METHODS FOR ASSESSMENT OF CARDIAC FIBROSIS. PART II

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ABSTRACT

Biomarkers could be used for evaluation of myocardial fibrosis. The most studied are the procollagen peptides, the matrix metalloproteinases, ST-2 and galectin-3. We have observed the best evidence in heart failure patients. Trials are conducted also in atrial fibrillation.

Keywords: cardiac fibrosis, biomarkers, procollagen peptides, matrix metalloproteinases, ST-2, galectin-3

Biomarkers play an important role in the diagnostics, treatment and follow-up of patients with cardiovascular diseases. The National Institute of Health, USA defines biomarkers as biological markers - cells, proteins and/or metabolite products, which can be measured objectively and evaluated as an indicator for normal biological processes, pathological processes or pharmaceutical response of therapeutic interventions (1). Markers of myocardial remodeling are of special interest. The most studied are markers associated with the synthesis of collagen - procollagen type I amino-terminal propeptide (PINP), procollagen type III amino-terminal propeptide (PIIINP) and carboxy-terminal propeptide of collagen I (PICP), proteases, providing collagen degradation – MMP and TIMP, as well as carboxyterminal peptide of collagen I fibrils (ICTP) – peptide that is released by the cleaving of collagen I from the collagenase. The procollagen peptides are easy to study (2,3). They reflect the quantity of atrial collagen. During the synthesis of fibrils forming collagen type I and type III, carboxy- and amino-terminal peptides are cleaving and can be measured in blood. The high degree of interstitial atrial fibrosis shows a high degree of spatial heterogeneity of the interstitial collagen. ICTP may serve as an index of the collagen degradation. Patients with atrial fibrillation (AF) have higher levels of PIIINP than controls. The biomarker correlates with left atrial fibrosis and may be a predictor of postoperative AF. It is used for monitoring of the anti-remodeling effect of some drugs as aldosterone antagonists (4-7).

The matrix metalloproteinases are a polygenic family of structurally and functionally homogenous proteolytic enzymes in balance with their tissue inhibitors (TIMPS). They regulate the turnover of the extracellular matrix and have a certain role in the atrial structural remodeling. During the collagen synthesis and degradation, an up-
regulation of MMPs occurs. In patients with permanent AF the levels of MMP-9 are significantly higher than in patients with paroxysmal AF or sinus rhythm (p<0.001). In all AF patients there is a rise of MMP-3. MMP-2 is significantly higher in paroxysmal than in permanent AF or controls (p<0.001 for both) with comparable levels between permanent AF and controls. In permanent AF the values of TIMP-I are lower than in paroxysmal. Angiotensin II, some inflammatory cytokines, the increased transmural stretching, and TGF beta-1 are potential inducers of the expression of MMP (4,8).

Another biomarker, which integrates fibrosis, inflammation, and ventricular stretching, is the soluble protein ST-2. It is used on top of the clinical, echographic and biochemical markers as N-terminal pro natriuretic peptide (NT-proBNP) for the assessment of the remodeling and prognosis of mortality in patients with acute and chronic heart failure (9). Recently there has been accumulation of evidence for galectin-3 (Gal-3), a new biomarker for fibrosis and remodeling (10). Galectins are a family of soluble β-galactoside binding lectins, which play an important role in inflammation, immunological response, and neoplastic growth. They bind specific carbohydrate molecules using a carbohydrate-recognition binding domain (11). Gal-3 is the best studied member of this family. It is a 29-35 kDa protein and is the only one having also an N-terminal domain consisting of tandem short amino acid segments. Gal-3 interacts with a number of ligands – carbohydrates, like N-acetylgalactosamine, and non-glycosylated molecules, like surface cell receptors (macrophages) and extracellular receptors (collagen type IV). The C-terminal domain is responsible for the lectin activity and the presence of the N-terminal domain is necessary for the full biological activity of Gal-3 (10). A number of tissues contain Gal-3 (12). It is found predominantly in the cytoplasm or sometimes in the nucleus of mitochondria. The expression of Gal-3 in healthy hearts is low, but with the development of a fibrotic process, there is a rapid and significant up-regulation (13-16). The exact localization of Gal-3 is not fully understood. Immunohistochemical and microscopic analyses of hypertrophied myocardium in rats show that Gal-3 binds predominantly in the matrix, fibroblasts, and macrophages (14). Gal-3 is necessary for the normal activity of phagocytes (17). Gal-3 stimulates the migration of macrophages (14,18). It liberates in ECM and circulation from activated macrophages as a response to inflammation. It is considered that Gal-3 stimulates the migration of macrophages. Gal-3 is detected on the fibrotic area together with fibroblasts and macrophages, but not with cardiomyocytes. In vitro trials on cultures of cardiac fibroblasts show that Gal-3 causes proliferation and collagen synthesis (13,19). The biomarker influences also the degradation of ECM components from TIMPs and MMPs (10).

Elevation of Gal-3 is observed in other organs affected by fibrotic diseases, such as liver cirrhosis, idiopathic lung fibrosis, and chronic pancreatitis (13,14,20). The expression of Gal-3 is temporally and spatially associated with fibrosis.
There is evidence in heart failure patients that Gal-3 is a marker of prognosis. Some studies show that high circulating levels are associated with a greater risk of AF onset. A correlation between Gal-3 values and the amount of myocardial fibrosis is found (22-24).

Myocardial fibrosis influences most of the cardiovascular diseases and its assessment is clinically relevant. Additional studies are needed to determine this method, which is reliable and can be incorporated in the everyday practice.

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**REFERENCES:**


