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REVIEW ARTICLE

The use of Cardiac ^{123}I-mIBG Scintigraphy in Clinical Practice: The Necessity to Standardize!

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Abstract

Cardiac adrenergic imaging has a great potential in a wide variety of clinical applications. Cardiac ^{123}I-*meta*-iodobenzylguanidine (^{123}I-*m*IBG) scintigraphy has a key role to assess chronic heart failure (CHF) by risk stratifying patients for cardiac events. The *m*IBG is a norepinephrine (NE) analogue that can evaluate cardiac sympathetic activity by assessing the down expression of β-adrenergic receptor (β-AR) in CHF. Furthermore, ^{123}I-mIBG scintigraphy in combination with other parameters of left ventricular function can be used to identify the best responder for implantable cardiac devices, as well as to assess oncological cardiotoxicity. Despite its usefulness, ^{123}I-mIBG scintigraphy is not widely performed because of the lack of standardization between different institutions. Thus, standardization and validation may contribute to its acceptance in clinical setting.

Introduction

The cardiac sympathetic system is an important neurohormonal compensation mechanism in the pathogenesis of chronic heart failure (CHF). Patients with CHF have increased cardiac sympathetic activity with increased exocytosis of norepinephrine (NE) from the presynaptic vesicles and impaired NE re-uptake via the norepinephrine transporter (NET) in the sympathetic terminal nerve axons. This results in increased NE levels in the synaptic cleft. Initially, β-adrenergic receptor (AR) stimulation by increased synaptic NE levels helps to compensate for impaired myocardial function. However, long-term NE excess has detrimental effects on myocardial structure and gives rise to a down regulation and availability of postsynaptic β-AR. This leads to left ventricular remodeling and is associated with increased mortality and morbidity in CHF.

Cardiac sympathetic activity can non-invasively be visualized by nuclear medicine techniques. The most clinically used tracer is the radiolabeled NE analogue ^{123}I-*meta*-iodobenzylguanidine (^{123}I-*m*IBG). From the planar ^{123}I-*m*IBG images, semi-quantitative measurements of myocardial ^{123}I-*m*IBG uptake can be derived: early heart-to-mediastinum (H/M) ratio (HMR), derived 15 min post injection (p.i.) of ^{123}I-*m*IBG; late HMR, derived 4 h p.i. of ^{123}I-*m*IBG; and ^{123}I-*m*IBG washout, calculated as the difference between early and late HMR and expressed as a percentage of the early HMR. While HMR reflects the ^{123}I-*m*IBG uptake in nerve terminals, washout rate indicates their integrity - neuronal retention.[1]

Although arrhythmia, lethal cardiac events and prognosis are multifactorial and have several determinants, cardiac ^{123}I-*m*IBG scintigraphy alone and more likely in combination with other determinants may be able to better select CHF patients at increased risk for events. Indeed, a large number of studies on the prognostic value of ^{123}I-*m*IBG-assessed cardiac sympathetic activity in CHF have been published. In addition, cardiac ^{123}I-*m*IBG scintigraphy can be used in other pathophysiological conditions, for example to assess chemotherapy-induced cardiotoxicity. However, the lack of standardization between different institutions have hampered wide scale clinical implementation.

The purpose of this paper is to discuss how to further standardization of cardiac ^{123}I-mIBG scintigraphy and to discuss the use of cardiac ^{123}I-*m*IBG in different patient populations.

Keywords

Heart Failure; Myocardium/diagnostic imaging; Radionuclide Imaging; 3-Iodobenzylguanidine; Sympathetic Nervous System.

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Physiology of cardiac sympathetic innervation and ^{123}I-*m*IBG uptake

The cardiac sympathetic nervous system is a complex agonist-receptor system with NE as neurotransmitter. Both β- and α-ARs belong to the G-protein family and have a transmembrane location. There are four types of β-AR that form the postsynaptic portion of sympathetic neurotransmission, the most abundant β-AR being β_1, β_2 and β_3. β_1- and β_2-ARs determine positive inotropic response. Two types of α-ARs have been identified (i.e. α_1 and α_2), each with three known subtypes.[2,3] The postsynaptic α_1-ARs are important to modulate cardiac inotropy and arterial vasoconstriction. The α_{2A}- and α_{2C}-ARs subtypes have a postsynaptic localization and regulate myocardial catecholamine release. The presynaptic α_{2B}-ARs seem to be associated with the pathogenesis of salt-induced hypertension. In addition, there are muscarine, angiotensin, adenosine, and cardiac opioid receptors.

