CARDIOLOGY, REVIEW

Sympathetic hyperactivity in chronic heart failure; the role of ^{123}I-MIBG for the assessment of appropriate device allocation

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Chronic heart failure

Chronic heart failure (CHF) is a complex syndrome characterized by impaired left ventricle function and increased activation of the sympathetic nervous system. The mortality rate is approximately 10% in the first month after onset and increases after 5 years up to 54% in men and 40% in women.[1] Although beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and diuretics have improved the prognosis of these patients, the outcome remains unfavorable.[2-4, 4] Even when treated according to the latest guidelines, most studies report annual mortality rates between 8 and 10 %. The majority of the mortality can be attributed to progression of heart failure, ventricular arrhythmias or sudden cardiac death. The use of devices like cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillators (ICD) have further improved the prognosis of CHF, but these devices have their disadvantages like high costs, operative complication and device malfunction.[5,6]. Although there is a plethora of parameters associated with fatal arrhythmias, cardiac death and long-term prognosis in patients with CHF, it remains a challenge to identify those patients who are at the highest risk of death and who are most likely to benefit from currently available therapies. In this setting the parameters most reported on in patients with CHF are amongst others decreased left ventricular systolic function, renal dysfunction, broadening of the QRS complex, lower blood pressure, lower functional capacity (i.e. higher NYHA functional class) and higher plasma concentration of brain natriuretic peptide (BNP). In addition to these patient driven issues, there are socio-economic considerations with respect to the ever increasing costs of healthcare and the inevitable subsequent constrains on healthcare budget, especially with the use of expensive devices. Taken these issues together there is pressing call to improve risk stratification for CHF patients, with a special focus on identification of patients likely to benefit from more aggressive and device driven therapies.

Key words: MIBG, heart failure, cardiac sympathetic imaging, prognosis

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Pathophysiology

The innervation of the heart is regulated by the autonomic nervous system and consists of both the sympathetic and the parasympathetic nervous systems. Sympathetic activation leads to increased heart rate, a more forceful contraction and increased atrioventricular conduction, while the parasympathetic system predominantly regulates the heart rate. Norepinephrine (NE) is the neurotransmitter of the sympathetic system and is stored in vesicles in the presynaptic nerve terminals. When NE is released in the synaptic cleft it stimulates the post-synaptic beta-receptors. **(Figure 1)**

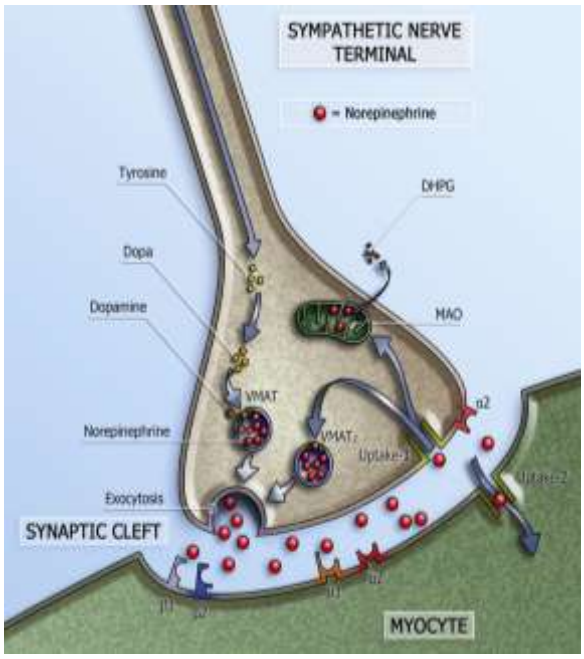

Figure 1. Schematic representation of the sympathetic synapse. Norepinephrine is synthesized within neurons by an enzymatic cascade. Dihydroxyphe-nylalanine (DOPA) is generated from tyrosine and subsequently converted to dopamine by DOPA decarboxylase. Dopamine is transported into storage vesicles by the energy-requiring vesicular monoamine transporter (VMAT). Norepin-ephrine is synthesized by dopamine β-hydroxylase within these vesicles. Neuronal stimulation leads to norepine-phrine release through fusion of vesicles with the neuronal membrane (exocytosis).

