Cardiac fibrosis is the consequence of extracellular cardiac matrix remodeling resulting from pathological processes, including ischemia, stretch, inflammation, and neurohormonal activation. Fibrosis can be reparative or reactive. At the site of a transmural myocardial infarction, fibrotic scarring provides protective strength and prevents myocardial rupture. Diffuse reactive fibrosis occurs remotely from the ischemic scar. It is associated with myocyte hypertrophy and contributes to the detrimental process of remodeling, increased ventricular stiffness, tissue disarray with consequent contractile heterogeneity, reduced contractile reserve, and arrhythmogenic anisotropy. Although most commonly found in the setting of ischemic heart disease, where it acts as a precursor to heart failure (HF), the more diffuse type of fibrosis is also an essential feature of idiopathic dilated cardiomyopathy, diabetic cardiomyopathy, hypertensive heart disease, and hypertrophic cardiomyopathy (HCM). Cardiac fibrosis results in an accumulation of proteins including collagen in the extracellular space, damage that has previously been considered irreversible in many cardiovascular (CV) diseases. It is now emerging as an important novel target for future CV antifibrotic therapies.12 Promising therapeutic candidates include antihypertensive therapies, antialdosterone agents, anti-inflammatory and antioxidant agents, growth factor inhibitors, matricellular proteins, and key miRNAs, as well as cell therapy or genetic interventions. It is therefore important to noninvasively identify, measure, image, and monitor the degree of cardiac fibrosis to better understand its pathophysiology and select optimal patients for antifibrotic therapy trials. Furthermore, noninvasive surrogate endpoints such as circulating biomarkers or magnetic resonance and molecular imaging should allow for larger proof-of-concept clinical trials than previously possible with endomyocardial biopsies.

Detection of cardiac fibrosis is based on the quantification of a diffuse excess of collagen fiber deposition in the interstitial space, as assessed by staining techniques. Fibrosis may also be monitored noninvasively using biochemical assessments at circulating levels of collagen substrates, enzymatic complexes, or end products. It may also be assessed using bioimaging. Both methods have relative merits and limitations; thus, they can be used in conjunction.3 Some degree of inference is required in the interpretation of these tests because they are noninvasive and have not always been validated against myocardial biopsy studies. Cardiac fibrosis has also been assessed indirectly by the evaluation of its functional consequences (ie, cardiac dysfunction, loss of contractile reserve, and abnormal myocardial stiffness). However, these functional tests may be heavily confounded by nonextracellular matrix (ECM)–related factors. Circulating cardiac fibrosis biomarkers have been developed, and many are associated with relevant clinical outcomes, have been shown to identify patients at risk, and may predict therapeutic response.4–10

In this issue of Circulation: Heart Failure, Ellims et al11 sought to measure the peripheral plasma levels and transcardiac gradients of byproducts of collagen synthesis and to investigate their relationships with cardiac magnetic resonance (CMR), echocardiographic, and hemodynamic correlates of myocardial fibrosis in patients with HCM. They found that plasma levels of N-terminal propeptide of procollagen I and N-terminal propeptide of procollagen III were similar in patients with HCM compared with healthy controls and that neither biomarker exhibited a significant transcardiac gradient. No significant correlations were observed between these procollagen propeptides and CMR-determined quantities of myocardial fibrosis. They concluded that the cardiac contribution to peripheral levels of collagen synthesis byproducts in patients with HCM is insignificant. Furthermore, the authors conclude that peripheral levels of collagen biomarkers do not reliably reflect myocardial collagen metabolism or content in patients with HCM.11 The careful reading of the work by Ellims et al11 actually does reveal that, in patients with HCM (but not in healthy controls), the coronary sinus level of the degradation end product type I collagen telopeptide was significantly higher than the arterial level (P<0.01), suggesting a higher ECM turnover in patients with HCM.11 Another work reported that neither peripheral collagen metabolites nor their transcardiac concentration gradients correlated with the extent of histological myocardial fibrosis.12 Kupari et al12 investigated circulating N-terminal propeptide of procollagen I, C-terminal telopeptide of collagen I, and N-terminal propeptide of procollagen III in peripheral blood, aorta-to-coronary sinus concentration gradients, and ventricular biopsies for the assessment of myocardial fibrosis in patients with severe aortic stenosis. These authors also concluded that circulating collagen metabolites are not reliable surrogate measures of myocardial fibrosis (in this
case, in aortic stenosis), despite C-terminal telopeptide of collagen I and N-terminal propeptide of procollagen III being strongly associated with heart failure and left ventricular dysfunction.12 Interestingly, this observation and a large body of evidence do relate circulating levels of cardiac fibrosis biomarkers to the severity of HF. Therefore, although circulating fibrosis biomarker levels might not necessarily reflect only the amount of collagen in the heart, they may integrate other sources of fibrosis, such as pulmonary fibrosis and renal fibrosis, both frequent comorbid conditions associated with HF and HCM when complicated with HF. Circulating biomarkers of collagen turnover may then retain their prognostic value although they may not reflect only cardiac fibrosis. It may be important for future fibrosis biomarker studies to investigate the extent to which circulating biomarkers originate from the heart, comparing venous blood levels with transcardiac levels and biopsy tissue levels. Only a few such studies have been reported,9,10 probably because they are invasive in nature and may pose some ethical problems, especially when applied to healthy controls. More importantly, to support clinical adoption of actionable biomarkers, the biomarker must identify patients at risk, be associated with relevant clinical outcomes, and reliably predict therapeutic response.13,14