Norepinephrine is synthesized from tyrosine and stored in high concentrations in vesicles in the presynaptic sympathetic nerve terminals. Upon stimulation, these vesicles release their content into the synaptic cleft. Most of the released NE is actively taken back up into the presynaptic sympathetic nerve terminals with a mechanism known as uptake-1 (i.e. the NET). This is a highly specific process, but with limited capacity. In addition, there is a less specific, but highly capable, postsynaptic re-uptake mechanism known as uptake-2.

Meta-iodobenzylguanidine is an analog of NE and can be radiolabeled with iodine. Radiolabeled *m*IBG follows the same re-uptake mechanism as NE (i.e. the NET). Once taken up in the presynaptic sympathetic nerve terminals, *m*IBG is not metabolized. ^{123}I-*m*IBG is not only used in the cardiac sympathetic nervous activity assessment. Of note, the first clinical application of radio-labeled *m*IBG (i.e. ^{131}I-*m*IBG) was the visualization of the adrenal medulla and different neural crest-derived tumors, such as pheochromocytomas and neuroblastomas. Radiolabeling with ^{131}I also enables radionuclide therapy for these types of neoplasms. The striking myocardial uptake, however, made Wieland et al.[4] suggest the potential use of radio-labeled *m*IBG for myocardial imaging.

Patient preparation for ^{123}I-*m*IBG cardiac scintigraphy

In our department, patients referred for ^{123}I-*m*IBG myocardial scintigraphy undergo a medical interview to obtain clinical information relevant to the procedure and to guide image interpretation, and to provide the patient with relevant explanation about the test. Special care should be taken regarding pregnant or breastfeeding women. Especially in these patients, it is necessary to discuss whether the procedure will bring real benefit, if the procedure could be rescheduled for later or if there are alternatives to evaluate the clinical question. Free iodine, either ^{123}I or ^{131}I, is excreted in breast milk. Therefore, it is recommended to interrupt breastfeeding for at least 36 hours when ^{123}I-*m*IBG is used, and to discontinue breastfeeding completely when ^{131}I-*m*IBG is used.[5,6]

Because of "free" iodine, the thyroid should be blocked with perchlorate, potassium iodide or Lugol's solution, at least 30 minutes before the administration of the ^{123}I/^{131}I-*m*IBG. Dose adjustment can be made taking into consideration the weight of the patient.

^{123}I has a half-life of 13.22 hours, it decays by electron capture to ^{123}Tellurium with gamma-ray emission of primarily 159 keV, which enables its use in obtaining images with a gamma camera. In addition, ^{123}I decays with a small fraction of high energy photons. ^{123}I is produced in a cyclotron by xenon irradiation.

Some food and drugs need to be discontinued before the administration of *m*IBG due to known or suspected interference with *m*IBG uptake. It is also recommended to discontinue the use of drugs, such as tricyclic antidepressants, antipsychotics, opioids, and sympathomimetics, at least for 5 biological half-lives prior to *m*IBG administration.[7] In addition, beta-blockers and angiotensin-converting-enzyme (ACE) inhibitors are also known to influence the uptake of *m*IBG. Sometimes the discontinuation of these medications is considered unethical, such as in psychotic and heart failure (HF) patients. Therefore, the recommendation to discontinue these medications is not always possible and the decision to discontinue the medication should always be made after carefully considerations and on an individual patient basis.

