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**Title:** Novel insights into cardiac imaging in cardiovascular disease  
**Date:** 2012-06-14
Chapter 11

Cardiac Iodine-123 Metaiodobenzylguanidine Imaging for Risk Stratification in Heart Failure Patients

A report on behalf of the European Council of Nuclear Cardiology (ECNC)

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Introduction

Chronic heart failure is an important health care problem in the developed world as incidence and prevalence numbers have increased rapidly over the last decades. Recently, the American Heart Association Statistics and Stroke Statistics committee reported that chronic heart failure affects 5.3 million patients in the USA, with approximately 660,000 newly diagnosed patients each year. In western Europe, approximately 4 million patients have been diagnosed with chronic heart failure.2

Moreover, in the USA, one million hospital admissions for (decompensated) heart failure have been reported annually, resulting in an exponential increase in direct and indirect cost involved with chronic heart failure. Even though significant progress in prevention, diagnostic and therapeutic strategies for chronic heart failure has been made, mortality rate still exceeds 50%.

Coronary artery disease was found to be the main cause of heart failure in nearly 70% of patients, and despite rapid developing treatment options for ischemic and non-ischemic heart failure, long-term prognosis remains poor. In 7,599 patients with NYHA class II-IV heart failure, originating from the CHARM study, cardiovascular outcome was studied over a mean follow-up of 3 years. In patients with a LV ejection fraction <33%, all-cause and cardiac mortality were 34% and 28%, respectively. Even higher mortality rates were reported by Levy et al. in the Framingham-based study population; cardiac mortality rate was more than 50%, over a mean follow-up of 5 years. These high mortality rates along with an increasing number of hospitalizations due to (decompensated) heart failure emphasize the need for better risk stratification.

Heart failure represents a complex clinical syndrome resulting from a reduced cardiac pump function. Progressive deterioration in cardiac function is based upon several interacting pathophysiological mechanisms, in which particularly the neurohormonal system (consisting of the adrenergic nervous system and renin-angiotensin-aldosteron system) plays an important role in chronic heart failure. Initially, neurohormonal feedback mechanisms tend to compensate hemodynamic consequences of cardiac dysfunction via positive inotropic and Chronotropic effects. However, in a chronic state these neurohormonal effects are detrimental and may cause cardiac hypertrophy and fibrosis, eventually resulting in remodeling. Moreover, desensitization and downregulation of myocardial beta-adrenoceptors, and alterations of postsynaptic signaling lead to further decline in cardiac function.

In addition, a dysfunctional cardiac autonomic nervous system may also be related to the development of ventricular arrhythmias. In this respect, exact mechanisms have to be elucidated and it has been suggested that regions with impaired innervation may be viable and hypersensitive to catecholamines, resulting in increased automaticity and enhanced triggering. In particular, the borderzone of myocardial scar tissue may be predisposed to develop reentrant circuits because these regions are viable but may have damaged
sympathetic nerves. The viable peri-infarct region can be (partially) denervated because sympathetic nerve fibers are more vulnerable to ischemia as compared to cardiomyocytes.

Consequently, important clinical and prognostic information in heart failure patients can be provided by assessment of cardiac sympathetic innervation and function. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are presently the only 2 imaging modalities to allow assessment of myocardial sympathetic nerve activation and innervation by visualization of uptake and storage of radiolabeled neurotransmitters into presynaptic nerve endings. Both imaging techniques can be used to assess global and regional myocardial sympathetic nerve innervation.

Presently, several PET tracers have been used to visualize sympathetic neurotransmission, including carbon-11 hydroxyephedrine (HED), C-11 epinephrine and F-18 fluorodopamine. At present, HED is the most frequently used PET tracer and allows absolute quantification of tracer uptake into sympathetic nerve terminals. One of the major advantages of HED is its capability to detect regional abnormalities in myocardial sympathetic innervation. Hartmann and colleagues have performed an important study which demonstrated regional heterogeneity of impaired cardiac sympathetic innervation in 29 patients with idiopathic dilated cardiomyopathy as compared to patients with normal cardiac function. In heart failure patients, PET with HED has also been used to evaluate the prognostic value of sympathetic nerve innervation. In an elegant study, Pietila et al. have demonstrated that global reduced HED accumulation was an independent predictor of adverse outcome in 46 patients with NYHA class II-III heart failure.

