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EDITORIAL COMMENT

Molecular Imaging and the Failing Heart

Through the Looking Glass*

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"The time has come," the Walrus said, "to talk of many things: Of shoes—and ships and sealing wax—and cabbages and kings, and why the sea is boiling hot—and whether pigs have wings."

—Lewis Carroll, Through the Looking Glass and What Alice Found There (1871) (1)

Despite the many strides in the management of heart failure during the past 2 decades, the efficacy of our current pharmacologic approach in heart failure is variable and is often unpredictable. Accordingly, there is growing need to develop personalized strategies for managing patients with heart failure. Although pharmacogenomics has been proposed as an important way to personalize heart failure therapy (2), it does not allow for optimization of drug dosage in individual patients. There

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has been growing interest in using molecular imaging for phenotypic characterization of the failing heart (reviewed in Jaffer and Weissleder [3]). In this issue of the *iJACC*, van den Borne et al. (4) report on the use of a novel arginine-glutamate-aspartate (RGD) peptide, technetium-99m-labeled Cy5.5-RGD-imaging peptide (CRIP) (5), to evaluate changes in collagen synthesis in mice that were treated with angiotensin and/or aldosterone antagonists, either alone and in combination, after acute coronary artery ligation. CRIP is a cyclic peptide that was originally developed to image integrins such as $\alpha_v\beta_{3/5}$, which are up-regulated during angiogenesis. Subsequently, CRIP was shown to bind to integrins expressed in activated myofibroblasts as well as to correlate with new collagen synthesis within the infarct zone (5). In the study in this issue of *iJACC*, CRIP was intravenously administered after 4 weeks after acute coronary occlusion in mice that were treated with a single neurohormonal antagonist (captopril, losartan, and spironolactone) or with combinations of neurohormonal antagonists. At the time of terminal study the hearts were characterized histopathologically for the presence of myofibroblasts and for thick and thin collagen fiber deposition with the use of picrosirius red staining. The authors found that CRIP uptake was maximal in the infarct zone of untreated mice (2.3 ± 0.14%) and was significantly decreased in the animals that were treated with a single neurohormonal antagonist (1.7 ± 0.35%; $p = 0.0002$). Importantly, the addition of 2 neurohormonal antagonists together (captopril + losartan, spironolactone + captopril or spironolactone + losartan) or all 3 neurohormonal antagonists (captopril + losartan + spironolactone) further reduced the uptake of ^{99m}Tc-labeled CRIP in the infarct zone (1.31 ± 0.40%; $p < 0.0001$ and 1.16 ± 0.26%; $p < 0.0001$, respectively). Importantly, the deposition of thin collagen fibers was significantly reduced in mice treated with the neurohormonal antagonists and was correlated with CRIP uptake. The authors conclude that molecular imaging with CRIP allows for the evaluation of the efficacy of neurohormonal antagonists. To place the study in proper perspective, it is helpful to digress for a moment and discuss what is known about the regulation of the extracellular matrix in the failing human heart.

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Alterations in the Extracellular Matrix in the Failing Heart

The cardiac fibroblast, which comprises the vast majority (>90%) of nonmyocyte cells in the heart, is the primary cell type that is responsible for the secretion of the majority of extracellular components in the heart, such as collagens I, III, and IV; laminin; and fibronectin. In response to mechanical stress and/or neurohormonal activation (e.g., angiotensin and/or aldosterone), a subset of fibroblasts undergo phenotypic conversion to myofibroblasts, that are characterized by increased expression of alpha-smooth muscle actin and enhanced secretory activity. Myofibroblasts also express increased levels of angiotensin receptors (6) and increased expression of $\alpha_v\beta_{3/5}$ integrins, which function as receptors for transforming growth factor β_1, an extremely profibrotic peptide (7). Myofibroblasts migrate into the area surrounding tissue injury, where they are responsible for the collagen secretion and contraction/realignment of the nascent collagen fibers and thus play an important role in the final scar formation at the site of injury. Thus, increased activation of myofibroblasts and increased collagen synthesis are believed to contribute to disease progression in heart failure. And indeed, studies in failing human myocardium have shown that there is a quantitative increase in collagen I, III, IV, and VI; fibronectin; laminin; and vimentin (8) and that the ratio of type I collagen to type III collagen is decreased in patients with ischemic cardiomyopathy (9). The accumulation of collagen, can occur on a "reactive" basis around intramural coronary arteries and arterioles (perivascular fibrosis) or in the interstitial space (interstitial fibrosis) and does not require myocyte cell death.