Protocol for ^{123}I-*m*IBG administration and planar image acquisition

We recommend administering the radiopharmaceutical via an intravenous catheter (e.g. in the antecubital vein), slowly, for about two minutes. This procedure prevents some side effects, such as dizziness, pruritus or blood pressure changes. Moreover, *m*IBG is considered contraindicated to patients with known hypersensitivity to iobenguane or iobenguane sulfate.[1]

As previously mentioned and despite their lower abundance, ^{123}I decay is accompanied with other higher-energy photons - 400 keV (2.87%) and 529 keV (1.28%). These high-energy photons may lead to the penetration of collimator septa. Therefore, some authors recommend acquiring images with a medium energy (ME) collimator for greater precision in the quantification of images.

The image acquisition protocols recommend an early acquisition 15 minutes after tracer injection and a late acquisition up to 4 hours after tracer injection. The planar images are recommended to be acquired in anterior projection for 10 minutes using a 128x128 or 256x256 matrix. Although a ME collimator seems to be preferred, these collimators are not widespread available. Because of their widespread availability, low-energy high-resolution (LEHR) collimators are very often used. Images can also be acquired using a count limit for the early acquisitions (e.g. 1 million counts), and then correct the duration of the late image acquisition for decay between the two acquisitions. It is important to exclude the liver as much as possible from the field of view, as this may deteriorate the myocardial image quality.[1]

Protocol for acquisition of SPECT images and quantification

For SPECT acquisition, a system similar to the acquisition of myocardial perfusion imaging is used, with 180-degree rotation, starting in 45-degree right anterior oblique rotating in counterclockwise direction to 45-degree left posterior oblique. It is recommended to acquire 64 projections (32 for each detector), going through 180 degrees. Reconstruction may be performed using established methods, such as filtered back-projection (FBP), or iterative methods, such as ordered subsets expectation maximization (OSEM).[1]

While various quantitation methods for measuring myocardial uptake have been used, the simplest and most practically used index has been HMR (Figure 1).[1] However, there are inter-institutional variations in HMR, even for normal values. Especially the choice of collimator introduces considerable variations.[8,9] Therefore, the need for standardization of ^{123}I-*m*IBG myocardial uptake has been recognized. However, the availability of practical clinical standardization approaches is limited. To overcome this variation and to unify HMRs from various data acquisition systems, a cross-calibration phantom was developed.[10,11] Using this cross-calibration phantom in Japan and Europe has resulted in conversion coefficients for many different gamma-camera collimator combinations.[11,12] There was a good agreement between Japanese and European LEHR, low-medium energy (LME) and medium-energy general purpose (MEGP) collimators. These findings are most likely a good basis for comparing the data from different camera collimator systems worldwide.

Use of ^{123}I-*m*IBG scintigraphy in CHF

The action of NE in association with myocardial β-AR is the trigger responsible for muscle contraction, involving the sequential action of adenylate cyclase and cAMP and, subsequently, transmembrane calcium influx.[13] In CHF, the initial beneficial adrenergic hyperstimulation has detrimental effects on the long term, and may result in cardiac remodeling.[14] In addition, there is a reduction in the sensitivity and the expression of β-AR, which contributes to progressive worsening of cardiac function.[15] Heart failure presents high mortality rates, and around 50% of deaths are related to sudden death.[16] In 2014, only in Brazil, more than 26,000 deaths were related to HF, and approximately half of them occurred in the southeast of the country.[17]

Although arrhythmia, lethal cardiac events and prognosis are multifactorial and have several determinants, cardiac ^{123}I-*m*IBG scintigraphy alone and more likely in combination with other determinants may be able to better select CHF patients with increased risk. Indeed, a large number of studies on the prognostic value of ^{123}I-*m*IBG assessed cardiac sympathetic activity in CHF have been published.

In 1992, Merlet et al.[18] demonstrated the prognostic value of ^{123}I-*m*IBG cardiac scintigraphy and its superiority over other diagnostic methods. In 90 patients with CHF (New York Heart Association - NYHA class II to IV) and left ventricular ejection fraction (LVEF) lower than 45% evaluated using radionuclide ventriculography (RV), late HMR was the best predictor of survival ($p < 0.0001$).[18] From then on, new studies emerged confirming those results. A Japanese study evaluated 414 consecutive patients with known or suspected cardiac disease and showed that, apart from the non-heart-related deaths, a compromised sympathetic innervation evaluated by ^{123}I-*m*IBG scintigraphy was the best predictor of cardiac death.[19]

