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Heart failure in SCA: still challenging

Nadjib Hammoudi and François Lionnet | Sorbonne Université, ACTION Study Group, and Hôpital Pitié-Salpêtrière

In this issue of *Blood*, Morin et al¹ report an increased myocardial extracellular volume (ECV) in patients with sickle cell anemia (SCA) despite early intervention with disease-modifying therapy.

Despite cardiomyopathy being a leading cause of death and negatively impacting the quality of life in SCA patients, this condition remains underrecognized in clinical practice.² In contrast with progressive damage involving other organs, such as kidney failure, there is no established algorithms for the diagnosis and management of SCA cardiomyopathy.^{2,3} The definitive diagnosis of this high-output form of heart failure is difficult and often performed at a late congestive stage. The symptoms, especially exercise intolerance, are often attributed to other causes including chronic anemia. In SCA patients, the left ventricular ejection fraction is usually preserved, and the analysis of diastolic function is challenging in the context of a chronic high-output state.² A better cardiac phenotyping and early diagnosis of heart involvement are required in order to develop therapeutic strategies targeting SCA cardiomyopathy and improve prognosis. Echocardiography is the most used method to investigate cardiac morphologic remodeling and hemodynamics, but this technique is incapable of reliably characterizing the myocardial tissue. The use of ECV measured by cardiac magnetic resonance imaging as a marker of cardiac damage has recently been found to correlate with myocardial fibrosis.⁴ Morin et al used this parameter to evaluate the potential beneficial heart effect of early initiation of disease-modifying therapy in SCA patients.

Increased ECV, as an index of diffuse myocardial fibrosis, was reported in several cardiac disorders to be linked to interstitial collagen deposition and to prognosis.⁴ In the context of volume overload, as observed in chronic primary

mitral regurgitation, diffuse myocardial fibrosis could be detected at an early stage while patients are asymptomatic without apparent alteration of left ventricular function.⁵ Importantly, mitral valve surgical repair seems to be associated with postoperative decrease of ECV, indicating a potential reverse interstitial remodeling.⁶ In addition to chronic volume overload and high output state due to anemia, SCA patients frequently have microvascular dysfunction related to repeated vasoocclusive events and nitric oxide deficiency due to chronic intravascular hemolysis. Other mechanisms such as kidney failure, which affects approximately one-third of adults, systemic hypertension, and altered red blood cells rheology also contribute to cardiac remodeling and diffuse myocardial fibrosis.² Hence, ECV may be a sensitive way to detect early cardiac involvement in SCA patients and also may be a potential endpoint to assess the impact of therapeutic interventions.

An earlier study by Niss et al⁷ reported markedly abnormal ECV values in all studied patients (n = 25). Interestingly, ECV was linked to left ventricular diastolic dysfunction and to lower hemoglobin level. More recently, the same team investigated 12 young SCA patients who had been all continuously treated with hydroxyurea or chronic transfusions since early childhood (initiated <6 years).⁸ Compared with the data from the first cohort, abnormal ECV was observed in "only" 4 (33%) patients, and the mean observed ECV value of 30% was significantly lower. Patients who received early treatment had smaller left ventricular volume, mass, and cardiac index, indicating an amelioration of the

hyperdynamic state of SCA. These data suggested that early initiation of disease-modifying therapies may prevent myocardial damage in SCA patients.

In their letter to the editor, Morin et al report conflicting results from a different cohort of pediatric and young adult patients, most of whom were treated with hydroxyurea and/or chronic monthly transfusion for a median exposure time of 9.6 years. This retrospective observational study included 31 SCA patients in whom a cardiac magnetic resonance imaging was performed to investigate a morphologic cardiac abnormality diagnosed by echocardiography. According to this selection bias, most of the patients (>75%) had left ventricular enlargement and increased cardiac index, and a left atrial dilation was observed in 42% of the patients. All patients had increased ECV (median value of 32%) compared with previously published normal values. The duration of exposure to disease-modifying therapies was not linked to ECV. Moreover, ECV values were similar in patients in whom disease-modifying therapies were begun early compared with the rest of the cohort. These conflicting results could be partially explained by the fact that many patients in the "no early therapy" group were treated with chronic transfusion, whereas Niss et al excluded these patients from their SCA control cohort.⁷ Interestingly, the patients in the study by Morin et al with pronounced cardiac remodeling had ECV values relatively close to those measured in the Niss et al investigation. Therefore, it is not possible to make a conclusion about the effect of early disease-modifying therapy on diffuse myocardial fibrosis. Moreover, both studies are small observational cross-sectional investigations of highly selected patients.

In the future, the causes of increased ECV in SCA patients need to be clarified. ECV is not a direct measure of fibrosis but a measure of total interstitial myocardial space that could also be affected in SCA patients by other mechanisms such as edema or inflammation.⁴ Moreover, the clinical significance of increased ECV deserves further investigations with correlation to clinical endpoints or alternatively to exercise tolerance, already shown to predict

prognosis. The ability of exercise to unmask latent heart failure at rest was recently reported in SCA patients.⁹ The alteration of exercise cardiac reserve, mostly due to diastolic dysfunction, was apparently not linked to the degree of left ventricular dilation nor to resting cardiac index. Some SCA patients exhibited a relatively adaptative cardiac remodeling as opposed to others who could develop progressive diffuse myocardial fibrosis.

To appropriately evaluate the therapeutic impact, serial cardiac magnetic resonance imaging studies before and after treatment are needed. In addition to disease-modifying therapies, specific heart failure drugs, such as mineralocorticoid inhibitors or sodium-glucose cotransporter-2 inhibitors,^{2,10} could be tested in SCA cardiomyopathy.

While awaiting further evidence of the impact on the heart, the use of hydroxyurea must be widely promoted as it reduces other complications of SCA

and tackles the pathophysiological processes causing cardiomyopathy.³

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