Apart from neuronal stimulation, release is also regulated by a number of presynaptic receptor systems, including α2–adrenergic receptors, which provide negative feedback for exocytosis. Most norepinephrine undergoes reuptake into nerve terminals by the presynaptic norepinephrine transporter (uptake-1 mechanism) and is re-stored in vesicles (following uptake by vesicular amine transporter 2 (VMAT2)) or is metabolized in cytosol dihydroxyphenylglycol (DHPG) by monoamine oxidase (MAO).

In patients with CHF compensation mechanisms like the Renine-Aldosterone-Angiotensin-System (RAAS) and the sympathetic nervous system are activated. Initially, stimulation by NE helps to compensate for impaired myocardial function, but long-term NE excess had detrimental effects on myocardial structure and function causing remodeling of the left ventricle. In CHF patients, exocytosis of NE from in the presynaptic vesicles is increased. In addition, the NE re-uptake via norepinephrine transporter (also called uptake-1) in the sympathetic terminal nerve axons is decreased. This results in increased NE concentration in the synaptic cleft which gives rise to a down regulation of post-synaptic beta-receptors.[7] In post mortal hearts from patients with severe CHF, 50% reduction in beta-adrenergic receptor density has been reported.[8] Down regulation of post-synaptic beta-adrenergic receptors leads to left ventricle remodeling. This phenomenon is also seen after myocardial infarction and in hypertrophic cardiomyopathy.[9, 10]
Sympathetic hyperactivity is an important factor in the genesis of potential lethal ventricular arrhythmias in patients with impaired ventricular function. These patients have an appropriate substrate that is able to develop rhythm abnormalities, which may be related to enhanced automaticity, triggered automaticity, and reentrant mechanisms. These mechanisms are

enhanced by release of NE. Still, the explanation for the link between sympathetic hyperactivity and ventricular arrhythmias is still not clear. One possible association is the fact that nonuniform denervated myocardium be viable and hyperresponsive to NE.[11] It is also possible that denervated but viable myocardium in the infarct zone may be prone to generate reentrant ventricular tachycardia circuits. Imaging studies with SPECT and PET have shown that the presence of denervated but still viable myocardium could contribute to the development of ventricular arrhythmias.[12-14]

Imaging cardiac sympathetic activity

Cardiac sympathetic activity can non-invasively be visualized by radionuclide imaging. At the pre-synaptic level, ^{18}F-Fluoridopine is available to assess NE synthesis.[15, 16] ^{11}C-hydroxyephedrine, ^{11}C-ephedrine and ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) are available to access the pre-synaptic NE reuptake and storage.[17-20] ^{11}C-carazolol and ^{11}C-CGP (4-(3-*t*-butylamino-2-hydroxypropoxy)-benzimidazol-1) are availa-ble to access beta-adrenergic receptor expression and density.[21] Of all these tracers only ^{123}I-MIBG can be used on conventional gamma-cameras. For the use of all other tracers a PET-camera is needed. Furthermore ^{123}I-MIBG requires no availability of on-site cyclotron, like the other tracers. Therefore it is the most widely used imaging agent for studying causes and effects of cardiac sympathetic hyperactivity.

