The extracellular matrix of the heart is made up of a number of structural proteins including fibrillar collagen, smaller amounts of elastin, laminin, fibronectin, and signaling peptides. The complex collagen 3-dimensional weave, mainly consisting of type I collagen, interconnects individual myocytes through a collagen–integrin–cytoskeletal–myofibril arrangement. This network supports cardiac myocytes during contraction and relaxation and also provides a mechanism for translating individual myocyte shortening and force generation into ventricular contraction. It is also responsible for much of the ventricle’s passive diastolic stiffness. In both human and animal studies, progressive left ventricular remodeling and dysfunction are associated with significant changes in the extracellular matrix.

The structural hallmark of prolonged pressure-overload hypertrophy is increased collagen accumulation between individual myocytes and myocyte fascicles (Figure 1). Thus, the highly organized architecture of the extracellular matrix undergoes significant alterations in collagen structure, composition, and geometry caused by increased collagen synthesis, postsynthetic processing, posttranslational modification, and decreased degradation and turnover. This “reactive” collagen deposition is characterized by both perivascular and interstitial fibrosis. The changes in collagen homeostasis that occur during the development of chronic pressure-overload hypertrophy are directly associated with increased myocardial diastolic stiffness properties, which in turn cause abnormal diastolic filling. Indeed, clinical evidence suggests that progressive extracellular matrix accumulation and diastolic dysfunction are important underlying pathophysiological mechanisms for heart failure in patients with pressure-overload hypertrophy.

In volume-overload hypertrophy because of the persistently elevated preload, a much different pattern of extracellular matrix remodeling occurs. In large-animal models of volume-overload hypertrophy caused by chronic mitral regurgitation, the left ventricular remodeling process is accompanied by increased degradation of collagen fibrils surrounding individual myocytes. These changes in extracellular matrix support are associated with changes in isolated left ventricular myocyte geometry.

Fibrillar collagen is dominant in the fibrotic myocardial interstitium and has been classified into several types according to the sequence and combination of α-chain amino acids. Five types of collagen (types I, III, IV, V, and VI) are found in the myocardium. The cardiac extracellular matrix is predominantly composed of fibrillar collagen type I (85%) and type III (11%). Collagen type I forms thicker fibers and is primarily responsible for the tensile strength of the heart. Collagen type III fibers have a relatively small diameter and provide elasticity to the myocardium and the structural integrity of the collagen network of the heart.

Both types I and III fibrillar collagens are secreted into the extracellular space as procollagens. Secreted type I and III procollagens have amino- and carboxyterminal extension.
between hs-cTNT levels and dysregulated collagen metabolism are stronger in patients with heart failure than in controls without heart failure. Although these findings may be important to the biology of myocardial fibrosis and the pathophysiology of heart failure, several questions remain to be elucidated.

Is Cardiac Troponin T Useful in Determining Collagen Synthesis or Degradation in Myocardial Microinjury?

Multiple potential mechanisms may contribute to the release of cardiac troponin in patients with heart failure, including subendocardial ischemia, cardiomyocyte damage from inflammatory cytokines or oxidative stress, hibernating myocardium, or apoptosis. Enzyme release may also occur early during reversible injury of myocardial cells as a result of transient leakage from the cytosolic component from loss of sarcolemmal integrity.

Detectable circulating cardiac troponin I is rare in the general population. Findings by Kop et al are in concordance with recent data from a large observational study in Europe that showed an association between low levels of circulating cardiac troponin and the development of heart failure in completely asymptomatic subjects. These data suggest that subclinical cardiomyocyte damage, as indicated by elevated serum levels of cardiac troponin I, may be an independent contributor to the development of heart failure in the community.

Multiple studies have subsequently examined the prevalence of transient or persistent elevation of serum cardiac troponin I or troponin T levels in the setting of advanced heart failure. In the Valsartan Heart Failure Trial, hs-cTNT was detectable in 92% of patients with stable chronic heart failure, and was a powerful predictor of adverse outcomes. The relationship between changes in hs-cTNT and the levels of CITP and PIIINP, but not with the levels of carboxyterminal propeptide of procollagen type I in the study by Kop et al suggests that although hs-cTNT release is a marker of nonspecific myocardial microinjury, it is associated with a rather distinct activation of different pathways of collagen metabolism. This indicates a limited value of using hs-cTNT levels for predicting myocardial collagen degradation or deposition with myocardial microinjury.

