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Think Small and Examine the Constituents of Left Ventricular Hypertrophy and Heart Failure: Cardiomyocytes Versus Fibroblasts, Collagen, and Capillaries in the Interstitium

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Left ventricular hypertrophy (LVH) and heart failure are prevalent and frequently encountered conditions, but several fundamental issues about LVH and heart failure remain unresolved. Although it is well known that hypertension can lead to LVH, which then heralds adverse events such as heart failure, arrhythmia, myocardial infarction, and mortality, the mechanisms mediating these events remain unclear. Weber and Brilla articulated this long-standing dilemma >20 years ago: "An explanation for why a presumptive adaptation such as LVH would prove pathological has been elusive."[1] They too cited even earlier investigators such as Wearn, who wrote in 1940, "The frequent finding at necropsy of a hypertrophied heart that has failed is familiar to all. Other than the hypertrophy, the muscle of these hearts often shows no abnormalities. Why, then, should an enlarged muscle without demonstrable abnormality fail? Hypertrophy is frequently spoken of as being compensatory. On the other hand, it is also considered to be one of the most dependable signs of heart damage."[2]

In this issue of the *Journal of the American Heart Association*, Tsao et al meticulously analyze carefully collected data from the Framingham Heart Study Offspring Cohort that exploit cardiovascular magnetic resonance measures of left ventricular mass and shape.[3] With cardiovascular magnetic resonance, one can measure LVH robustly by measures of basal wall thickness or global myocardial mass after slicing the heart like a loaf of bread. Tsao et al used sophisticated statistical measures of "added prognostic value" to demonstrate, again, that LVH predicts adverse events beyond traditional risk factors even though participants had no manifestations of cardiovascular disease. In addition, going beyond simply LVH measurement, they reported that further alterations in shape and geometry, such as increases in mass/volume "concentricity" ratios, were also linked to adverse outcomes even after accounting for the changes in left ventricular mass.

The fundamental paradox, however, remains unexplained: Why does an ostensibly compensatory mechanism lead to adverse outcomes? As a matter of convenience, many conceptualize LVH as increased muscle mass, but is it really so simple? We routinely measure the quantity of myocardial mass but seldom consider its quality.

Perspectives on the persistent paradox may emerge by "thinking small" and examining the myocardium itself at the microscopic level. The difference between adaptive LVH (eg, athletic heart) and maladaptive pathologic LVH (eg, hypertensive heart disease and diabetic cardiomyopathy) might relate to the microarchitecture and whether myocardial fibrosis (including arteriolar perivascular fibrosis) and capillary rarefaction are present. The heart may be like other vital organs such as liver, lung, and kidney, in which organ dysfunction ensues following expansion of the interstitium by excessive collagen (fibrosis) or amyloid protein. These distinctions of parenchymal versus stromal disease are critically important for developing therapy because the focus for therapeutic targets shifts away from the cardiomyocyte toward the interstitium, specifically, the fibroblast, collagen, and regulatory enzymes contained within.

Distinctions of parenchymal versus stromal disease also imply that cardiomyocyte dysfunction can result simply from a perturbed stromal milieu. In an elegant proof-of-concept study, Thum et al demonstrated precisely such a phenomenon.[4] By selectively activating myocardial fibroblasts with microRNA to create myocardial fibrosis, they could

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create LVH and a heart failure phenotype in rodents. They went on to propose a new paradigm that "assigns a primary role to cardiac fibroblast activation in myocardial disease, rather than regarding [myocardial] fibrosis as secondary to cardiomyocyte damage." Bollano et al also showed systolic dysfunction from myocardial fibrosis without any evidence of disturbed energetics (phosphocreatine:ATP ratios) in a rodent diabetes model.[5] In a sense, this interstitial heart disease paradigm adheres to the physiology of cardiac amyloidosis, in which interstitial expansion from presumably inert amyloid proteins leads to profound cardiac dysfunction, smoldering myocardial damage manifest by persistent low-level troponin elevation, severe heart failure, arrhythmia, and a dismal prognosis with high mortality rates. Perhaps one can construe myocardial fibrosis as "amyloid lite," given its lesser interstitial expansion relative to cardiac amyloidosis.

The interstitial heart disease paradigm is summarized in Figure. In further support of this concept that myocardial fibrosis damages the myocardium, Mohammed et al recently reported autopsy data from patients with LVH and heart failure with preserved ejection fraction. They demonstrated both myocardial fibrosis (ie, increased collagen concentration) and decreased microvascular density (ie, rarefaction), regardless of whether epicardial coronary disease was present.[6]

Myocardial fibrosis is reversible, but capillary rarefaction might not reverse.[7] In an experimental model of LVH, Tyralla et al again observed decreased capillary density and myocardial fibrosis, but only the myocardial fibrosis reversed with angiotensin-converting enzyme inhibition with captopril; decreased capillary density was not restored.[8] Furthermore, treatment with alternative hypertension medications not expected to reverse fibrosis (eg, furosemide/dihydralazine) had no effect on either capillary density or myocardial fibrosis.