Meta-iodobenzylguanidine (MIBG) is a NE analog and shares the same presynaptic uptake, storage and release mechanism as NE, but is not metabolized, allowing imaging. The first clinical application of ^{123}I-MIBG was imaging of the adrenal medulla and neural crest-derived tumors such as pheochromo-cytoma and neuroblastoma.[22, 23] In 1980 the potential use of ^{123}I-MIBG for cardiac imaging was suggested.[20, 24]

Imaging techniques and quantification with ^{123}I-MIBG

Recently Flotats et al. have published a recommendation for standardization of cardiac ^{123}I-MIBG scintigraphy.[25] In short the publication recommends the following protocol: 30 minutes before injection of 185 MBq of ^{123}I-MIBG the thyroid is blocked by potassium perchlorate or potassium iodine. A 10 minute planar image is acquired from an anterior thoracic view (128x128 or 256x256 matrix) at 10 to 15 minutes (early image) and at 4 hours (late image) post injection of ^{123}I-MIBG using a gamma-camera equipped with a low energy general purpose (LEHR) collimator, but a medium collimator is preferable. This approach provides a highly reproducible index of cardiac sympathetic activity.[26] The ^{123}I-MIBG uptake is semi-quantified by calculating a heart-mediastinum (H/M) ratio by manually drawing a region of interest (ROI) over the left ventricle compared with a fix position in the upper mediastinum.[25, 27-29] **(Figure 2)** The washout (WO) rate from early to late images can be calculated (see formula). The early H/M ratio reflects the integrity of sympathetic nerve terminals. The late H/M ratio offers information about neuronal function resulting from uptake, storage and release. The WO reflects neuronal integrity of sympathetic tone/drive.

Washout (WO) =

$$\left\{\frac{(\text{early H/M} - (\text{late H/M})}{\text{early H/M}}\right\} x100\%$$

Optional a 30 minute single photon emission tomography (SPECT) image can be preformed, allowing evaluation of regional sympathetic activity. From these images polar maps can be reconstructed for assessment of the defect extent en severity. ^{123}I-MIBG SPECT images can easily be used to compare with the SPECT myocardial perfusion images to examine the difference between regional innervation and perfusion.[30]

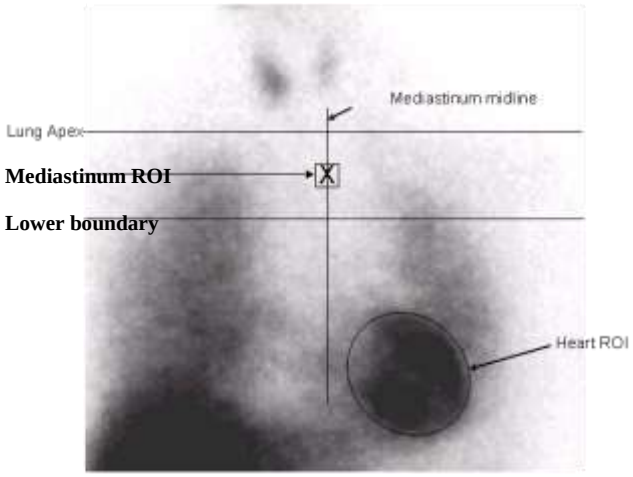

Figure 2. Example of processing procedure for late planar 123I-MIBG images. The positioning of the mediastinal ROI was standardized in relation to the lung apex, the lower boundary of the upper mediastinum, and the midline between the lungs.

CHF therapy and sympathetic activity

Pharmacological treatment using beta-blockers, ACE- inhibitors, and angiotensin receptor blockers is recognized as an initial standard strategy for patients with CHF.[2-4]. This has been shown to ameliorate long-term prognosis by improving LVEF and functional capacity. Using semi-quantitative analysis, these beneficial effects are associated with an increase of myocardial ^{123}I-MIBG uptake and reduced ^{123}I-MIBG washout.[31-37]

One of the factors that is related to mortality in CHF patients is a wide QRS complex on the electrocardiogram, indicative of ventricular dyssynchrony, which is present in 25-50% of the patients with chronic heart failure.[38] Dyssynchronic mechanical activation of the left ventricle increases left ventricular systolic dysfunction and results in additional activation of neurohormonal systems, like elevated plasma B-type natriuretic peptide (BNP), rennin angiotensin aldosteron system and the sympathetic nervous system.

