Noninvasive Quantification of Myocardial β-Adrenergic Receptors
A First Step

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The modern era of the study of adrenergic receptors was begun in 1948, when Ahlquist described the relative potencies of norepinephrine, epinephrine, and isoproterenol in mediating smooth muscle contraction or relaxation. Since then, analysis of α- and β-adrenergic receptors has progressed largely on the basis of technical and methodological advances. The first β-adrenergic antagonist, dichloroisoproterenol, was described in 1958. Contemporary radioligand binding assays, dependent on highly specific and potent drugs labeled to high specific activities, became a reality in the early 1970s. The widespread application of new “classic” methods of molecular biology in the late 1980s and the marriage of the molecular approach to basic electrophysiology led to the stunning delineation of receptor gene families encoding proteins with seven membrane-spanning domains and communicating with effectors via complex and multivalent G-protein interactions.

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The extraordinary progress in characterizing the pharmacology, biochemistry, and molecular biology of adrenergic receptors has outpaced the success of efforts to understand pathophysiological roles of adrenergic receptors in important human diseases such as congestive heart failure, systemic hypertension, asthma, thyroid disorders, and neurological and psychiatric disorders related to autonomic dysfunction or derangements in catecholamine metabolism. The reasons are obvious. Physiological and pathophysiological responses to agonists or antagonists are complex. They reflect the actions of multiple components (receptors, G-proteins, effectors, and post-effector biochemical changes) in tissues composed of multiple cell types bearing multiple receptor subtypes. Moreover, opportunities to study human disease are limited by inaccessibility of critical tissues and difficulties in longitudinal assessment of receptor function. Certainly, insights have been gained by studying animal models of human diseases and by gleaning information from accessible human material such as blood plasma and cells or small tissue biopsies. Clearly, however, a major barrier to progress has been the lack of a direct quantitative method to characterize receptors noninvasively. With publication of the study of Merlet et al in this issue of Circulation, an important first step toward this goal has been made. With it comes the potential to more directly study the pathophysiology of β-adrenergic receptors in human congestive heart failure.

Patients with congestive heart failure have long been known to have elevated plasma levels of norepinephrine, reflecting augmentation of sympathetic nervous activity. This compensatory response increases cardiac output by increasing heart rate, enhancing myocardial contractility, and perhaps by stimulating hypertrophy of cardiac myocytes and salutary remodeling of the ventricle. However, these compensatory mechanisms fail in the long term, and most patients eventually deteriorate clinically. Early studies of β-adrenergic receptors in patients with congestive heart failure used peripheral blood lymphocytes as a target tissue. Lymphocytes of patients with severe left ventricular dysfunction were found to produce subnormal amounts of cAMP in response to isoproterenol and to contain fewer β-adrenergic receptors as measured in radioligand binding assays. However, lymphocytes contain mainly β2-receptors, whereas the heart has mainly the β1-subtype and circulating lymphocytes are not exposed to the local milieu of neurally released catecholamines seen in the myocardial interstitium. Thus, the relevance of these early findings to pathophysiological mechanisms in the failing heart was difficult to determine.

The first direct analysis of β-receptors in the failing human heart was reported by Bristow et al, who performed functional studies and radioligand binding assays in samples of end-stage hearts excised from cardiac transplant recipients. These investigators demonstrated markedly reduced contractile responses to β-adrenergic agonists and a significant reduction in myocardial β-adrenergic receptor density. An important finding reported by this same group was that downregulation of β-adrenergic receptors in the failing heart involved primarily β1-receptors, an observation that takes on added significance in view of reports of improved function in patients treated with β1-agonists such as metoprolol.

Since the pioneering studies of Bristow et al, further advances have been made. Improvements in the sensi-
tivity of radioligand binding assays now permit analyses in small tissue samples such as those obtained by percutaneous endomyocardial biopsy. Quantitative autoradiographic analyses of receptor distributions in transmural slices of failing human myocardium have revealed that downregulation occurs nonuniformly in the transmural distribution and is most pronounced in the subendocardium. This observation raises the possibility that heterogeneity in receptor distribution in the failing heart may contribute to electrophysiological heterogeneity and, thereby, to arrhythmogenesis. The non-uniform transmural distribution of adrenergic receptors in diseased ventricles is also consistent with independent studies suggesting that adrenergic neuroeffector abnormalities in the failing human heart are primarily due to local rather than systemic mechanisms. Despite the technical advances and the insights gained, however, opportunities to directly quantify β-adrenergic receptors in patients and to use this approach to monitor the natural history of their disease and their response to therapy are still highly limited. 