A retrospective European multicenter study used ^{123}I-*m*IBG scintigraphy to determine the risk of cardiac

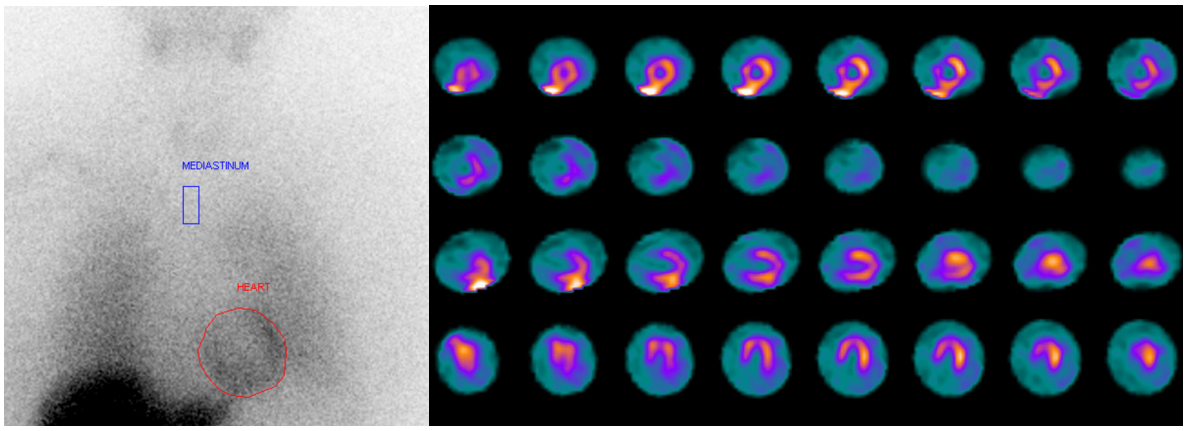

Figure 1 – *Examples of normal cardiac ^{123}I-mIBG images. Early planar image showing regions of interest (ROI) in the heart (red) and mediastinum (blue) for determination of heart-to-mediastinum ratio (A). Early SPECT images showing uniform distribution of ^{123}I-mIBG on the walls of the left ventricle (B).*

events in patients with CHF. Cardiac events were defined as cardiac death from any cause, cardiac transplantation and potentially fatal arrhythmias. It was shown that patients with events had lower HMR than those without events (average HMR of 1.51 and 1.97, respectively, $p < 0.0001$). Patients with a HMR lower than 1.75 had a higher risk of events with an odds ratio of 7.6 ($p < 0.0001$). Furthermore, 2-year event-free survival using an optimum HMR threshold of 1.75 was 62% for HMR less than 1.75, and 95% for HMR greater than or equal to 1.75 ($p < 0.0001$).[20] In a systematic review, Verberne et al. analyzed 18 studies including 1,755 patients, and observed a worse prognosis in patients with CHF and a reduced late HMR and increased cardiac washout.[21]

In 2010, the publication of ADMIRE-HF, a prospective multicenter study, confirmed the prognostic value of ^{123}I-*m*IBG cardiac scintigraphy in CHF. The late HMR was a prognostic predictor independent from other markers, such as brain natriuretic peptide (BNP) and LVEF. That study included 961 CHF patients with NYHA class II or III HF, LVEF ≤ 35% and optimized medical therapy. Progression of HF, potentially fatal arrhythmias and cardiac death were defined as cardiac events. The risk of event occurrence was significantly higher in patients who presented HMR < 1.6, with a 2-year event rate of 38% ($p < 0.001$). Moreover, the 2-year death rate, whether cardiac or all-cause, decreases linearly with increased HMR, dropping from 20% with HMR < 1.1 to 0% with HMR ≥ 1.8.[22] Other studies confirmed the power of ^{123}I-*m*IBG scintigraphy in the evaluation of cardiac risk in patients with CHF. Currently, there is an effort to better understand the relation between ^{123}I-*m*IBG scintigraphy findings and the occurrence of arrhythmic events. It appears that there is no linear relation between HMR and occurrence of arrhythmia, thus suggesting that the evaluation of the risk of arrhythmic events may be focused on SPECT,[14,23] as similarly demonstrated in a PET study.[24]