According to the European Society of Cardiology (ESC) guidelines (Dickstein 2008), primary management of chronic heart failure consists of general advice and measures concerning diet, weight, smoking and exercise, and pharmacological therapy. When these measures fail to improve the clinical situation, cardiac resynchronization therapy (CRT) is indicated in a selected patient group. There is an international class I level of evidence A indication for CRT to reduce morbidity and mortality in patients with chronic heart failure and a wide QRS complex ≥120 ms (≥130 ms if chronic atrial fibrillation is present) that remain symptomatic in NYHA function class III/IV, or a wide QRS complex ≥150 ms in class II NYHA, despite optimal pharmacological therapy in combination with a left ventricular ejection fraction (LVEF) ≤35% (normal >50%).[2, 39]

The rationale for CRT is based upon the observation that the presence of ventricular dyssynchrony (a wide QRS complex) can induce systolic dysfunction and thereby worsen heart failure. To correct ventricular dyssynchrony, three pacing leads are implanted via a transvenous approach and connected to the CRT device. One lead is positioned in the right atrial appendage or interatrial septum; a second lead is implanted in the right ventricular apex or septum; the third lead is positioned at the left ventricular free wall via the coronary sinus. This has favorable effects on LVEF, symptoms and plasma BNP.[40, 41] In addition, it improves functional capacity, reduces all-cause hospitalization and has a beneficial effect on mortality.[6]

Despite remarkable improvement in some CRT patients, there is still a clinical or echocardiographical non-responder rate of up to one third of the patients according to the guidelines. This could partly be due to inadequate selection criteria and/or the inability of the current criteria to encompass the entire pathophysiological set of determinants.

In the search for additional selection criteria to improve the responder rate in CHF patients subjected to CRT, several molecular imaging study parameters have been proposed: Phase analysis of (dys)synchrony in gated myocardial perfusion single photon emission computed

tomography (SPECT).[42] Infarct burden as measured by myocardial perfusion SPECT.[43] Uptake and washout of cardiac MIBG, measures for cardiac sympathetic nervous tone.{Burri, 2008 50 /id;EROL-YILMAZ, 2005 78 /id;Ewe, 2011 84 /id;Merlet, 1993 58 /id;Nishioka, 2011 85 /id} CRT has also a beneficial effect on cardiac sympathetic activity. CRT increases ^{123}I-MIBG uptake and reduces ^{123}I-MIBG washout. [44, 45]

^{123}I-MIBG as predictor of inducible ventricular arrhythmia

Bax et al. presented a prospective pilot study to examine the relationship between cardiac sympathetic innervation visualized by ^{123}I-MIBG and the inducibility of ventricular arrhythmias during electrophysiological (EP) testing in patients with a previous myocardial infarction.{Bax, 2008 22 /id} The primary objective was to evaluate the predictive value of inducible potentially fatal arrhythmias during EP testing with planar ^{123}I-MIBG imaging and the combination of SPECT ^{123}I-MIBG imaging with ^{99}Tc-tertrofosmin perfusion imaging. Patients with a history of myocardial infarction, impaired left ventricular function, referred for EP study because of syncope or non-sustained ventricular tachycardia were included. In a multivariate analysis using ^{123}I-MIBG and ^{99}Tc-tertrofosmin SPECT measures, the only variable that could discriminate between patients with inducible ventricular arrhythmias and those without was the 4 hour ^{123}I-MIBG SPECT uptake. A 4 hours ^{123}I-MIBG SPECT defect score ≥ 37 had a sensitivity of 77% and specificity of 75% for predicting EP results. Late H/M ratio per se was not able to stratify arrhythmic risk in this population with ischemic CMP. Nevertheless the extend of denervated myocardium, as calculated by 4 hour ^{123}I-MIBG SPECT, correlated well with inducibility of ventricular arrhythmias during EP testing.

