Molecular Imaging of the Remodeling Heart: The Next Step Forward*

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Cardiac remodeling is the term used to describe changes in cardiac structure that occur following injury to the heart and/or in response to long-standing increases in loading conditions. Regardless of the nature of the initial insult, the remodeling process tends to be more or less uniform in nature. Relatively well-described changes in gene expression produce prototypic phenotypic changes in cardiac myocytes and fibroblasts that result in progressive deterioration in cardiac function and the development of heart failure.

Imaging of the remodeling heart has enabled us to define the timing of the process, magnitude of increase in muscle mass and chamber volumes that occur in various settings, presence of conformational changes in the heart, and, to a limited extent, the tissue that is involved (e.g., amount of fibrosis).

Currently available methods that focus on structural and geometric changes, however, provide little insight into the molecular mechanisms involved and as such they describe relatively late downstream events in the remodeling process. Theoretically, information depicting changes at the molecular level in cardiac cells should help identify individuals at risk for remodeling as well as new targets for therapy. Moreover, if such imaging could be performed noninvasively with little risk to the patient, sequential information obtained over time could provide novel mechanistic insights and assess the adequacy of therapeutic interventions.

The renin-angiotensin system (RAS) plays a major role in cardiac remodeling. Angiotensin (Ang) II, the key effector molecule of the RAS, interacts with specific cell surface receptors to initiate changes that are critical to the progression of the remodeling process. Although several Ang peptide receptors have been identified, the most important of these is the type 1 or AT$_1$ receptor. Interestingly, this receptor is considerably more abundant on cardiac fibroblasts than on myocytes (1). In the post-myocardial infarction (MI) remodeling heart, the density of the AT$_1$-receptor population on cardiac fibroblasts is increased, a process that appears to be driven by release of proinflammatory cytokines (2,3). The AT$_1$ receptor on fibroblasts mediates Ang II-stimulated production of extracellular matrix proteins (ECMs) and also tissue inhibitors of metalloproteinases that regulate ECM breakdown. Increases in receptor density have been shown to significantly enhance these Ang II effects (4). Evidence that Ang II-stimulated cardiac myocyte hypertrophy is dependent on the release of secondary growth factors from fibroblasts further emphasizes the central role of the AT$_1$ receptor on cardiac fibroblasts in the remodeling process (5). In the remodeling heart, increased AT$_1$ receptor density occurs at a time when local production of Ang II is increased, providing conditions for a “perfect storm” as far as remodeling is concerned.

In the present study, evidence of AT$_1$ receptor up-regulation in the infarct and border zones was seen during the period when post-MI remodeling is most intense. Rapid replacement of devitalized myocardium with firm scar tissue prevents cardiac rupture and also helps reduce wall stress by limiting chamber expansion. In that regard, the initial RAS activation in the infarct zone is helpful because the transformed myofibroblasts that migrate to the region play a major role in breaking down existing scaffolding and generating

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From the University of California, San Diego. H. William Strauss, MD, served as Guest Editor for this article.
the ECM proteins that form the replacement scar. These same processes, however, are activated in remote noninfarcted regions of myocardium where they lead to the deposition of perivascular and interstitial fibrosis. The resultant disordering of the ECM and increase in fibrous tissue adversely affects both systolic and diastolic functions of the heart. Efforts to counteract RAS activation with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers inhibit remodeling and favorably alter the natural history of heart failure in both experimental animal models and human patients (6–9). As a result, these agents are strongly recommended in heart failure guidelines with increasing emphasis on early recognition and treatment of patients at risk (10).

In this issue of JACC: Cardiovascular Imaging, Verjans et al. (11) provide exciting information about imaging of Ang receptors in the post-MI remodeling heart. To accomplish this, they used 2 complimentary approaches. In the first, a fluorescein-labeled Ang peptide analogue was administered intravenously to mice beginning at 30 min and then at various times up to 12 weeks after left anterior descending coronary artery ligation. Real-time in vivo optical imaging of open-chested mice was performed using a fluorescence stereomicroscope attached to a camera. Their results show that uptake of tracer was observed in the infarct region as early as 1 day post-MI and that it had increased substantially at 1 week. By 6 weeks, fluorescence (seen predominantly in the border zone at this time) was decreased, a process that continued until the last measurement 12 weeks post-MI. This time course, which paralleled the development of echocardiographic LV dilation, is consistent with previous reports of post-MI remodeling in this model (12). Subsequent examination of cardiac tissue indicated that the source of fluorescence was the population of collagen-producing myofibroblasts located in the infarct and border zones. Previous reports have documented an influx of these cells and up-regulation in their AT1-receptor density post-MI that closely parallels the findings in the present study (3).

The investigators also performed micro–single-photon emission computed tomography (SPECT) and micro-computed tomography imaging using radiolabeled losartan at 3 weeks post-MI. Specificity of this compound for the AT1 receptor confirmed that the signal originated from tracer binding at this receptor rather than at the AT2 or other Ang receptors. Uptake was seen in the anterolateral cardiac image by SPECT, and ex vivo imaging confirmed that this originated from the infarct and border zones. Quantitative assessment indicated that uptake was significantly higher in post-MI than in noninfarcted control hearts.

The ability to visualize changes in the expression of the AT1 receptor in the remodeling heart in vivo represents an important step in our efforts to prevent and/or inhibit remodeling. In a sense, it brings us “closer” to the action and as such holds the promise of allowing early identification of patients at risk and also of determining the adequacy of therapies designed to inactivate the RAS. In this particular case, one could imagine using AT1-receptor imaging to define patients who are at risk for remodeling in a variety of settings including post-MI. If such patients were then treated with an angiotensin-receptor blocker, imaging could be used to determine how effective the agent and dose was in blocking tracer uptake within the heart. Continued high levels of signal despite therapy might indicate that additional drugs or approaches are required. The demonstration that molecular pathways within the remodeling heart are approachable by in vivo imaging also indicates that it is possible to assess trafficking within critical signaling pathways stimulated by the RAS and other systems that are believed to play a role in cardiac remodeling. Information from future studies could thus provide powerful insights into the activation of these systems as well as the effects of various treatments.

It is important to recognize that as exciting as these results are, much work still needs to be done. Imaging in these experiments was performed in an open-chest model and translation of these results to a closed-chest human patient who may have postoperative fibrotic tissue as well as considerable amounts of muscle, adipose tissue, or air (in the case of the emphysematous patient) between the heart and the camera will obviously take considerable amounts of work. In addition, imaging of the AT1 receptor in the infarct and peri-infarct zone represents a relatively easy target because the increase is concentrated into relatively circumscribed zones. Imaging of more diffuse signals that originate in noninfarcted myocardium where AT1-receptor effects are more clearly deleterious is likely to be challenging. If this approach is going to be important in determining adequacy of therapy, an important early step would be to assess the effect of treatment with agents such as angiotensin-receptor blockers on the intensity of the signal that originates from the AT1 receptor.
Nonetheless, the results reported here are impressive and the promise for future advances that they imply is considerable. The investigators deserve much credit for demonstrating that a physiologically relevant molecule whose expression is altered in remodeling hearts could be imaged in a living animal. Although it may be only a step, it clearly is an important one. Further work in this area will hopefully move along quickly so that in vivo imaging of molecular events in the remodeling heart will become a reality in patients in the not so distant future.

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