Alternatively collagen accumulation can occur as a result of microscopic scarring (replacement fibrosis), which develops in response to cardiac myocyte cell loss. This scarring or "replacement fibrosis" is an adaptation to the loss of parenchyma and is therefore critical to preserve the structural integrity of the heart. Indeed, the prevention of fibrosis immediately after infarction (i.e., disruption of wound healing) has been associated with untoward clinical outcomes in clinical trials (10). However, the increase in structural integrity that is provided by increased collagen synthesis/accumulation comes at a cost. That is, the increased fibrous tissue leads to increased myocardial stiffness, which would presumably result in decreased myocardial shortening for a given degree of afterload. In addition, myocardial fibrosis may provide the structural substrate for atrial and ventricular arrhythmias, thus potentially contributing to sudden death. Accordingly, the ability to monitor both the development of myocardial fibrosis, as well as the total amount of collagen deposition in individual patients after an acute myocardial infarction and/or in the failing heart, would represent a significant positive step toward individualizing heart failure therapy and would therefore be of significant clinical importance.

Although myocardial fibrosis (i.e., collagen content) can be detected by late gadolinium-enhancement and cardiac magnetic resonance imaging (11), our ability to monitor ongoing de novo collagen synthesis in the failing heart is limited to monitoring circulating levels of fragments of collagen propeptides (e.g., N-terminal peptide collagen propeptides and C-terminal peptides) (12). However, although these circulating levels of these biomarkers decrease in heart failure patients that have been treated with neurohormonal antagonists (13), these biomarkers are nonspecific insofar as they reflect ongoing collagen synthesis in the body (e.g., bone turnover), and may therefore have limited applicability in terms of guiding heart failure therapies. Thus, the current study may be important clinically because it would allow for direct monitoring of ongoing collagen synthesis in patients after an acute myocardial infarction. This in turn would allow for optimization of pharmacological approaches for these patients.

However, there are 2 potential limitations of this novel imaging approach that warrant further discussion. First, the in vivo data suggest that CRIP binds predominately to $\alpha_v\beta_{3/5}$ integrins on activated myofibroblasts. It bears emphasis that $\alpha_v\beta_{3/5}$ integrins are expressed on a variety of cell types, including macrophages, intimal and medial smooth cells, endothelial cells of microvessels, and platelets. Although CRIP binding was largely confined to the infarct zone in the previous study by van den Borne et al. (5), this finding may have occurred because there was a predominance of myofibroblasts at the time radiolabeled CRIP was administered. Thus, the signal-to-noise ratio of this novel molecular imaging agent may become problematic in the clinical setting, wherein the timing of infarction is not as well known and/or patients are being administered anti-inflammatory agents (e.g., aspirin and statins) that decrease inflammatory signaling, which might decrease the conversion of fibroblasts to myofibroblasts. Second, it is unclear from these studies in which the authors used acute coronary

artery occlusions whether the signal from radiolabeled CRIP is sufficient to image myocardial fibrosis in smaller infarcts (e.g., non–ST-segment infarcts) and/or myocardial fibrosis after reperfusion injury, wherein there is an influx of inflammatory cells that express $\alpha_v\beta_{3/5}$ integrins.

Notwithstanding these potential therapeutic limitations, the initial use of CRIP appears promising in studies in patients with ischemic cardiomyopathy (14) and offers a potentially exciting new "looking glass" for monitoring the development and progression of myocardial fibrosis during cardiac remodeling. As with all things in heart failure, progress in the use of molecular imaging agents to monitor heart failure therapy will require the collaborative efforts between basic scientists and clinical scientists to perform the requisite target validation and the careful clinical phenotyping that are required to move from the bench to the bedside. To this end, the study by van den Borne et al. (4) in the current issue of the *Journal* represents an important step.

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