^{123}I-MIBG as predictor of ICD therapy

Prophylactic use of ICD's is recommended by the guidelines in patients with impaired ventricular function or symptomatic heart failure with a high risk of life-threatening ventricular tachyarrhythmias. A rapid increase in the use of ICD therapy as primary treatment for this condition has been demonstrated.[49, 50] ICD's as a primary or secondary prevention reduce the relative risk for death by 20%. The MADIT II study, however, showed that the actual reduction of fatal events was 5.6 percentage points (from 19.8 to 14.2).[51] In addition, the SCD-HeFT trial showed that the annual rate of ICD shock was 7.1% and of appropriate shock for rapid ventricular tachycardia or ventricular fibrillation was 5.1%, with a total of 21% patients receiving appropriate shocks over 5 years.[5] Of all patients receiving an ICD for primary prevention 65% never receive ICD therapy 3 years after implantation.[52] This percentage is high so more precise identification of responders is important from a clinical and economic point of view. Indentifying the patient who most likely will benefit from ICD therapy remains challenging.

Recently, Boogers et al. published a prospective study showing that sympathetic innervation as measured by ^{123}I-MIBG SPECT could predict ventricular arrhythmias causing appropriate ICD therapy and cardiac death in patients with CHF.[30] Patients were referred for ICD implantation for primary or secondary prevention. In a multivariable analysis, the only independent predictor for appropriate ICD therapy and cardiac death was the late ^{123}I-MIBG SPECT defect score. Cumulative event rate of appropriate ICD therapy during 3-years follow-up were significantly higher if late ^{123}I-MIBG SPECT defect score was higher than 26.

Recently the first large, multicenter, prospective study: the ADMIRE-HF study has again demonstrated that ^{123}I-MIBG uptake is a prognostic marker in CHF patients treated on guidelines based contemporary therapy.[53] In total 961 patients were included with stable CHF, functional class II/III and LVEF < 35% and treated with beta-blocker, ACE-inhibitor or angiotensin receptor blockers and diuretics. A reduced late H/M ratio < 1.6 was an independent predictor of the composite

endpoint of cardiac events as well as for each component of the composite study endpoint: progression of heart failure, potentially lethal arrhythmia and sudden cardiac death (SCD). A late H/M ratio ≤ 1.60, reduced LVEF, elevated BNP and NYHA functional class III indicated poor clinical outcomes. Taking these results even further it appears that despite optimal treatment of patients with CHF there seems to be an additional role for ^{123}I-MIBG scintigraphy as a tool for estimating prognosis and for identifying patients who are at risk for potential lethal ventricular arrhythmias who may benefit the most from ICD therapy.

Challenge for the future

The increase use of ICD therapy has an increasing economic impact on the health care budgets in the USA and Europe. [54, 55] In the USA the costs of CHF treatment are 39.2 billion dollars annually, mainly due to hospitalization and device implantation like CRT and ICD. Since the majority of patients in these patients remains without life-threatening arrhythmias, it is of the utmost importance to find risk stratification tools to identify patients most likely to benefit from ICD leading to higher cost-effectiveness. Yet, there is no single powerful predictor of arrhythmic death and effectiveness of prophylactic ICD use, because arrhythmia, lethal cardiac events and prognosis are multifactorial and have several determinants. However, ^{123}I-MIBG alone and more likely in combination with others determinants may be able to better discriminate CHF patients with appropriate ICD discharge from those patients without any or inappropriate ICD discharge. Therefore, new prospective multicenter studies are needed to study the prognostic value of ^{123}I-MIBG for prediction ICD therapy in the setting of primary prevention.

Conclusion

Patients with CHF are characterized by cardiac sympathetic hyperactivity which is related to sudden cardiac death due to ventricular arrhythmias. ^{123}I-MIBG scintigraphy can be used to non-invasively measure cardiac sympathetic activity and may be valuable for the selection of patients who mostly benefit from ICD implantation. The exact role of ^{123}I-MIBG for clinical decision making has yet to be established in new and currently ongoing trials.

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