**Cardiac 123-I MIBG Scintigraphy**

Most studies on cardiac sympathetic innervation have been performed with 123-iodine metaiodobenzylguanidine (MIBG) scintigraphy. The labeling of MIBG with 123-iodine permits visualization of myocardial sympathetic neuronal uptake. MIBG is a false neurotransmitter, an analog of norepinephrine, which uses similar uptake mechanisms in the presynaptic nerve terminals as norepinephrine. The tracer is primarily transported into the presynaptic nerve terminal by sodium- and ATP-dependent transporters, referred to as uptake-1. In the nerve terminal, no degradation of MIBG takes places resulting in an accumulation of MIBG with high signal intensity. These signals are used for planar and tomographic (SPECT) imaging. Early planar imaging and SPECT are performed at 10-20 min after MIBG administration, whereas delayed planar imaging and SPECT are performed 3-4 h after tracer injection. From planar images, global cardiac MIBG uptake can be assessed visually or semi-quantitatively using early and late heart-to-mediastinum (H/M) ratio (Figure 1). To calculate H/M ratio, regions of interest are manually drawn over the heart and upper mediastinum and the mean of myocardial counts per pixel is divided by the mean of mediastinal counts per pixel. Another planar-based parameter is the cardiac washout rate which indicates the rate by which MIBG is released from the myocardium between early
and delayed imaging. To calculate cardiac washout rate, late H/M ratio is subtracted from the early H/M ratio and divided by the early H/M ratio.

These planar-based parameters have been studied extensively in heart failure patients. In particular, the prognostic value of global MIBG uptake has been studied by Merlet and colleagues. Initially, these authors have studied 90 patients with moderate-to-severe heart failure, who underwent MIBG scintigraphy, chest X-ray, echocardiography and radionuclide angiography. After follow-up of 27 months, cardiac death and cardiac transplantations were reported in 22 and 10 patients, respectively. H/M ratio on delayed images was found to be the best independent predictor for cardiovascular death. Of note, patients with cardiac transplants were discarded from the survival analysis, whereas the second prognostic study performed by Merlet et al. included patients who underwent cardiac transplantation. In this study, 112 patients with NYHA class II-IV heart failure and LV ejection fraction <40% (measured with radionuclide angiography), underwent MIBG scintigraphy, right-sided invasive angiography, and routine clinical care (echocardiography, chest X-ray and peak exercise testing). After a mean follow-up of 27±20 months, cardiac death was noted in 25 patients, and cardiac transplantation was performed in 19. As illustrated in Figure 2, late H/M ratio was significantly lower in patients with major cardiac events as compared to patients without major cardiac events. Furthermore, the authors
have demonstrated that the only independent predictors for adverse outcome were reduced myocardial MIBG uptake on delayed planar images and depressed LV ejection fraction.

Besides the prognostic value of global MIBG uptake on delayed images, several studies have reported on cardiac washout rate as a potential predictor for adverse cardiovascular outcome. In 59 patients with NYHA class II-IV and dilated cardiomyopathy, the predictive value of MIBG parameters was studied by Momose and coworkers; among all planar MIBG parameters cardiac washout rate was the most powerful predictor of cardiac death, over a mean follow-up of 25±13 months. For cardiac washout rate, a threshold level of 52% showed optimal predictive value for cardiac death. In addition, similar results were demonstrated by Yamada et al. in 65 heart failure patients. Over a mean follow-up of 34±19 months, cardiac washout rate was the only independent predictor for cardiac events. Furthermore, patients with cardiac events showed significant higher myocardial washout rate in comparison to patients without cardiac events, as illustrated in Figure 3. However, importantly, different threshold levels for cardiac washout rate were used in these two studies. Yamada et al. used a cutoff value of 27% for myocardial washout rate, whereas Momose and coworkers used a threshold level of 52%.

Presently, no consensus exists on the optimal cutoff values for early and late H/M ratios, cardiac washout rate, or the defect score on SPECT for prediction of outcome. Agostini et al. have performed in this respect an important retrospective study on 290 heart failure patients from 6 centers across Europe. According to the study protocol, planar and SPECT examinations were re-analyzed in a core laboratory by 3 independent observers who were
blinded to all other data. Over a follow-up of 2 year, major cardiac events were noted, including cardiac death, cardiac transplantation, potential lethal ventricular arrhythmias or appropriate ICD therapy. The authors showed that patients with a major cardiac event had significant lower H/M ratio on delayed images as compared to patients without a major cardiac event within the 2-year follow-up period. Moreover, for late H/M ratio, the optimal threshold to predict cardiac events was defined at 1.75, and yielded a sensitivity of 84% and specificity of 60%.

