Imaging of Infarct Healing Predicts Left Ventricular Remodeling and Evolution of Heart Failure

Focus on Protease Activity

Matthias Nahrendorf, MD, PhD

Current state-of-the-art care ensures that most patients with myocardial infarction (MI) survive the acute ischemic event. There is strong evidence that timely reperfusion therapy limits the loss of myocardium, preserves cardiac function, and improves survival. Conversely, delayed or insufficient tissue reperfusion results in prolonged ischemia and myocyte death. Necrotic cell death initiates the wound-healing process that parallels the response of the body to other sterile injuries. Unlike other injuries, for instance, a bone fracture for which a plaster cast can reduce tissue movement during repair, wound healing after MI can be greatly affected by cardiac motion and wall stress. The efficacy of healing is important, and suboptimal healing leads to weakened resistance to mechanical forces, which in turn results in infarct expansion, adverse remodeling, and ultimately, heart failure.

Angiotensin-converting enzyme inhibitors and β-blockers help reduce adverse remodeling, the desire to regenerate functioning heart muscle has motivated considerable interest in stem cell research, and recent discoveries on myocyte turnover are fueling the hope that one day “regrown” myocytes can replace the lost contractile units. Because there will be no plaster cast for the heart, tweaking the body’s inflammatory response to myocyte death and optimization of infarct healing could complement the efforts on regenerative strategies.

There are 2 major aspects of how imaging can facilitate these efforts. First, the ability to noninvasively study molecular and cellular biology provides an opportunity to understand and then therapeutically target key aspects of disease processes. Why is that the case? We can avoid in vitro artifacts, follow the time course of biomarkers in their undisturbed environment, and correlate molecular and cellular players to each other and to changes in heart function and anatomy, as done by Sahul et al in this issue of Circulation: Cardiovascular Imaging, and to outcomes. Second, in parallel to driving the therapeutic discovery for more efficient means to attenuate left ventricular remodeling, we must develop the tools to monitor therapeutic effects and identify patients at risk for post-MI heart failure.

Such tools can accelerate research by using surrogate end points, which could make clinical studies more efficient and faster and reduce research and development costs that are currently so high that pharmaceutical companies are shying away from cardiovascular drug development.

A variety of imaging approaches, spanning many healing biomarkers and all major imaging modalities, have been developed toward these goals (Table). These include cell death; upregulation of chemokines and adhesion molecules; phagocytic, myeloperoxidase, protease and transglutaminase activity; angiogenesis; myofibroblasts; collagen production; and receptors that are targeted with current heart failure medication.

In the current study, Sahul et al take their long-standing effort on imaging matrix metalloproteinases (MMPs) to the next level. Because of their central role in disease, proteases, and among them MMPs, are especially promising imaging targets. Some protease activity is probably needed during wound healing. Macrophage mobility in tissue depends on proteases, and these cells are crucial for the clearance of necrotic debris after ischemic tissue injury. However, if inflammation is enhanced and protease activity exceeds normal levels, the tissue is destabilized beyond integrity. Transgenic mice with increased MMP activity are prone to infarct rupture and post-MI heart failure. The Yale group has pioneered the use of nuclear probes that bind to the active site of MMPs and hence report on the activity of the enzyme. The current work describes that previous data obtained in rodents translates into a clinically relevant large-animal model, thus motivating a clinical trial. Importantly, the probe uptake correlated with left ventricular volume, which, in conjunction with the data on infarct rupture reviewed by Spinale, suggests that higher MMP activity promotes infarct expansion and probably also side-to-side slippage of myocytes in the remote myocardium. Excessive protease activity may impair the integrity of the extracellular matrix, which then gives way to the intraventricular pressure, leading to ventricular dilation.

The elegant multimodality study correlated MMP activity, regional myocardial function, and left ventricular volumes in otherwise healthy pigs that had a comparable...
Table. Imaging Approaches and Healing Biomarkers

<table>
<thead>
<tr>
<th>Process</th>
<th>Target</th>
<th>Time After MI</th>
<th>Probe</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell death</td>
<td>Phosphatidylserine</td>
<td>Hours</td>
<td>Annexin V-CLIO⁴</td>
<td>MRI (T2)</td>
</tr>
<tr>
<td>Leukocyte recruitment</td>
<td>VCAM-1</td>
<td>Days</td>
<td>¹⁸F-EP⁻⁴</td>
<td>PET/CT</td>
</tr>
<tr>
<td>Phagocytosis</td>
<td>Neutrophils</td>
<td>Days</td>
<td>Microbubbles</td>
<td>Ultrasound, fluorescence molecular tomography, MRI (T2, F19 fluorine)</td>
</tr>
<tr>
<td></td>
<td>Monocytes</td>
<td></td>
<td>CLIO nanoparticles</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Macrophages</td>
<td></td>
<td>Liposomes</td>
<td></td>
</tr>
<tr>
<td>Procoagulase</td>
<td>MMPs</td>
<td>Days to weeks</td>
<td>⁹⁹⁹Tc-RP805⁵,¹⁶</td>
<td>SPECT/CT, fluorescence molecular tomography</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Cathepsins</td>
<td></td>
<td>MPO-6d⁹</td>
<td>MRI (T1)</td>
</tr>
<tr>
<td>Matrix cross-linking</td>
<td>Transglutaminase Factor XIII</td>
<td>Days</td>
<td>¹¹¹Ind-FXIII⁹¹⁰</td>
<td>SPECT</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>Integrin</td>
<td>2 Weeks</td>
<td>¹⁸F-Galaktoto-RGD¹¹</td>
<td>PET/CT</td>
</tr>
<tr>
<td>Matrix</td>
<td>Collagen</td>
<td>Days</td>
<td>Collagen-specific peptide EP-3533¹⁹</td>
<td>MRI (T1)</td>
</tr>
<tr>
<td>Myofibroblasts</td>
<td>Integrin</td>
<td>3 and 8 Weeks</td>
<td>RGD peptide RIP²²</td>
<td>SPECT/CT</td>
</tr>
</tbody>
</table>

PET indicates positron emission tomography; CT, computed tomography; and SPECT, single-photon emission computed tomography.

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Disclosures

None.

References


infarct size of about 22%. Despite this fairly homogeneous cohort, interindividual differences in healing led to data scatter and allowed significant correlation of the molecular signal and left ventricular size. There probably is even higher heterogeneity in patients, given their variability in age, infarct size, comorbidity, and genetics. Importantly, patients—unlike the pigs in the current study—have preexisting atherosclerosis, a chronic inflammatory disease associated with blood monocytosis. Clinical studies have shown that high numbers of protease-rich circulating monocytes correlate closely with outcome and the degree of heart failure.¹⁸ We have recently found that coronary ligation in apoE⁻/⁻ mice with atherosclerosis causes excessive monocyte recruitment, higher infarct protease activity, impaired resolution of inflammation, and worse infarct healing.⁶ In these mice, infarcts expanded and left ventricular dilation increased. Taken together, these considerations support the hypothesis that the molecular imaging agent used by Sahul et al in a porcine model will predict left ventricular remodeling and prognosis in patients after MI. Hopefully, we will soon read about a clinical protease imaging trial.


**Key Words:** Editorials • myocardial infarction • molecular imaging • healing • matrix metalloproteinase
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