

What Is the Clinical Role of Neuronal Imaging?

Cardiac function is controlled by the autonomic nervous systems, which act via adrenoceptors and muscarinic acetylcholine receptors. The modulation of functional and electrophysiologic properties of the heart by the autonomic nervous system has become a focus of interest in the field of cardiovascular research. The neuronal function of the heart is compromised in various cardiac disorders, such as congestive heart failure, ischemia, cardiac arrhythmias, and certain cardiomyopathies (1). More importantly, the assessment of neuronal alteration may provide valuable information for disease severity and for appropriate treatments. Tracer approaches involving radionuclide imaging are uniquely suited for in vivo characterization of neuronal function in the myocardium.

The autonomic nervous system components include the synthesis and storage of neurotransmitters and their release, reuptake, metabolism, and interaction with presynaptic and postsynaptic receptor function. The activation of the sympathetic nervous system and associated parasympathetic withdrawal play an important role in the progression of congestive heart failure. In heart failure, plasma norepinephrine (NE) is elevated, and such an increase in plasma NE is an independent prognostic indicator (2). Such an NE increase may be the result of severe heart failure but may also increase the heart rate and reduce the heart rate variability, which may provoke ventricular tachyarrhythmias (3). As a result of increased synaptic NE levels, postsynaptic adrenergic receptors become

desensitized, probably due to the reduction of receptor density. Thus, unopposed sympathetic dominance governs several key features of congestive heart failure. The treatment with adrenergic β -blocking agents has emerged as a promising therapy for patients with heart failure (4). However, the therapeutic mechanisms that have been focused on the upregulation of the β -receptor and the direct protection against an excess of circulating catecholamine remain unknown.

Several radiotracers have been introduced to probe the steps of adrenergic neuronal function for in vivo imaging (5–7). The NE analogs, radioiodinated metaiodobenzylguanidine (MIBG) and ^{11}C -hydroxyephedrine (HED), permit noninvasive assessment of the NE reuptake and storage system in presynaptic terminals. On the other hand, one of the β -receptor antagonists, ^{11}C -CGP 12177, with PET, allows measurement of β -adrenergic receptor density and affinity.

Altered adrenergic neuronal function has been well demonstrated in many experimental and clinical studies using these radiotracers in various myocardial disorders (8–13). Of particular interest, the cardiac sympathetic nerve terminal is abnormal in congestive heart failure, with a decrease in NE uptake and NE uptake-1 site density. This may be explained by the response to the increased cardiac interstitial NE concentration, because similar changes may be seen after NE infusion in animals (14). One of the potential mechanisms is a persistent increase in synaptic NE concentration, which may decrease in NE analog reuptake with concomitant downregulation of the NE transporter and β -adrenoreceptor (15,16). Although decreased uptake and abnormal kinetics of MIBG or HED have been shown in many experimental and clinical conditions, the precise mechanisms of such

altered tracer kinetics and the relationship to the complications remain unknown.

Mardon et al. (17), in this issue of *The Journal of Nuclear Medicine*, describe the effects of elevated plasma NE concentrations on the pre- and postsynaptic functions of the β -adrenergic system in the myocardium in chronic rat experiments. They used ^3H -NE, ^{123}I -MIBG, and ^3H -CGP 12177 to compare the findings with tissue assay techniques. They demonstrated that the increased plasma NE was associated with reduced uptake of ^3H -NE and β -adrenergic receptors and in adenylyl cyclase activity. The authors conclude that the decrease both in radiolabeled NE analog uptake and myocardial β -adrenergic receptors may be related to the functional mechanisms of NE-induced downregulation of both β -adrenergic receptor and uptake-1 carrier sites.

This is a well-written article with the conclusions drawn clearly supported by their observations. This study indicates a potential mechanism of the decrease in the myocardial fixation of radiolabeled NE analogs in patients with congestive heart failure. This phenomenon is associated with downregulation of uptake-1 sites with parallel downregulation of β -adrenergic receptor in response to a chronic increase in plasma NE.

Their findings also create new issues to be solved, particularly for clinical use. First, it would be interesting to observe the concordance or discordance of the pre- and postsynaptic functions. We wonder whether the uptake-1 decrease may be proportionally decreased to the β -receptor downregulation under the chronic NE administration. It would be nice to see the correlation between the reduction of uptake-1 and β -receptor downregulation under various NE doses. If a linear

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correlation is observed, a simple radiotracer study, using the SPECT radiotracer ^{123}I -MIBG, may be a method of choice to assess both pre- and postsynaptic functions. One should remember that the PET radioligand ^{11}C -CGP 12177 is rather difficult to synthesize with high specific activity, and it is difficult to distribute this PET tracer to many clinical centers because of the short physical half-life.

The second issue is how to quantify the tracer distribution as a marker of neuronal function. Although the dynamic tracer kinetic study may not be available in a tissue-counting method, this method permits quantification of tracer concentration in the myocardium. But how do researchers extrapolate these parameters into the clinical setting? Several reports used the heart-to-mediastinum count ratio of ^{123}I -MIBG as a marker of neuronal function (5–9). Although this index seems to be suitable for risk stratification in patients with congestive heart failure, this may be significantly variable with operator and camera or collimator dependencies. The washout kinetics may be an alternative way for quantitative assessment of neuronal function. On the other hand, the washout rate of ^{123}I -MIBG may reflect not only uptake-1 but also NE washout kinetics as well. Furthermore, the washout rate may fluctuate in cases with no or very low initial uptake of MIBG in the myocardium. In this respect, ^{11}C -HED and PET may provide a key role for quantitative analysis of uptake-1 function in vivo. A quantitative method has been introduced for the assessment of β -receptor density and affinity using 2 separate injections of ^{11}C -CGP 12177 and dynamic PET (18,19). However, dynamic PET with the 2 tracer administrations of high-specific activity ^{11}C -CGP 12177 followed by low-specific activity ^{11}C -CGP 12177 seems to be

quite cumbersome for the clinical setting.

Regional analysis of the tracer distribution may be quite attractive in altered neuronal function. Although many studies have focused on global alteration of neuronal function, regional heterogeneity also has been a focus in cardiomyopathies and ischemic heart disease (20,21). If such regional analysis provides a clinical impact for assessing neuronal function, such in vivo imaging without quantitation may become quite feasible in the clinical setting, in a similar way as myocardial perfusion imaging without quantifying myocardial blood flow.

The ability to investigate this process at the level of molecular medicine is a new challenging field of nuclear medicine. Further effort is needed to translate the research results of neuronal function studies into clinical diagnosis and evaluation of various cardiac disorders.

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