It is for these reasons that the study by Merlet and colleagues is important. Using methods developed and validated in animal studies, these authors measured myocardial β-adrenergic receptors in patients with idiopathic dilated cardiomyopathy using positron emission tomography (PET). In this first noninvasive assessment of β-receptor density in human subjects, Merlet et al observed the disparity in receptor density that distinguishes the normal and failing ventricles and which, heretofore, has only been observed in excised human tissues analyzed with conventional radioligand binding assays. 

The PET approach has obvious advantages. It is noninvasive and amenable to rigorous quantification. With selection of appropriate radioligands, the distribution of specific subsets of receptors may be elucidated. Merlet et al used the potent β-adrenergic antagonist CGP-12177, an extremely hydrophilic ligand that, because of its inability to penetrate lipid bilayers, selectively labels receptors on cell surfaces. A wide range of compounds having distinct pharmacological and biophysical properties may permit future analyses of the distribution of β1- and β2-receptors as well as receptor subclasses with different agonist affinity binding states reflecting different degrees of coupling to G-proteins and adenyl cyclase. With PET, multiple studies may be feasible in patients to characterize the natural history of receptor alterations in diseased myocardium and to monitor the effects of therapy designed to enhance myocardial performance by correcting inherent defects in adrenergic signaling in chronic congestive heart failure. 

The work of Merlet et al is only the first step. Significant technical challenges must be met before meaningful measurements of β-receptor density in cardiac myocytes in vivo can be achieved. For example, the amount of nonspecifically bound radioligand, although probably modest, was not directly determined. With intravascular delivery, the extent to which receptor labeling occurred in the vasculature as opposed to cardiac myocytes is uncertain. Limited resolution and potential PET artifacts associated with wall motion and partial volume effects preclude, at the present time, anatomically detailed characterization of regional heterogeneity in receptor density. The functional state of the receptors identified with the positron-emitting antagonist is not yet known. Clearly, much more work will be required before the intricacies of altered adrenergic receptor signal transduction can be probed with this noninvasive approach.

In what ways might PET scanning be used to improve diagnosis and management in patients with congestive heart failure and reveal pathophysiological mechanisms? Whereas downregulation of β-adrenergic function and receptor density are well documented in the end-stage failing ventricle, the natural history of this process and its temporal relation to the development and progression of congestive heart failure are not well characterized. Sequential PET scans might, therefore, provide information on this relation and predict the clinical course or response to therapy in patients with the new onset of symptoms. Interest has been focused recently on the salutary effects of metoprolol therapy in some patients with dilated cardiomyopathy and the possibility that such therapy improves cardiac function by upregulating myocardial β1-adrenergic receptors. Heilbrunn and coworkers have demonstrated that long-term metoprolol therapy is associated with increased β-receptor density and improved hemodynamic responses to catecholamine stimulation in patients with dilated cardiomyopathy, but these observations were made in membranes prepared from right ventricular endomyocardial biopsies. The tissue content of β-adrenergic receptor subtypes present before therapy was initiated, and changes in receptor subtype populations during the therapeutic course could not be determined for obvious practical reasons. Certainly, PET has the potential to overcome these limitations and to clarify the controversial role of metoprolol therapy in the treatment of chronic congestive heart failure.

The spectacular successes of PET in elucidating cerebral physiology and pathophysiology have not been matched in applications of this technology to the heart. The complex anatomic–functional topography of the brain is lacking in the heart, and heart diseases are more global in nature. Wall motion and geometric considerations further complicate cardiac PET. Nevertheless, the achievements to date, including those of Merlet et al, hold great promise that physicians of the future will order "receptor scans" as part of the routine diagnostic workup and assessment of therapeutic efficacy in patients with congestive heart failure and other diseases in which the adrenergic nervous system plays a critical role.

References


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