Many potentially useful circulating biomarkers have been investigated and may yield additional information to those assessed in the work of Ellims et al.11 These include (and are not limited to) active matrix metalloproteinase 2, active matrix metalloproteinase 9, and total tissue inhibitor of metalloproteinase 1, which were found to be abnormal in various HF populations including HCM.12 This observation suggests that a multimarker strategy is needed. A more comprehensive exploration of cardiac ECM turnover should include assessment of ECM synthesis biomarkers (procollagen types I and III), ECM degradation end products (type I collagen telopeptide), degradation enzymatic complexes of metalloproteinases, and their tissue inhibitors, various ratios of collagen types (procollagen types I and III), degradation balance (matrix metalloproteinase/tissue inhibitor of metalloproteinase), and synthesis/degradation balance (PIP/type I collagen telopeptide).9,10 Additional markers might also be informative but are yet to be validated extensively as clinical biomarkers in CV disease states. These include matricellular proteins that modulate cell–ECM interactions, collagen fibril assembly, and post-synthetic procollagen processing (eg, secreted protein, acidic and rich in cysteine). Actually, myocardial interstitial fibrosis is synthesized and degraded in a process of continual tissue growth and repair. Disruption of the delicate and sophisticated regulation of ECM may occur at several levels of the upstream regulatory pathways, as well as the downstream regulation of collagen synthesis and degradation. Therefore, structural and functional consequences of cardiac fibrosis are not only related to the amount of collagen fibers but also to their qualitative properties, that is, the relative proportions of collagen type I and III fibers, the degree of collagen cross-linking among collagen fibrils (determines the insolubility, stiffness, and resistance to degradation of the resulting fibers), and the diameter and spatial alignment of the collagen fibers. Further research in the area of multimarker strategies is warranted.

Fibrosis in HCM is associated with poor outcome, including sudden cardiac death, ventricular arrhythmias, left ventricular dysfunction, and HF. It is present as replacement fibrosis and interstitial fibrosis and is activated early before LVH is detectable and when cardiac morphology seems normal. Therefore, early noninvasive diagnosis may be potentially useful, although evidence-based therapy guided by the presence and the degree of fibrosis in HCM is still an unmet need. Autopsy studies in young, previously asymptomatic patients with HCM who died suddenly could show that cardiac ECM is morphologically abnormal and substantially increased in size. The enlarged matrix collagen compartment likely represents a primary morphological abnormality in this disease, supporting the view that the complex HCM disease process is not confined to sarcomere protein abnormalities but also involves ECM primary abnormalities. However, the precise triggers that lead to the development of fibrosis are unknown. Also, it is unknown whether these triggers and the consequent precise features of ECM changes in HCM are similar to those seen in ischemic heart disease and HF that are the more reparative and reactive fibrosis types. Therefore, the clinical validation of circulating biomarkers and fibrosis imaging in HCM may not rely entirely on extrapolation from studies in patients with other CV diseases. With this in mind, the work of Ellims et al11 is to be lauded. It intriguingly raises the possibility that the significance of circulating cardiac fibrosis biomarkers may be different in HCM and other cardiac disease states.

Although circulating biochemical markers may offer the advantage of availability, relative ease of collection and storage, and lower cost, they may not prove as sensitive as imaging markers in the detection or assessment of disease. Several imaging methods are used to visualize fibrosis, including CMR imaging, nuclear imaging, and integrated echocardiographic backscatter. None has become a routine part of evidence-based practice.