Use of ^{123}I-*m*IBG scintigraphy in the selection of patients for implantable cardiac devices

Another promising application of ^{123}I-*m*IBG myocardial scintigraphy is to better identify CHF patients who will benefit from implantable cardioverter-defibrillators (ICD) or cardiac resynchronization therapy (CRT). The implantation of these devices has contributed to significantly modify the survival of CHF patients,[25,26] and it is indicated in several guidelines.[27,28] Nevertheless, there still is a large number of patients that do not benefit from implantation (i.e. no therapeutic effects from CRT or no therapeutic discharge from ICD).[29-31] In light of the increasing incidence of HF and the concomitantly increasing costs associated with HF, a better selection of patients for these expensive devices is mandatory. In this context, ^{123}I-*m*IBG scintigraphy could possibly be used to better discriminate between patients who most likely will benefit from these device implantations and patients who will not.

Publications on this subject are encouraging, but with a limited number of patients evaluated. With 30 patients, Nishioka et al.[32] demonstrated that HMR was an independent predictor of CRT response ($p = 0.01$).

A HMR > 1.36 had a sensitivity of 75% and specificity of 71% for the identification of potential CRT responders. Response to CRT with functional improvement of LVEF was also found in significantly higher frequency in patients with left ventricular dyssynchrony and late HMR ≥ 1.6 in a study performed by Tanaka et al.[33] Moreover, the evolution of this group over 3 years was significantly more favorable than that of patients whose sympathetic function was more impaired. Moreover, CRT not only improves left ventricular function, but is also associated with an improved HMR.[34] This supports the close relation between cardiac autonomic nervous activity and left ventricular function.

Regarding ICD, the ADMIRE-HF study already showed that possible fatal arrhythmias could be predicted by a HMR < 1.6.[22] A better selection of patients for ICD is above all related to prevention (i.e. primary prevention) and not those patients referred for already proven (possible) lethal arrhythmias (i.e. secondary prevention). Nagahara et al.[35] showed that late HMR was a predictor of the occurrence of ICD shock in patients with HF and LVEF < 50% and BNP > 187 pg/ml. When combined with high levels of BNP, HMR < 1.95 had a specificity of 94% and a positive predictive value of 82% for the appropriate use of ICD.[35]

In addition to global cardiac sympathetic activity assessed with ^{123}I-*m*IBG scintigraphy, there is evidence that, in ischemic HF, regional innervation/perfusion mismatch with a larger defect size on ^{123}I-*m*IBG SPECT than on myocardial perfusion imaging SPECT predisposes to ventricular arrhythmias.[36-38] In a large prospective study in 116 CHF patients, eligible for ICD implantation for both primary and secondary prevention of sudden cardiac death (SCD), ^{123}I-*m*IBG SPECT was shown to be an independent predictor of appropriate ICD therapy and cardiac death.[39] The cumulative incidence of appropriate ICD therapy during 3 years of follow-up was significantly higher when a relatively large ^{123}I-*m*IBG SPECT defect (median summed score ≥ 26) was present. Similar results have been shown in a prospective PET study using ^{11}C-hydroxyephedrine for assessing sympathetic activity in ischemic heart disease (n=204), in which the innervation defect size predicted cause-specific mortality from SCD independently of LVEF and infarct volume.[24]

The screening ^{123}I-*m*IBG scintigraphy for a better selection of ICD candidates seems to be cost-effective. Screening is associated with a reduction in ICD utilization of 21%, resulting in a number needed to screen to prevent 1 ICD implantation of 5. Screening reduced the costs per patient by US$5500 and US$13,431 (in 2013 dollars) over 2 and 10 years, respectively, in comparison with no screening, and resulted in losses of 0.001 and 0.040 life-years, respectively, over 2 and 10 years.[40] These findings are encouraging in better discriminating responders from non-responders to ICD. However, larger studies are necessary to better define the role of ^{123}I-*m*IBG cardiac scintigraphy in identifying responders to ICD in HF. The results of a large randomized trial (i.e. ADMIRE-ICD) are therefore awaited with great anticipation.

