Fibrosis-specific biomarkers and interstitial fibrosis in hypertrophic cardiomyopathy

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Related article
by Karabinowska-Małocha et al.

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Hypertrophic cardiomyopathy (HCM) is a cardiac muscle disorder characterized by generally asymmetric abnormal hypertrophy of the left ventricle without abnormal loading conditions (such as hypertension or valvular heart disease) [1]. HCM is an autosomal-dominant genetic cardiomyopathy, and mutations in the genes encoding sarcomeric proteins are identified in 30%–60% of cases [1]. The presence of this genetic mutation carries more than a 2-fold increased risk of ventricular arrhythmias. Genetic and myocardial substrates, including fibrosis, ventricular hypertrophy, and microvascular ischemia, play a role as arrhythmogenic determinants [1].

Cardiopulmonary exercise testing seems to improve contemporary strategies for SCD risk stratification [2–4]. However, the development of new drugs for HF and cardiomyopathies should focus on the direct effect on cardiomyocytes, coronary microcirculation, and the myocardial interstitium. Detailed knowledge of interstitium and cardiomyocyte biology becomes essential [5]. The myocardial interstitium is an elaborate and active micro-habitat within the myocardium [6]. HF fibrotic changes in the interstitium and near capillaries are featured by extracellular matrix (ECM) expansion and myofibroblast secretion of type I collagen [5]. A cardiac magnetic resonance imaging technique, T1 mapping, which measures extracellular volume fraction [ECV] in the human myocardium, permits the distinction of different components of the interstitium (cardiomyocytes and connective tissue) and a more precise definition of myocardial fibrosis [5].

To develop new drugs for HF and cardiomyopathies, it is fundamental to identify and match the drugs with the most suitable patient population. In this way, biomarkers might better characterize different patients and who could benefit most from novel drugs and treatments [7]. Biomarkers of extracellular matrix remodeling may be important for the prediction of heart failure with the development of preserved ejection fraction (HFpEF) [8]. Levels of both C-terminal propeptide and C-terminal telopeptide of type-1 collagen as well as N-terminal peptide of procollagen type III show the presence of fibrosis in HF [9]. Both matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are involved in cardiac remodeling; MMP2, MMP3, and MMP9 seem to play a role in the development of HF [10]. MMP2 may make an early prediction of the cardiovascular prognosis [11].

The protein galectin-3 (gal-3) is a biomarker of fibrosis, inflammation, and oxidative stress. In a failing heart, gal-3 is released by activated cardiac macrophages and cardiac fibroblasts, which take part in ventricular remodeling [12].

In this issue of *Kardiologia Polska* (*Polish Heart Journal*), Karabinowska-Małocha et al. [13] present an interesting prospective single-center observational study. They hypothesized that cardiac- and fibrosis-specific biomarkers might also be related to interstitial fibrosis in HCM. Their study aimed to compare the circulating levels of cardiac- and fibrosis-specific biomarkers between

HCM patients and patients with high and low burdens of interstitial fibrosis.

The topic of interstitial fibrosis and its relationship with serum biomarkers is little studied, with few publications centered on cardiac-specific markers in the setting of interstitial fibrosis in HCM. The choice of this topic is one of the main merits of the article written by Karabinowska-Małocha et al. [13].

The final study population, in which ECV and biomarkers values were obtained, included 49 patients. Patients were divided based on their median ECV value, which was 28.1%. So, HCM patients stratified according to median ECV differed in terms of body mass index (BMI), late gadolinium enhancement (LGE) extent and mass, as well as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and gal-3 levels.

The authors [13] demonstrated that cardiac-specific biomarkers (troponin T [TnT], NT-proBNP) are weakly related to both replacement and interstitial fibrosis, and markers of collagen turnover, as well as transforming growth factor-β1 (TGF-β1) seem to be inadequate as fibrosis-related biomarkers in HCM. On the other hand, gal-3 appears to be strongly related to interstitial fibrosis in HCM, making it a strong candidate for being a potential biomarker in this setting.

In particular, cardiac-specific (NT-proBNP and TnT) as well as gal-3 correlated with ECV, whereas only TnT correlated with LGE extent. Gal-3 and BMI were found to be independently associated with interstitial fibrosis (ECV). In this study [13], the authors showed a positive correlation between LGE extent and TnT levels (in agreement with data derived from other studies) [14, 15]. The authors did not observe any correlation between NT-proBNP levels and LGE, similar to previous researchers. Additionally, in the plasma fibrosis-specific biomarkers, no association with LGE was observed [13]. No such associations have been found in HCM between fibrosis-specific markers and replacement fibrosis [13].

Aleksandra Karabinowska-Małocha et al. confirmed the lack of associations between collagen turnover-related biomarkers (PICP, PIIINP) and TGF-β1 with interstitial fibrosis. These data are consistent with other studies conducted so far. This is the first study to reveal a relatively strong relationship between gal-3 and interstitial fibrosis in HCM. The observed association between gal-3 and ECV (interstitial fibrosis) and the lack of any relationship between gal-3 and LGE (replacement fibrosis) points to distinct metabolic pathways and the significance of these two types of fibrosis in HCM. However, this relationship needs further attention and in-depth research.

Article information

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