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CLINICAL TRIALS AND OBSERVATIONS

Comment on Niss et al, page 1322

Diffuse myocardial fibrosis as an SCD biomarker

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In this issue of *Blood*, Niss et al[1] posit that early initiation of disease-modifying therapy can mitigate sickle myocardial fibrosis by using extracellular volume (ECV) fraction as a potential imaging biomarker.

Cardiovascular complications account for a third of the premature mortality rate in patients with sickle cell disease (SCD).[2] Underlying this cardiac risk is a progressive cardiomyopathy which is closely linked to the severity of anemia and impaired diastolic function.[3,4] In an earlier study,[5] Niss et al used cardiac magnetic resonance (CMR) imaging to measure ECV in a cohort of 25 patients with SCD and found markedly increased ECV in all of them, indicating diffuse myocardial fibrosis. In the current study,[1] the authors asked whether early intervention with disease-modifying therapy could mitigate cardiac complications of SCD. Twelve children and young adults who initiated hydroxyurea or blood transfusion at age younger than 6 years and who had at least 5 years of uninterrupted therapy,[1] were found to have ECV levels comparable to those of normal controls and significantly lower than a comparator group of 25 patients who did not have early therapy.

Diffuse myocardial fibrosis occurs from deposition of collagen in the myocardial interstitium, and its detrimental effects include systolic and diastolic dysfunction and the potential for arrhythmia. It can be detected in aging and in many chronic cardiac conditions, and its severity has been associated with an increased risk of adverse events.[6] Endomyocardial biopsies have shown direct correlations between ECV and collagen deposition in heart failure, but this has not been seen in other conditions, suggesting that patterns of deposition may vary significantly based on the underlying conditions.[6] Because ECV measures the total interstitial space, myocardial edema and/or inflammation are important potential confounders of an increased ECV, which is particularly relevant in patients with SCD.

In their letter to the editor, Niss et al addressed an important and interesting issue in sickle cardiomyopathy, and although their cohort was small, it is hypothesis generating and provides evidence for proceeding to larger studies that use CMR imaging. An important question is whether ECV provides incremental benefit over other parameters for the assessment of cardiac dysfunction. Echo studies have demonstrated that diastolic dysfunction is an independent risk factor for mortality in SCD, yet the diagnosis of diastolic dysfunction by echo is complex and varies from study to study.[3,7,8] There are no accepted methods for assessing diastolic function in SCD, and guidelines specifically mention that echo parameters may suggest chronically elevated left ventricular filling pressures in the *absence* of anemia. A heart failure scenario that is typically encountered in patients with SCD is one of high output with increased blood volume, and many imaging parameters (eg, left atrial volume) and Doppler parameters may not have the same normal thresholds as those in patients who do not have SCD. In this setting of diagnostic complexity, a new imaging marker of high risk in patients with SCD would be a welcome addition. As seen in this[1] and other studies, diastolic classifications are not always aligned. It has been suggested that myocardial fibrosis precedes diastolic dysfunction, and yet 1 of the 12 patients in the Niss et al study with a normal ECV had inconclusive diastolic function. Niss et al and others have previously demonstrated a link between ECV and diastolic echo parameters, but these measures are not provided in their current study, so it is difficult to discern whether ECV had greater value than commonly used echo parameters such as tricuspid regurgitant jet velocity. Unfortunately, there are few CMR imaging studies in patients with SCD, and until many more patients undergo ECV assessment, the relationship between ECV and outcomes will remain unknown. ECV measurement, which requires infusion of gadolinium contrast, provides additional information about cardiac morphology, but whether it adds incremental value to existing echo parameters or laboratory markers such as N-terminal prohormone brain natriuretic peptide remains unknown.

In this observational study,[1] ECV values in treated patients approached the normal range compared with high values in untreated patients. With this type of cross-sectional analysis, it is difficult to evaluate differences in disease severity between groups and no causal relationships can be determined. So far, CMR studies of ECV[1,5] have included highly selected patients and small numbers of patients, so the prevalence of diffuse myocardial fibrosis in patients with SCD is unknown. Early initiation of disease-modifying therapy would and should prevent the accumulation of damage to various organs, including the heart, but questions remain about how early to begin therapy, how the presence of high ECV might impact treatment decisions, and what markers can be used to monitor the response to an intervention.

Although there were no differences in cardiac parameters and hemoglobin

levels between the groups that had early therapy and those that had no early therapy in this study,[1] it is likely that the mechanistic basis for limiting damage is sustaining an acceptable hemoglobin level thereby reducing the anemia. Furthermore, both blood transfusion and hydroxyurea should also reduce acute vaso-occlusive episodes that are frequently accompanied by acute-on-chronic hemolysis. Hydroxyurea therapy has been reported to improve left ventricular size and hypertrophy in children.[9] Although patients undergoing successful transplant for SCD also have improvements in left ventricular size, approximately one-third of them continue to have LV dilation.[7] These reports suggest that disease-modifying therapy needs to be initiated before organ damage becomes irreversible. In patients who do not have SCD, diffuse myocardial fibrosis may play an important role in the development of heart failure, and clinically available drugs for treating heart failure, including lisinopril, losartan, spironolactone, and torsemide, have shown antifibrotic effects as well as improvements in diastolic function and/or symptoms.[6] As we build evidence for the clinical implications of diffuse myocardial fibrosis in patients with SCD and its value in relation to other parameters, these drugs may present attractive options for evaluating treatment response.

Cardiac impairment impacts functioning of other vital organs, including the lungs, kidneys, and liver, which contributes to earlier mortality. Advanced cardiac imaging that includes newer parameters such as ECV allows us to improve cardiac phenotyping and gain greater insights into cardiac abnormalities, but ongoing work with cluster analysis, machine learning,[10] and other advanced analytic methods that integrate imaging, clinical, and laboratory parameters from multiple organ systems will allow us to do more comprehensive risk stratification and assessment of disease severity.

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