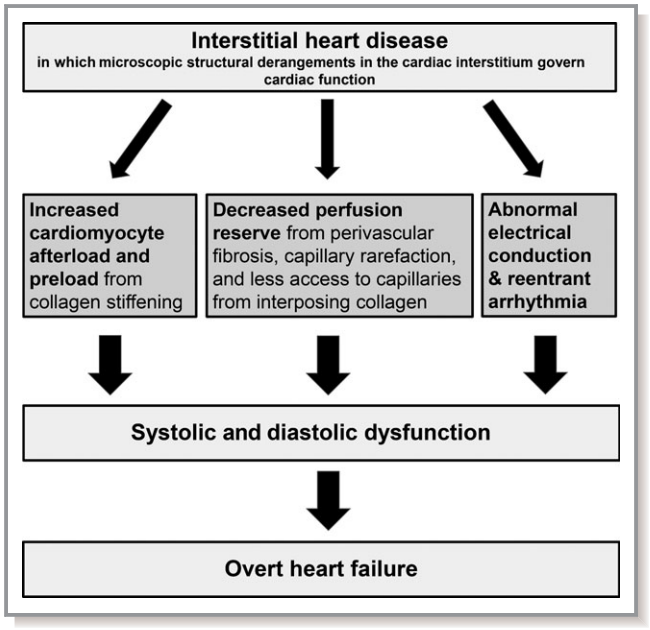

Figure. Interstitial heart disease represents microscopic changes in the myocardial stroma mediated by excess collagen (mostly type I but also type III) secreted primarily by cardiac fibroblasts in the interstitium, a situation in which synthesis predominates over degradation.

Despite the apparent lack of recovery in capillary density, in a study involving patients with LVH and hypertension, 12 months of angiotensin-converting enzyme inhibition with perindopril still culminated in recovery of perfusion reserve due to regression of perivascular fibrosis accompanied by LVH regression.[9] Essentially, treatment with agents that inhibit the renin–angiotensin–aldosterone system reverses fibrosis and then culminates in improvement in mechanical function and perfusion reserve. Importantly, these same agents also improved outcomes in heart failure trials. Nevertheless, the efficacy of renin–angiotensin–aldosterone system agents is modest, and more potent antifibrotic agents are under development. These observations have been summarized previously.[7]

How would one evaluate new antifibrotic agents? It is challenging to understand things that one cannot measure. Fortunately, novel cardiovascular magnetic resonance techniques developed after Tsao et al commenced their study can now routinely measure the extracellular volume fraction (ECV) in human myocardium. ECV simply exploits the extracellular nature of gadolinium contrast and uses it as an extracellular space marker.[10] After ≈10 minutes following a contrast bolus to permit equilibration between plasma and interstitial fluid, the myocardial uptake of gadolinium contrast relative to plasma is then a direct measure of the myocardial extracellular space. ECV is well validated and correlates highly with the collagen volume fraction, exhibiting high R^2 values in the absence of myocardial edema or amyloidosis (ascertained clinically).[11–15] ECV is also highly reproducible across separate cardiovascular magnetic resonance scans.[7] Given the robustness of ECV measures and the biological importance of the cardiac interstitium, ECV predicts outcomes[16–20] as robustly as ejection fraction, underscoring the negative impact of interstitial expansion.

ECV essentially allows one to dichotomize the myocardium into its cardiomyocyte and interstitial components and to define the spectrum of myocardial fibrosis precisely. ECV is a powerful tool to investigate issues related to left ventricular "quantity" (eg, LVH) and compare it against measures of left ventricular quality (eg, myocardial fibrosis or even amyloidosis, depending on the clinical setting) in terms of their relationships to symptoms or prognosis. The cardiology community is finally poised to address paradoxical LVH observations by investigators over the past several decades.

The work by Tsao et al[3] further solidifies and refines our understanding of the role of left ventricular mass and

geometry in mediating cardiovascular outcomes. We hope they and others will extend their observations using new cardiovascular magnetic resonance techniques to examine the role of the cardiomyocyte compartment versus the interstitium compartment in health and disease among the Framingham Heart Study participants. With the evolution of newer cardiovascular magnetic resonance tools, we can begin making significant advances in understanding the meaning of the fundamental changes occurring at the microscopic level that are now detectable in human myocardium. Even more important, ECV can be used as a tool in phase II trials to judge the efficacy of novel anti–myocardial fibrosis therapeutics in development. These capabilities might change the way we conceptualize and treat LVH.

Disclosures

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