Echocardiographic backscatter is an indirect consequence of cardiac fibrosis. The correlation between backscatter and histologically quantified collagen has been well validated.7 Noninvasively, amplitudes of integrated backscatter have also been correlated with elevated procollagen concentration.18 Since the pioneering work of Wu et al,19 CMR has become the noninvasive gold standard for quantification of focal myocardial fibrosis.20 Areas of high-intensity signal of late gadolinium enhancement (LGE) highlights regions of scar or fibrosis as small as 0.16 g. In nonischemic cardiomyopathies, including HCM, the fibrotic process is often diffuse and LGE is potentially limited because of the lack of a normal reference nonfibrotic myocardium. Another method relies on contrast-enhanced T1 mapping where the T1 time is an index of diffuse fibrosis. This method does not rely on contrasting signal intensity and can therefore enable detection of diffuse fibrosis. The group from Melbourne who authored the article prompting the present editorial21 has substantially contributed to this area of research and has also demonstrated that shorter T1 time correlates to increased myocardial fibrosis as measured by myocardial biopsy in patients with HF.21 Most recently, they demonstrated that diffuse myocardial fibrosis, assessed by postcontrast myocardial T1 time, correlates with invasively demonstrated left ventricular stiffness in cardiac
transplant recipients.\textsuperscript{22} Importantly, in patients with HCM, myocardial fibrosis (as measured by LGE CMR) is an independent predictor of adverse outcome.\textsuperscript{23}

Whether CMR will become a clinically actionable method that may be able to guide therapy is an area for investigation.\textsuperscript{24} It has been suggested that patients with advanced cardiomyopathy and myocardial fibrosis demonstrated by LGE on CMR imaging have a high likelihood of appropriate ICD therapy. Correspondingly, the absence of LGE may indicate a lower risk for malignant ventricular arrhythmias.\textsuperscript{25} The amount of cardiac fibrosis by contrast-enhanced MRI (and correspondingly by histopathology) was found to be associated with the degree of left ventricular functional improvement and all-cause mortality late after aortic valve replacement in patients with severe aortic valve disease.\textsuperscript{26}

Several ECM regulation pathways have been identified as potential therapeutic targets that may be modulated with antifibrotic drugs or cell therapy. The validation of these pathways as potential biotargets is an important area of research that may yield innovative antifibrotic therapies (www.fibrotargets.eu). Many of the key molecular pathways may also be monitored using tissue and circulating biomarkers that may be key elements for guiding future personalized CV medicine (www.homage-hf.eu). Such biotarget-biomarkers describe mechanistic phenotypes that may help selecting specific subgroups of patients likely to respond to individual antifibrotic therapies targeted toward discrete underlying mechanisms. However, during the past decade, biomarker and bioimaging research has erred too much into the science of prognostication, and the literature is flooded with publications of small series of patients with single biomarkers that are more or less statistically associated with disease severity and outcomes. Oncologists have done a better job till date using biomarker science to define onctype diagnostic assays based on multimarker profiling to assess safer and more effective therapeutic options. For instance, estrogen receptor status in breast cancer directly dictates treatment with tamoxifen, thus mechanistically linking the marker to a biological process and treatment, a success that has not yet been achieved in CV medicine. The direct mechanistic coupling of biological processes and therapeutics achieved in cancer treatment remains elusive in CV disease, and till date, clinical trials and meta-analyses of biomarker-guided therapies in CV disease have produced conflicting evidence. It is time that personalized CV medicine catches up. Some of the most important research challenges in this area have become the focus of international institutions and research organizations and can be summarized under the following 4 areas: (1) facilitating interaction between different disciplines from basic to clinical research by creating appropriate interfaces for collaboration and discussion among stakeholders; (2) adapting research tools for clinical use by developing common standards (eg, for data collection and linking clinical data with molecular profiles, translating -omics research into clinical application); (3) finding new approaches for the identification, qualification, and clinical validation of all types of biomarkers; and (4) improving the use of biomarkers for optimizing the use of existing therapies and adaptive clinical trial methodologies.

A concerted international action is thus the ideal platform for matching and leveraging expertise, infrastructure, intellectual property, biomarker developments, paradigms, and research projects with the goal of creating a basis for introducing a range of actionable CV biomarker tests and establishing efficient personalized medicine into clinical practice. Individual clinical investigators and clinical research groups should be working less in isolation and devote less effort to reporting results of single biomarkers in small series of patients, which usually lack statistical power and miss the multifactorial spectrum of CV disease. Several mechanisms exist to encourage investigators to join efforts and work collaboratively within large networks and consortia dedicated to the nascent area of personalized CV medicine.

Disclosures

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References


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What Is Measured by Cardiac Fibrosis Biomarkers and Imaging?
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