Are Markers of Collagen Metabolism Specific for Heart Failure With Preserved Versus Reduced Systolic Function?

The study by Kop et al found significant correlations between baseline and changes in hs-cTNT levels over time with CITP that were similar for patients with heart failure with reduced and preserved ejection fraction. However, whereas PIIINP was associated with both baseline and changes in hs-cTNT levels over time in patients with heart failure with reduced ejection fraction, PIIINP only correlated with baseline hs-cTNT levels in patients with heart failure with preserved ejection fraction. A recent study by Zile et al demonstrated that in patients with heart failure with preserved ejection fraction, there are significant increases in both PIIINP and CITP; however, PIIINP, together with 3 other biomarkers, but not CITP, were predictive of the presence of diastolic heart failure. These data emphasize the concept that the use of a single

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**Figure 2.** Scanning electron micrographs taken from normal canine left ventricular myocardium following chronic mitral regurgitation that causes a volume-overload hypertrophy (VOH). In this model of VOH, a loss of normal extracellular matrix architecture was demonstrated between individual myocytes (arrows), and the collagen supporting network is poorly organized. Reproduced with permission.
measurement in a dynamic, diverse, and complex structure such as the myocardial extracellular matrix and the clinical syndrome of heart failure may be insufficient to assess the usefulness of biomarkers for the detection and prediction of left ventricular hypertrophy and diastolic heart failure. To our knowledge, no studies have compared the specific changes in cardiac collagen homeostasis in patients with heart failure with preserved versus reduced systolic function.

Are Markers of Collagen Metabolism Reliable Surrogates for Myocardial Fibrosis?
Clinical evaluation of the presence and magnitude of extracellular matrix accumulation in the heart is difficult. The gold standard for such evaluation is myocardial biopsy, but even then, fibrosis may be missed if it is nonhomogeneously distributed throughout the heart. Various imaging modalities have been proposed in an attempt to quantitate pathological extracellular matrix distribution, but these may suffer from methodological deficiencies in identifying true pathological fibrosis. Are biochemical markers of collagen turnover promising in this regard? Plasma biomarkers reflect changes in the ongoing process of collagen synthesis, processing, and degradation. Other biomarkers such as matrix metalloproteinases and tissue inhibitors of metalloproteinases reflect the regulatory control mechanisms effecting collagen homeostasis. These biomarkers do not directly assess collagen content, composition, or geometry within the myocardium; however, assessment of these biomarkers certainly do reflect directional changes in extracellular matrix homeostasis and collagen. For example, the ratio of the markers of collagen synthesis versus collagen degradation may indicate the direction of changes in the extracellular matrix, toward collagen accumulation and fibrosis or toward collagen degradation and collagen loss.

Conclusion
Collagen metabolism markers are of scientific interest because they provide insight into the complex pathophysiology of left ventricular dysfunction in heart failure. Although hs-cTNT release reflects myocardial microinjury, it cannot specify the related changes in collagen metabolism, toward collagen synthesis or degradation. The specific changes in serological markers of collagen turnover occurring in heart failure with preserved versus reduced systolic function remain to be elucidated. Collagen markers are reasonable candidates for use as research and clinical tools to estimate the extracellular matrix metabolism. They can be measured in blood samples, allowing repeated determinations, which may permit monitoring reparative processes and the effect of treatment. Further advances in our understanding of collagen metabolism may facilitate improved characterization of myocardial extracellular matrix remodeling and promote new directions for fundamental research or the development of new therapies.

Disclosures
None.

References


**Key Words:** Editorial ▪ heart failure ▪ biomarkers ▪ troponin ▪ hs-troponin T ▪ collagen metabolism
Troponin T and Plasma Collagen Peptides in Heart Failure
Viorel G. Florea and Inder S. Anand

Circ Heart Fail. 2012;5:394-397
doi: 10.1161/CIRCHEARTFAILURE.112.969279
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/5/4/394

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