Use of ^{123}I-*m*IBG scintigraphy in the evaluation of cardiotoxicity

Anthracyclines have been used as antineoplastic agents in a wide variety of hematological and solid tumors. It is a powerful therapeutic agent, but with cardiotoxic effects.[41] Cardiotoxicity may be acute or chronic, the latter could arise months or years later.[41] Some risk factors are known, such as cumulative dose, female sex, age, previous irradiation, other concomitant chemotherapeutic drugs, and existing cardiac dysfunction.[42] Mechanisms involved may include free radicals, myocyte death due to calcium overload and altered adrenergic function.[42]

Preventive measures have been adopted in experimental studies. Some studies have demonstrated that amifostine may be useful in the bleaching of hydroxyl and superoxide radicals.[43] Other agents used are probucol, selenium and L-carnitine. Dexrazoxane has been very useful as a cardioprotector against the cardiotoxic effects of anthracyclines. Dexrazoxane is an iron chelator and results in the reduction of free radicals. However, its use in children has been questioned for possible interference with the antitumor effect of anthracyclines. Beta-blockers and ACE inhibitors, which are part of the arsenal in the treatment of HF, have also been employed, and have been useful to treat cardiotoxicity caused by anthracyclines. However, these drugs do not protect the myocardium from possible anthracycline cardiotoxicity. Monitoring cardiotoxicity is a challenge and involves a series of procedures such as endomyocardial biopsy that, despite providing a histopathological diagnosis, is an invasive procedure and requires evaluation by an experienced pathologist.[44]

Left ventricular dysfunction is the most common manifestation found in cardiotoxicity and may contribute to an increased mortality rate. Traditional non-invasive imaging methods, such as RV and echocardiography

(ECHO), can be used to show changes, even if subtle, before the heart starts to fail. RV does not only provide a LVEF but also generates other information on left ventricular function that can be very useful, such as peak filling rate. All these parameters can be used to evaluate systolic and diastolic function, respectively. Ejection fraction and peak filling rate seem to correlate with the early stages of cardiotoxicity.[45]

Nousiainen et al. prospectively evaluated late impairment of cardiac function in 30 patients with non-Hodgkin lymphoma who were submitted to doxorubicin treatment in a low cumulative dose. The authors found that > 4% reduction after a 200-mg cumulative dose had a sensitivity of 90% and specificity of 72% to induce late cardiotoxicity.[46] It should be taken into account that a certain cell mass should be damaged before the LVEF begins to fail due to myocardial compensatory reserve. In this way, the evaluation of ventricular (dys) function is the most appropriate approach.

Another study by Dos Santos et al.[47] evaluated the late cardiotoxic effect of anthracyclines by assessing sympathetic activity with ^{123}I-*m*IBG. That study was performed in a sample of 89 young patients with mean age of 5.4 years and similar sex distribution. While patients receiving chemotherapy had a reduction in LVEF compared to controls, there was no difference in early or late HMR uptake ratios or washout rates of ^{123}I-*m*IBG.[47] ^{123}I-*m*IBG has good reproducibility and seems sensitive enough to detect alterations in adrenergic innervation before ventricular dysfunction occurs.

A recent study looked at the interrelation between HMR and washout rate and parameters obtained through ECHO, such as GLS and GRS (global longitudinal and radial strain), and serum markers. The authors evaluated 59 women with breast cancer, 1 year after treatment with anthracycline. The parameters found as the most robust were those obtained with ^{123}I-*m*IBG scintigraphy - late HMR and washout rate. Nevertheless, it is important to emphasize that there was a significant correlation between HMR and GRS.[48]

In another smaller study (n=9), the use of ^{123}I-*m*IBG scintigraphy for the evaluation of trastuzumab-related cardiotoxicity and ventricular (dys)function was investigated. The data suggest that, in patients with a persistently decreased LVEF, ^{123}I-*m*IBG scintigraphy might indicate whether recovery will occur and, consequently, whether retreatment may be initiated.[49] Taking all these preliminary data into account, it seems feasible to assess cardiotoxicity with cardiac ^{123}I-*m*IBG scintigraphy. ^{123}I-*m*IBG scintigraphy in combination with parameters of left ventricular mechanical function seem to be promising for the routine clinical use in these oncology patients.