The available studies have focused on an index MIBG study and its relation to cardiac outcome. However, several studies used imaging before and after heart failure therapy and demonstrated improved MIBG uptake after optimization of heart failure medication; currently, limited information is available on the predictive value of serial MIBG studies.\textsuperscript{34-37} Recently, Kasama et al.\textsuperscript{38} have reported on the predictive value of serial MIBG imaging in 208 heart failure patients with a LV ejection fraction <45%. According to the study design, MIBG scintigraphy was performed at baseline and at 6 months follow-up. During a mean follow-up of 5±2 months, cardiac death was reported in 56 patients. The authors have reported that a 6-month change in washout rate >5%, was an independent predictor for all-cause cardiac death and sudden cardiac death.

\textbf{Figure 3.} Difference in myocardial washout rate between heart failure patients with adverse cardiac outcome (cardiac death or hospitalization) and heart failure patients without adverse cardiac outcome (data based on reference 31). Patients with adverse cardiac outcome demonstrated significant higher myocardial washout rate as compared to patients without adverse cardiac outcome (44.0±14.7% vs. 25.6±12.8%, p<0.05).
**Prediction of Ventricular Arrhythmia**

Although most prognostic studies used all-cause mortality, cardiac mortality (progressive heart failure), or cardiac transplantation as endpoints, some studies suggested that MIBG imaging can also be used for prediction of ventricular arrhythmias and sudden cardiac death.\(^{39-41}\) At present, it is known that parasympathetic stimulation of the ventricles exerts anti-fibrillatory effects on the myocardium, whereas sympathetic activation of the ventricles appears to have a pro-arrhythogenic effect on the myocardium. In patients with heart failure, the increased sympathetic tone along with a decreased parasympathetic activation can cause ventricular arrhythmias by enhancing cardiomyocyte pacemaker activity and reentrant excitation.\(^{39-41}\) Moreover, the presence of sympathetic denervated regions alongside regions with preserved sympathetic innervation can lead to an inhomogeneous neuronal release of norepinephrine, which subsequently, can cause marked alterations in action potential duration and configuration of the cardiomyocytes. Therefore, the electrical signaling of the heart becomes non-uniform (electrophysiologic heterogeneity) which contributes to its vulnerability for development of ventricular arrhythmias.

Arora et al.\(^{39}\) have evaluated the role of MIBG imaging in 17 patients with an implantable cardioverter-defibrillator (ICD). In total, 10 patients received appropriate ICD discharges (reflecting potential lethal ventricular arrhythmias or sudden cardiac death) and these patients showed significant lower global (early) and regional (early and late) MIBG uptake as compared to patients who did not receive appropriate ICD discharges. Furthermore, comparable results were reported by Nagahara and colleagues\(^{41}\) who evaluated whether MIBG scintigraphy was useful for prediction of appropriate ICD therapy in 54 patients, after a mean follow-up of 15 months. Ten patients who received appropriate ICD therapy showed significantly lower late MIBG uptake as compared to patients who did not receive appropriate ICD therapy. Moreover, H/M ratio on delayed images was found to be an independent predictor for appropriate ICD therapy.

MIBG studies have reported on planar imaging as a potential tool for risk stratification in heart failure patients. Although some innervation studies have employed regional MIBG uptake as a prognostic marker, the role of SPECT for prognostification of heart failure patients is unclear.\(^{42-44}\) In particular, the role of regional sympathetic denervated myocardium in the genesis of spontaneous ventricular arrhythmias has to be further elucidated.\(^{14-18}\) Bax et al.\(^{45}\) have studied whether abnormalities in sympathetic innervation on MIBG SPECT could predict inducibility of ventricular arrhythmias on electrophysiologic testing in 50 patients with coronary artery disease and LV ejection fraction ≤40%. The MIBG SPECT defect score was significantly larger in the 30 patients with a positive electrophysiologic test as compared to patients without inducible ventricular arrhythmias, as illustrated in Figure 4.

In conclusion, the available studies have shown that cardiac innervation imaging holds great potential for risk stratification of heart failure patients. Recent studies suggest that particularly MIBG imaging may play a major role in identifying patients with LV dysfunction.
Figure 4. Defect score on late single photon emission computed tomography (SPECT) in patients with positive and negative electrophysiologic (EP) test (data based on reference 45). Patients with inducible ventricular tachyarrhythmias during EP testing showed significantly higher defect score on SPECT as compared to patients without inducible ventricular arrhythmias (42.7±8.8 vs. 34.9±9.8, p<0.05).

at elevated risk of heart failure death or arrhythmic death. The results of these initial studies are promising, and more studies will help to determine the precise role of innervation imaging in risk stratification of heart failure patients.
Reference List


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