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REVIEW TOPIC OF THE WEEK

Circulating Biomarkers of Myocardial Fibrosis

The Need for a Reappraisal

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ABSTRACT

Myocardial fibrosis impairs cardiac function, in addition to facilitating arrhythmias and ischemia, and thus influences the evolution and outcome of cardiac diseases. Its assessment is therefore clinically relevant. Although tissue biopsy is the gold standard for the diagnosis of myocardial fibrosis, a number of circulating biomarkers have been proposed for the noninvasive assessment of this lesion. A review of the published clinical data available on these biomarkers shows that most of them lack proof that they actually reflect the myocardial accumulation of fibrous tissue. In this "call to action" article, we propose that this absence of proof may lead to misinterpretations when considering the incremental value provided by the biomarkers with respect to traditional diagnostic tools in the clinical handling of patients. We thus argue that strategies are needed to more strictly validate whether a given circulating biomarker actually reflects histologically proven myocardial fibrosis before it is applied clinically. (J Am Coll Cardiol 2015;65:2449–56) © 2015 by the American College of Cardiology Foundation.

The search for biomarkers of structural myocardial remodeling with potential usefulness for the clinical handling of cardiac diseases has been a prolific field in the last few years. The investigation of circulating biomarkers for myocardial fibrosis, 1 key component of structural myocardial remodeling, has been accelerating at a remarkable pace. These investigations have deluged the clinical and research communities, however, with numerous candidates, few of which are likely to survive as useful clinical tools in terms of diagnosis, prognosis, and therapy monitoring (1,2). One possible explanation for this failure is that most of the proposed biomarkers lack proof that they actually reflect the quantitative and qualitative changes in collagen tissue characteristic of myocardial fibrosis. The present article focused on the necessity of accurately histologically validating each circulating molecule before it can be considered as a true biomarker of myocardial fibrosis in cardiac patients.

THE RELEVANCE OF ASSESSING MYOCARDIAL FIBROSIS IN CARDIAC PATIENTS

The predominance of the synthesis of collagen types I and III over their degradation results in the

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ABBREVIATIONS AND ACRONYMS

C_IVF = myocardial collagen type I volume fraction

C_{III}VF = myocardial collagen type III volume fraction

CVF = collagen volume fraction

DCM = dilated cardiomyopathy

HF = heart failure

HHD = hypertensive heart disease

LV = left ventricular

LVAD = left ventricular assist device

MMP = matrix metalloproteinase

PICP = carboxy-terminal propeptide of procollagen type I

PIIINP = amino-terminal propeptide of procollagen type III

TGF = transforming growth factor

accumulation within the myocardium of an excess of collagen type I and type III fibers that characterizes fibrosis (**Figure 1**). Two distinct patterns of collagen accumulation can be distinguished in myocardial fibrosis (3): focal, to replace dead cardiomyocytes and form scars (replacement fibrosis), and diffuse, which occurs in the interstitial and perivascular space without notable cell loss (reactive fibrosis). Although both patterns are observed in the heart after acute myocardial infarction, the second affects a large portion of the elderly population, and it is often a common feature of chronic cardiac diseases such as hypertensive heart disease, aortic valve stenosis, diabetic cardiomyopathy, and hypertrophic cardiomyopathy. The present review therefore focuses on reactive myocardial fibrosis.

The composition of fibrotic tissue in reactive myocardial fibrosis is characterized by an excess of collagen type I, highly cross-linked, large-diameter fibers, to the detriment of collagen type III, essentially non-cross-linked, small-diameter fibers (4) (**Figure 1**). Because of the different biophysical properties of the 2 types of collagen, small increases in the collagen type I:III content ratio have been shown to enhance myocardial stiffness. Finally, changes in collagen organization (i.e., alignment of collagen fibers relative to the cardiomyocytes), also seen in myocardial fibrosis, impair the transmission of the force generated by these cells to the ventricular chamber, thus exerting a detrimental effect on myocardial contractility.

Myocardial fibrosis is involved in the pathophysiology and clinical course of cardiac diseases (**Figure 1**). In fact, both quantitative and qualitative aspects of myocardial fibrosis (as evaluated on biopsy samples) have been shown to be associated with increased left ventricular (LV) stiffness and diastolic dysfunction (5), impaired LV contraction and systolic dysfunction (6), arrhythmias (7), and impaired coronary blood flow (8) in patients with heart failure (HF) of various etiologies. In addition, the presence of severe fibrosis in biopsy samples is reportedly a useful indicator for long-term mortality in patients with HF (9,10). Importantly, fibrosis can be seen in the myocardium of HF patients despite the fact that they are receiving adequate treatment as recommended by official guidelines (5–12). In addition, the extent of fibrosis may be an important factor in predicting the effectiveness of long-term HF therapy (e.g., beta-blocker therapy) (13). Therefore, the assessment of myocardial fibrosis is important in gaining a better pathophysiological understanding of the clinical picture, as well as establishing the prognosis and determining therapy in patients with HF.

VALIDATION OF A CIRCULATING MOLECULE AS A BIOMARKER OF MYOCARDIAL FIBROSIS

Any candidate biomarker of myocardial fibrosis must be compared with the current gold standard for diagnosis of myocardial fibrosis, which is the histopathological analysis of myocardial tissue. In addition to its clinical roles, endomyocardial biopsy may be used as a research tool to better understand the cellular and molecular pathophysiology of cardiac diseases, as well as to identify new diagnostic and therapeutic targets (as reviewed by Cooper et al. [14]). In this conceptual framework, the identification of a given circulating molecule as a true biomarker of myocardial fibrosis requires demonstration that its blood levels directly correlate with quantitative parameters used to define fibrosis in endomyocardial biopsy specimens.

The percentage of total myocardial tissue occupied by collagen fibers or myocardial collagen volume fraction (CVF) can be determined with automated image analysis systems in myocardial samples with collagen-specific staining. Similarly, the use of monoclonal antibodies against collagen type I and collagen type III allows the determination of the myocardial CVF occupied by either collagen type I (C_IVF) or collagen type III (C_{III}VF) fibers, respectively. Thus, myocardial fibrosis is characterized by abnormally high values of CVF, C_IVF, and C_{III}VF and/or of the ratio of C_IVF:C_{III}VF (15).

Because of the patchy distribution of myocardial fibrosis, the greatest potential limitation to endomyocardial biopsy evaluation is sampling error. Therefore, the analysis of several tissue fragments is important for diagnostic accuracy and interpretation. A biopsy of the left ventricle may seem diagnostically more contributive than a biopsy of the right ventricle in some cardiomyopathies. However, Pearlman et al. (16), using postmortem tissue from cardiac patients without HF, found that myocardial fibrosis (assessed as the CVF) is a generalized process similarly affecting the 2 cardiac chambers. Furthermore, we reported that fibrosis (assessed as the CVF) present in biopsy specimens of the right side of the interventricular septum is similar to fibrosis present in the free wall of the left ventricle in HF patients (17).

Importantly, the endomyocardial biopsy is a safe procedure. It has a rate of transient complications of <0.5% and a risk of cardiac perforation with tamponade of <0.05% (18).