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iREVIEWS

STATE-OF-THE-ART PAPERS

# Cardiac Sympathetic Imaging With *m*IBG in Heart Failure

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Cardiac sympathetic imaging with *meta*-iodobenzylguanidine (*m*IBG) is a noninvasive tool to risk stratify patients with heart failure (HF). In patients with ischemic and nonischemic cardiomyopathy, cardiac *m*IBG activity is a very powerful predictor of survival. Cardiac sympathetic imaging can help in understanding how sympathetic overactivity exerts its deleterious actions, which may result in better therapy and outcome for patients with HF. (J Am Coll Cardiol Img 2010;3:92–100) © 2010 by the American College of Cardiology Foundation

## Current Challenges in Heart Failure (HF)

The prognosis of HF has improved in the past 20 years, but it remains a serious condition with a markedly increased risk of death in the early period after onset of the syndrome (1). In population studies, there is a 10% mortality by 30 days. For those who survive this early high-risk period, the 5-year mortality is 54% in men and 40% in women (1). Mortality for patients in most recent clinical trials, with a background of appropriate pharmacological neurohormonal blockade, is around 8% to 10% per annum. Device therapy, with cardiac resynchronization with or without an implantable cardioverter-defibrillator further improves the prognosis (2–4), but at a relatively high additional financial cost initially.

In clinical trials of chronic HF therapy, 50% of deaths are due to sudden death, and progressive HF accounts for around 30% of deaths, this latter proportion increasing as symptomatic severity increases (5). In population studies including patients with new-onset HF, progressive HF appears to be the single most common cause of death (52%), with sudden death accounting for only 22% of deaths within the first 6 months of diagnosis (6,7).

Identifying those patients most at risk of death, and those most likely to benefit from currently available treatment technologies, remains a challenge. Identifying the risk of sudden, presumed arrhythmic, death, is particularly difficult. In general, older age, greater functional impairment, poorer systolic function of the left ventricle, lower serum sodium, poorer renal function, broader QRS complex, lower blood pressure, and inability to tolerate disease-modifying drugs such as angiotensin-converting enzyme (ACE) inhibitors are associated with a poorer prognosis and are men-

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tioned in guidelines for HF management (8,9). Poorer adherence to evidence-based treatment by the physician has also been shown to be independently associated with a worse prognosis (10). There is a pressing need for improved risk stratification for patients developing HF, with the goal of better identification of those for whom more aggressive therapy is likely to be beneficial.

## Pathophysiologic Basis for Cardiac Sympathetic Imaging

Compared with myocardium of healthy controls, the myocardium of patients with chronic left ventricular dysfunction is characterized by a significant reduction of pre-synaptic norepinephrine (NE) uptake and post-synaptic beta-adrenoceptor density (11,12). There is increased sympathetic activity in the hearts of patients with congestive HF, which is a generalized rather than a regional phenomenon and might contribute to the remodeling process of the whole left ventricle. This concept is consistent with the finding that down-regulation of myocardial beta-adrenoceptor density, measured using positron emission tomography (PET) with 11C-CGP-12177, soon after acute myocardial infarction is predictive of the occurrence of left ventricular dilatation at follow-up (13). Myocardial beta-adrenoceptor density appears reduced in patients with HF due to dilated cardiomyopathy (14) and down-regulation of myocardial beta-adrenoceptor is more pronounced in patients with hypertrophic cardiomyopathy who proceed to left ventricular dilation and HF (15). Therefore, myocardial beta-adrenoceptor down-regulation may be a general nonspecific response to stress and could be due to a locally increased amount of NE in the synaptic cleft. The sustained hyperactivity of the sympathetic nervous system observed in HF is the consequence of several mechanisms including increased central sympathetic outflow, altered neuronal NE reuptake, and facilitation of cardiovascular response to sympathetic stimulation by angiotensin II.

As a single-photon emission computed tomography (SPECT) tracer whose use does not require availability of an on-site cyclotron, $^{123}$I-*meta*-iodobenzylguanidine (*m*IBG) has been the most widely used imaging agent for studying causes and effects of cardiac sympathetic hyperactivity. *m*IBG was developed through a modification of the potent neuron-blocking agent guanethidine that acts selectively on sympathetic nerve endings. Uptake of $^{123}$I-*m*IBG into neurons is achieved mainly through the uptake-1 mechanism, a homeostatic system responsible for the reuptake of NE. Unlike NE, *m*IBG is not metabolized, allowing it to be imaged. The uptake-1 mechanism is one of the main NE disposal systems, and its malfunction may lead to abnormal catecholamine concentration in the synaptic cleft.

## Imaging Techniques and Quantification With *m*IBG

A complete imaging protocol typically includes planar and SPECT images obtained 15 to 30 min (early) and 3 to 4 h (delayed) after intravenous injection of 111 to 370 MBq (3 to 10 mCi) $^{123}$I-*m*IBG (Fig. 1) (16). Myocardial uptake and distribution is visually assessed. *m*IBG uptake is semiquantified by calculating a heart-to-mediastinum ratio (HMR) after drawing regions of interest over the heart and mediastinum (Fig. 1). This approach provides a highly reproducible index of cardiac sympathetic activity (16). By comparing early and delayed activities, the *m*IBG wash-out (WO) rate from the myocardium can be derived, providing a parameter that reflects retention of NE by sympathetic neurons (17).

SPECT images of the heart allow evaluation of the regional sympathetic activity. Polar maps of the myocardium can be constructed from the SPECT images and allow assessment of the defect extent and severity. Such polar maps can be easily compared with those of healthy individuals (Fig. 2). $^{123}$I-*m*IBG SPECT images can also be compared with SPECT myocardial perfusion images to examine differences between regional innervation and perfusion. In making such comparisons, it is important to be aware of differences between normal innervation and perfusion patterns, such as lower uptake of $^{123}$I-*m*IBG seen in the posterior inferior wall, especially in elderly persons (18,19).

**ABBREVIATIONS AND ACRONYMS**

**ACE** = angiotensin-converting enzyme
**BNP** = brain natriuretic peptide
**EP** = electrophysiology
**HF** = heart failure
**HMR** = heart-to-mediastinum ratio
**LVEF** = left ventricular ejection fraction
***m*IBG** = *meta*-iodobenzylguanidine
**MPI** = myocardial perfusion imaging
**NE** = norepinephrine
**NYHA** = New York Heart Association
**SPECT** = single-photon emission computed tomography
**WO** = wash-out

## Imaging With $^{123}$I-*m*IBG in Ischemic Heart Disease

The sympathetic nervous tissue is more sensitive to the effects of ischemia than the myocardial tissue (20). It has been shown that the uptake of $^{123}$I-*m*IBG is significantly reduced in areas of myocardial infarction (21), and adjacent noninfarcted regions (22) as well as in areas with acute and chronic ischemia (23,24). It is likely that ischemia damages sympathetic neurons