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EDITORIAL COMMENT

Sickle Cardiomyopathy

The Missing Forest in the Trees*

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Of the known cardiac manifestations of sickle cell disease (SCD), none has received more attention than pulmonary hypertension. Elevated tricuspid regurgitant jet velocities (TRVs), even those too mild to be considered diagnostic of pulmonary hypertension, have been shown to predict mortality in adult patients with SCD (1). Consequently, echocardiography screening programs have proliferated over the past 10 years, encouraged by the possibility that pulmonary hypertension could be managed by pharmacotherapy. Yet, nagging questions remain. What is the causal mechanism of an elevated TRV in patients with SCD? Is it due to pulmonary vascular disease or pulmonary venous hypertension? What is its pathophysiological link to death? Patients with SCD and an elevated TRV, although less likely to survive, do not usually die of right heart failure (2). Much more often, these patients meet their demise from sudden cardiac death. Could our watchful vigilance over the tricuspid regurgitation be obscuring the broader picture? Niss et al. (3) raise the possibility.

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In this issue of *iJACC*, Niss et al. (3) summarize the cardiac presentation of SCD patients and describe a cardiomyopathy that they consider unique to SCD. This cardiomyopathy, although characterized by diastolic dysfunction, is distinguished from classic definitions of restrictive cardiomyopathy by the presence of dilated ventricles. Backed by a meta-analysis of 68 studies from the published literature, as well as the results from their own echocardiography laboratory, Niss et al. (3) report left atrial and ventricular dilation, diastolic dysfunction, normal ejection fraction, and catheter-confirmed pulmonary venous hypertension in patients with SCD. From the collection of cross-sectional studies examining pediatric and adult populations, they speculate that the sickle cardiomyopathy begins in childhood, with the earliest sign evidenced by left atrial dilation. The authors hypothesize that elevations in TRV are the result of restrictive physiology and theorize that patients with the sickle cardiomyopathy are predisposed to fatal arrhythmias, similar to patients with other forms of restrictive cardiomyopathy. Finally, Niss et al. (3) conclude that elevations in TRV are markers of this cardiomyopathy, a greater concern in the medical management of SCD patients than the pulmonary hypertension per se.

With a birth prevalence of ~0.2% in African Americans (4), SCD is rare, challenging efforts to enroll adequate sample sizes for clinical investigations. Niss et al. (3) clear this hurdle by meta-analyzing SCD patients from around the world, augmenting the initial sample size of 134 to >2,000, depending on the parameter of interest being analyzed. Yet, meta-analyses of diverse populations are not without their own challenge, namely, between-study heterogeneity. Variation among studies is expected, and summary estimates are best expressed by the mean of the random-effects distribution. However, even with the caveat that summary estimates do not represent a single, true "fixed" effect across populations, between-study heterogeneity needs to be considered. In meta-analyses, this heterogeneity is often assessed by 95% prediction intervals (5), and by I^2, a value derived from the squared deviation of individual study estimates from the summary estimate (6). Low, moderate, and high amounts of between-study heterogeneity are often considered I^2 values of 25%, 50%, and 75%, respectively. As with previous meta-analyses of echocardiographic measurements in SCD populations (7,8), the analysis by Niss et al. (3). encompasses

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substantial between-study heterogeneity (with I^2 values ranging from 76% to 94%).

In light of the considerable heterogeneity of the studies evaluated, the meta-analytic summary estimates should be interpreted with caution. Nonetheless, a pattern of left ventricular diastolic dysfunction with hyperdynamic physiology emerges, as described previously in some of the individual cohorts. Whether elevations in TRV are solely the result of diastolic dysfunction, however, remains controversial. Restrictive physiology is a plausible cause of elevated TRV in SCD patients, but it is not likely to be the only cause. Numerous publications support a multifactorial etiology, citing diastolic dysfunction, anemia-induced elevations in stroke volume, thromboembolism, sleep apnea, and pulmonary vasculopathy among the causal determinants (9,10). In autopsy series, medial hypertrophy, intimal hyperplasia, and fibrosis of the pulmonary artery are noted in the majority of SCD patients, regardless of the cause of death (11,12). Whether these changes are the result of endothelial dysfunction, increased stroke volume, or downstream venous pressures is uncertain. The assertion by Niss et al. (3) that left atrial enlargement precedes pan-chamber dilation is also inconclusive and, lacking longitudinal data, remains an interesting but purely speculative idea.

Despite these limitations, the meta-analysis by Niss et al. (3) should be recognized for its novel interpretation of cardiomyopathy in SCD patients. Perhaps it is time for a paradigm shift, with a greater emphasis placed on cardiomyopathy in echocardiography screening programs. Future investigations of the natural history of SCD-related cardiomyopathy could be conducted, facilitated by the recommendation from the American Thoracic Society for episodic echocardiograms (13). It would also be instructive to determine once and for all why mild elevations in tricuspid regurgitation predict mortality in SCD patients. If Niss et al. are correct, we have been missing the forest for all of the trees, and mildly elevated TRVs, at least in many of our patients, are but a marker of cardiomyopathy.

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