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 2-fold increased risk for ventricular arrhythmias. Genetic and myocardial substrate, including fibrosis, ventricular hypertrophy and microvascular ischemia, play a role as arrhythmogenic determinants [1]. Cardiopulmonary exercise test seems to improve contemporary strategies for SCD risk stratification [2–4].

However, the development of new drugs for HF and cardiomyopathies should focus on direct effect on cardiomyocytes, coronary microcirculation, and myocardial interstitium. The detailed knowledge of interstitium and of cardiomyocyte biology becomes essential [5]. 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 cMRI technique, the T1 mapping (measures the extracellular volume fraction, ECV in human myocardium) permits the distinction of different components of interstitium (cardiomyocytes and connective tissue) and a more precise definition of myocardial fibrosis [5].

For the development of new drugs for HF and cardiomyopathies, it is fundamental identifying and matching the drugs with the most suitable patient population. In this way, biomarkers might better characterize the 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 preserved ejection fraction (HFPEF) development [8]. Levels of both C-terminal propeptide and C-terminal telopeptide of type-1 collagen as well as the N-terminal peptide of procollagen type III identify the presence of fibrosis in HF [9]. Both MMPs and TIMPs are involved in cardiac remodeling; MMP2, MMP3, and MMP9 seem to play a role in the development of HF[10]. MMP2 may early predict cardiovascular prognosis[11].

The protein galectin-3 (Gal-3) is a biomarker of fibrosis, inflammation, and oxidative stress. In the failing heart, Gal-3 is released by activated cardiac macrophages and cardiac fibroblasts, taking 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 may also be related with interstitial fibrosis in HCM. The aim of the study was to compare the circulating levels of cardiac- and fibrosis-specific biomarkers between HCM 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 papers centred 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].

Final study population from whom ECV and biomarkers values were obtained consisted of 49 patients. Patients were divided based on their median value of ECV, which was 28.1%. So, HCM patients stratified according to median ECV differ in terms of BMI, LGE extent and mass, as well as NT-proBNP and gal-3 levels.

The authors [13] demonstrate cardiac-specific biomarkers (troponin, NT-proBNP) are weakly related with both replacement and interstitial fibrosis, and markers of collagen turnover as well
as TGF-β1 seem to be inadequate as fibrosis-related biomarkers in HCM. On the other hand, Gal-3 appears to be strongly related with 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 positive correlation between LGE extent and TnT levels (in agreement with data derived by other studies [14,15]. The authors did not observe any correlation between NT-proBNP levels and LGE, similar to previous researchers.

In this study [13] among the plasma fibrosis-specific biomarkers no association with LGE was observed. Between fibrosis-specific markers and replacement fibrosis no such associations have been found in HCM.

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 strong enough 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) clearly points to distinct metabolic pathways and the significance of these two types of fibrosis in HCM. However, this relationship needs of further attention and in-depth research.

**Article information**

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