies of mortality among sickle cell patients.

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REFERENCES


Reply

We appreciate the important information presented by Dr. Ntim and colleagues in reference to our report on diastolic dysfunction in sickle cell disease (SCD) patients. They suggest that renal insufficiency in our cohort may have been underestimated by using absolute serum creatinine levels instead of creatinine clearance. We have found in our sickle cell patient cohort that absolute creatinine levels correlate well with estimated creatinine clearance using the Modification of Diet in Renal Disease (MDRD) study equation and Cockcroft-Galt (CG) formulas (Spearman ρ = −0.91, p < 0.0001 and ρ = −0.71, p < 0.0001, respectively). Indeed, renal disease characterized by any of these measures is an important risk factor in the SCD population, and we reported in our initial study (1) that, “besides the tricuspid regurgitant jet velocity, the only significant univariate correlate of the risk of death was the creatinine level (p = 0.007).” In the present study (2), we found a good correlation between the creatinine level and the E/A ratio (ρ = −0.46; p < 0.0001); however, the E/A ratio remained significantly associated with mortality after adjustment for log10 creatinine. Similarly, when we adjusted for the MDRD GFR and CG GFR, the E/A ratio remained significantly associated with mortality (p = 0.0001 and p = 0.0002, respectively).

Although our study shows evidence of diastolic dysfunction in the SCD population, the etiology of this is likely to be multifactorial and may include relative systemic hypertension, microvascular vaso-occlusive disease, and iron overload. The presence of iron in the myocardium can be detected by advanced imaging techniques, including tissue Doppler echocardiography (3) and magnetic resonance imaging (4). We certainly agree that more accurate population-based measures of iron burden would be of great value to this field of research.
Dr. Ntim and colleagues cite reports of narcotic use being associated with prolonged QT and arrhythmic events. This is an interesting observation that requires follow-up, because the proximate cause of death in many SCD patients remains unknown. This being said, it is important to note that many of our patients with severe pulmonary hypertension and high hemolytic rate manifest a low frequency of vaso-occlusive crisis and many rarely use narcotics. This is consistent with the observation that patients with hemolytic anemia secondary to thalassemia and other hereditary hemolytic conditions develop pulmonary hypertension but do not have hemoglobin S or vaso-occlusive pain crises. We have suggested a paradigm in which hemolytic anemia leads to distinct complications associated with low nitric oxide bioavailability and vasculopathy, including priapism, cutaneous leg ulcerations, sudden death, and pulmonary hypertension (5). In contrast, high steady-state hemoglobin and leukocytosis are risk factors for frequency of vaso-occlusive pain crisis, acute chest syndrome, and increased narcotic usage.

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REFERENCES