Exposing *ACE* up the Sleeve. . .

All uncertainty is fruitful. . .so long as it is accompanied by the wish to understand.
Antonio Machado

There is unequivocal evidence that an excess of angiotensin-converting enzyme (ACE), a transmembrane dipeptidyl peptidase enzyme that generates angiotensin II and increases bradykinin and other peptide substrates of as yet unclear significance, has a potent adverse effect on the heart and the vascular system. Increased levels of ACE and other components of the renin–angiotensin system have consistently been found in patients with myocardial infarction, patients with myocardial infarction in transition to heart failure through the process of ventricular remodeling, and patients

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with established ischemic cardiomyopathy and heart failure. Not surprisingly, ACE inhibitors protect against cardiovascular damage in several heart disease states, including incipient, early-stage, and late-stage heart disease (*1–3*). However, there is also emerging evidence that not all patients need or indeed benefit from ACE inhibitors (*4*). In addition, given the possibility of intolerance to and adverse effects from ACE inhibitors, the ability to predetermine who will benefit from ACE inhibitors is likely to be useful for clinical therapeutics. The article by Dilsizian et al. (*5*) in this issue of *The Journal of Nuclear Medicine* suggests the feasibility of such a phenomenon by using molecular imaging techniques to quantify tissue ACE (*5*). This method, along with other possible techniques to quantitate ACE activity in vivo using PET (*6*), multiphoton in vivo imaging, or specific indicator extraction (*7*) methods, might help clinicians understand and predict the benefits of ACE inhibitors. These kinds of noninvasive capabilities are welcome and might be even more relevant given the newer data that ACE might have actions beyond those that can be blocked by ACE inhibitors.

Apart from the quantity of ACE inhibitor, its distribution, which can be revealed clearly by imaging techniques, is also of great interest. Normally, ACE is present mostly on the luminal surface of the vascular endothelium, particularly in the lungs (*8*). In the normal heart, it is found mainly on the valves and the arterial vasculature, with little in the endocardium (*9*). Cardiovascular abnormalities change this distribution, with ACE being localized mainly to areas of injury and repair; the atherosclerotic coronary artery carries ACE in the media, in vascular macrophages (*10*), and in complicated plaques (*11*). An even more impressive change occurs in the infarcted heart, with significant localization in the fibroblasts and in the myocytes of infarcted and periinfarcted tissues (*12*). These changes have firmly been linked to the process of ventricular remodeling. More important, the predominant site of ACE storage changes from the pulmonary endothelium to the injured myocardium (*13*). Because transfecting ACE into the heart mediates left ventricular hypertrophy and fibrotic remodeling (*14*), it is obvious that tissue ACE levels have a direct pathophysiologic import. What is not known is the level of dynamic change with and without ACE inhibitor therapy and whether such changes can predict who will respond to ACE inhibitors and to what extent. With a clear pathogenetic role for tissue ACE in tissue damage and healing, many of the data underscore the importance of being able to quantitate organ-specific tissue ACE activity.

How will imaging ACE help in managing patients with heart disease? Conceptually, an ability to noninvasively image dynamic changes in tissue ACE is likely to help us understand how ACE and ACE inhibitors work, identify patients in whom ACE inhibitors may work, and possibly predict prognostic outcomes even before ACE inhibitors are started. There is convincing evidence that the ability to noninvasively monitor fibrosis (one of the important endpoints of increased ACE activity) has helped in heart failure and antihypertensive therapy (*15*). This evidence might suggest that ACE itself might be a good marker of outcomes. However, this technique will have to cross quite a few hurdles. For one, it has to be specific to tissue ACE, work well in vivo, and be sufficiently sensitive to minor dynamic changes in ACE levels. Proof is needed that small changes in ACE, detectable by in vivo imaging, correlate proportionally to pathologic changes. Furthermore, non-ACE pathways such as chymases are important in human heart failure (*16*), and demonstration would be needed that changes in myocardial ACE are important even in the presence of alternate pathways. Finally, one would need to generate data correlating ACE imaging to outcomes.

One could reasonably argue, on the basis of the large volume of clinical trial data, that we should just use ACE inhibitors and that ACE imaging may be superfluous. However, the economic

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burden of ACE inhibition, approximately $7 billion every year, is based entirely on the recommendations of large randomized clinical studies that ignored individual variability in ACE inhibitor efficacy. Indeed, some studies (*4*) have identified patient populations that did not benefit from ACE inhibitors. In addition, ACE inhibitor–related side effects are not inconsequential, and restricting ACE inhibitors to patients who we know would be responders might be useful. Furthermore, recent reports indicate that the effect of ACE inhibitors is due to more than just ACE inhibition! In fact, the very process of an antagonist's binding to ACE actively signals to the nucleus via the CK2-ACE–associated Jun N-terminal kinase–phosphorylated c-Jun and activator protein-1 (AP-1) pathways, and this may be responsible for some of the benefits seen with ACE inhibition (*17*). If this signaling were shown to be a major effector pathway, the ability to image the available ACE might be of true importance. Finally, extending ACE imaging to ACE-2 (a potent anti-ACE pathway that has protective effects in the cardiovascular system (*18*)) may allow us to comprehensively estimate prodamage and antidamage pathways in the myocardium. This estimation would be similar to standard measurements of other benefit-to-damage ratios, such as Bcl2/BAX (B-cell lymphoma-2 protein/Bcl2-associated X protein).

The feasibility of the approach, proposed by Dilsizian et al. (*5*), of exposing the magnitude of intracellular ACE upregulation will need to be proven by in vivo imaging studies. In the past, the likelihood of imaging an intracellular target and retaining the probe has often been hampered by practical difficulties. In vivo studies of radiolabeled ACE inhibitor uptake will also be necessary to evaluate the extent of background noise in nontarget tissues of high constitutive ACE activity, such as the lungs. Adequate myocardial uptake and low pulmonary uptake will be mandatory for the development of an imaging technique of incremental clinical utility. Nonetheless, the current proposal spearheads other active efforts to develop novel tracers and techniques for molecular imaging of ACE (*19,20*). Targeting of the other components of the renin–angiotensin system, such as angiotensin receptors by angiotensin II fragments and angiotensin receptor type I blocking agents (*21*), also offers the promise of being able to noninvasively monitor neurohumoral perturbations in the myocardium in health and disease. In a best-case scenario, such quantitation might help us target and alter the natural history of many stage B heart failure patients before they transition to the more undesirable and advanced stages C and D. Molecular imaging has opened new frontiers in our understanding of pathophysiology and therapeutics. Much is not yet known about ACE and ACE inhibitors despite their widespread use. An ability to use these sophisticated techniques in imaging ACE, as shown by Dilsizian et al., along with other similar components of renin–angiotensin cascade may yield rich dividends down the road.

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