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EDITORIAL COMMENT

Myocardial Fibrosis in Hypertensive Heart Failure

Does Quality Rather Than Quantity Matter?*

James C. Moon, MD,†‡ Thomas A. Treibel, MBBS,†‡ Erik B. Schelbert, MD, MS§

"It is quality rather than quantity that matters."
—Lucius Annaeus Seneca (1)

The biology of heart failure is complex and diverse (2), posing challenges for developing efficacious therapies. All but one recent phase III heart failure trial failed to reduce mortality (3). Unlike oncology, we do not split heart failure into subtypes on the basis of disease pathways (4). We need a more targeted approach, not only for drug development, but also for drug response monitoring. Myocardial fibrosis is an attractive biomarker—fibrosis is already an established marker in the liver, kidneys, and lung—and likely a causal disease pathway mediating outcomes. Cardiac fibrosis can be measured on myocardial biopsy and tracks disease severity and outcome (5,6). But biopsy is invasive and impractical for routine clinical diagnosis and monitoring (7). Many of our current measurements are partial surrogates for fibrosis (e.g., imaging for cardiac remodeling, systolic and diastolic function), but more are needed, particularly circulating blood biomarkers. Cardiology quantifies only 2 myocardial processes routinely using such biomarkers: cardiomyocyte death (troponins) and nonspecific strain (B-type natriuretic peptides). Imagine the clinical impact if dozens more were available, specific for different activated myocardial disease pathways. Circulating collagen turnover biomarkers are attractive candidates. However, the heart is just one intermediate-sized organ releasing markers of (non-organ-specific) collagen pathways into the bloodstream. To date, collagen turnover does not sufficiently pass the litmus test of correlating with the gold standard of cardiac histology, tracking intervention, or adding value for diagnosis, prognosis, and therapeutic monitoring (8,9). New approaches are needed. Fibrosis pathways are complex, and lurking within may be more cardiac-specific processes.

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In this issue of the *Journal*, López et al. (10) investigated patients with a subset of heart failure, hypertensive heart failure. Rather than analyzing standard biomarkers of collagen quantity, they focused on collagen quality, specifically, collagen cross-linking (CCL), which has been shown to increase myocardial stiffness. The ratio of soluble and insoluble collagen by histology reflects CCL (11).

First, the authors invasively measured on biopsy CCL in health and in 38 hypertensive heart failure patients, who they dichotomized into normal and high CLL groups. Interestingly, the 2 groups did not differ in total collagen or collagen I volume fractions. But the collagen quality (via CCL) correlated well at baseline with left ventricular ejection fraction, diastolic function, and N-terminal pro-B-type natriuretic peptide, and with risk of hospitalization for heart failure (HHF) over 7 years.

Secondly, they developed biomarkers of CCL. Collagen I degradation occurs via cleavage by matrix

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From the †Department of Cardiac Imaging, Barts Heart Centre, St. Bartholomew's Hospital, London, United Kingdom; ‡Institute of Cardiovascular Science, University College London, London, United Kingdom; and the §UPMC Heart and Vascular Institute, University of Pittsburgh, Pittsburgh, Pennsylvania. Prof. Moon is directly and indirectly supported by the University College London Hospital's NIHR Biomedical Research Centre and the Biomedical Research Unit at Barts Hospital, respectively. Dr. Treibel is supported by a doctoral research fellowship from the National Institute of Health Research (NIHR; DRF-2013-06-102). Dr. Schelbert was supported by grants from The Pittsburgh Foundation (M2009-0068) and the American Heart Association Scientist Development fund (09SDG2180083). Dr. Schelbert has received contrast material from Bracco Diagnostics donated for research purposes.

metalloproteinase (MMP)-1, which generates the degradation product C-terminal telopeptide of collagen type I (CITP). However, when extensive cross-linking occurs, CITP production is lower. The ratio of MMP-1 to CITP is, therefore, a potential biomarker of cardiac CCL. They showed that the CITP:MMP-1 ratio inversely correlated with CCL; receiver-operating characteristic analysis showed reasonable sensitivity (82%) and specificity (70%), and identified a cutoff point for predicting high myocardial CCL (≤1.968).

Thirdly, in a new cohort of hypertensive HF patients (n = 203, 4.5-year follow-up), the CITP:MMP-1 ratio was measured and the cohort dichotomized into low ratio (high CCL) and normal (normal CCL). A low CITP:MMP-1 ratio was associated with higher rates of hospitalization (54% vs. 34%), increased risk of HHF on multivariate analysis (adjusted hazard ratio: 2.22), and improved risk prediction of HHF. There was no difference in cardiovascular mortality.

How does this story differ from other candidate biomarker stories? First, it tracked qualitative as well as quantitative changes. Secondly, it surpassed other candidates (e.g., osteopontin) as a histological fibrosis measure and appeared to add value beyond the raw collagen volume fraction (12). Thirdly, it predicted outcome. The downsides of the story are limited generalizability, as it focuses on hypertensive HF—although a homogeneous HF subset avoids the pitfalls of mixing the various HF etiologies in an attempt to increase sample size.

Other questions remain. Collagen metabolism is not organ-specific (13,14). Even if linked to outcome, the source of the CITP:MMP-1 is not definitively the heart—these pathways are, for example, active in the arterial wall, causing arterial stiffness (and peripheral blood correlated better to CCL than the coronary sinus samples) (15). Using a ratio of 2 biomarkers feels suspect—with X biomarkers, X factorial combinations are possible—finding positive statistical associations by chance becomes easier (multiple comparisons), even if combinations are constrained to plausible biological pathways. Outcome-linked confounders (noncardiac fibrotic disease, renal dysfunction) also may generate noncausative associations.

The heart shares many disease pathways observed in other organs. Current proteomics can detect 4,000 myocardial proteins active in hundreds of pathways (16). The high concentration of proteins and obvious pathways may not yield peripheral cardiac-specific biomarkers. New myocardium-specific imaging biomarkers, such as the extracellular volume fraction by cardiovascular magnetic resonance, quantify the whole spectrum of myocardial fibrosis noninvasively, and early data show it predicts outcome robustly (17); combining this with markers of collagen quality is an attractive avenue. Nevertheless, the authors deserve praise for their innovative approach to translate myocardial fibrosis into the clinical arena. Their remarkable efforts—multidecadal basic science, discovery in tissue, passing tests by correlation with organ-specific imaging surrogates, translation to circulating biomarkers, and validation in large external cohorts—all informed by clinical need—advances our knowledge significantly.

REPRINT REQUESTS AND CORRESPONDENCE: Prof. James C. Moon, Department of Cardiac Imaging, Barts Heart Centre, St Bartholomew's Hospital, 2nd Floor, King George V Block, London EC1A 7BE, United Kingdom. E-mail: j.moon@ucl.ac.uk.

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