Use of ^{123}I-*m*IBG scintigraphy in the evaluation of ischemia and diabetes mellitus

The potential use of ^{123}I-*m*IBG scintigraphy has also found its place in the evaluation of ischemia and in patients with diabetes mellitus (DM). It is important to highlight the association of DM with autonomic neuropathy. The evaluation of ischemia with ^{123}I-*m*IBG is of interest as sympathetic innervation is more susceptible to ischemia as compared to myocytes. This difference in ischemia susceptibility may be at the base of arrhythmogenicity.[50]

Simões et al. evaluated electrophysiological findings in denervated myocardium of 67 patients with acute myocardial infarction treated with early reperfusion. They correlated these electrophysiological findings with rest ^{201}TI perfusion scintigraphy and sympathetic innervation with ^{123}I-*m*IBG. The data showed disagreement in size on perfusion imaging compared to ^{123}I-*m*IBG in 90% of the patients. In other words, ischemia-related adrenergic changes are more pronounced than perfusion defects alone. In addition, electrophysiological findings showed that these areas with perfusion innervation mismatch were correlated with prolonged repolarization.[36]

Diabetic autonomic neuropathy is the most common and troublesome complication of DM. Although involvement of the autonomic nervous system is generally diffuse, symptoms may be confined to a single target organ or organ system. The exact mechanism has not been elucidated yet. As with other diseases, cardiac ^{123}I-*m*IBG scintigraphy allows for the assessment of the sympathetic activity. Numerous reports have shown that in diabetic patients, uptake abnormalities of ^{123}I-*m*IBG are correlated with a poor prognosis, even in the absence of clinical neuropathy.[51,52] Impaired glucose tolerance (IGT) is associated with an increased risk of type 2 DM and cardiovascular disease. However, Asgahr et al.[53] showed that global and regional measures of ^{123}I-*m*IBG uptake and washout, as well as cardiac autonomic function, did not differ between subjects with IGT and healthy controls.

Another study looked at the impact of DM on cardiac sympathetic innervation in patients with HF. Diabetic patients with HF showed lower cardiac ^{123}I-*m*IBG

uptake than HF patients not having DM or than DM patients with a similar degree of autonomic dysfunction not having HF. HbA1c correlated with the degree of reduction in cardiac ^{123}I-*m*IBG uptake.[54] So it is important to realize that DM may have an impact on myocardial sympathetic activity and that these patients may be at an increased risk for events.

Conclusion

Cardiac sympathetic activity can be assessed non-invasively by cardiac ^{123}I-*m*IBG scintigraphy. However, the lack of standardization of acquisition and post-acquisition analysis has hampered comparison between different institutions, and therefore wide scale clinical implementation. Cross-calibration of gamma-camera collimator combinations results in a good reproducibility with a small inter- and intra-observer variation. Moreover, the standardized cardiac ^{123}I-*m*IBG scintigraphy outcomes seem to have good prognostic value. Therefore, major objections for clinical implementation seem to have been overcome. Furthermore, the use of standardized HMR allows for the development of universal prognostic cut-off values (high vs. low risk). These cut-off values can be calculated by re-analysis of the data of previous published multicenter studies. Finally, it should be stressed that standardization of the HMR is essential for the preparation of adequate risk models. In conclusion, improving standardization and validation of cardiac ^{123}I-*m*IBG scintigraphy will lead to a much more accepted application for individual HF management.

Author contributions

Conception and design of the research: Rocha ET, Alves WEFM, Verschure DO, Verberne HJ. Acquisition of data: Rocha ET, Alves WEFM, Verschure DO, Verberne HJ. Analysis and interpretation of the data: Rocha ET, Alves WEFM, Verschure DO, Verberne HJ. Writing of the manuscript: Rocha ET, Alves WEFM, Verschure DO, Verberne HJ. Critical revision of the manuscript for intellectual content: Rocha ET, Alves WEFM, Verschure DO, Verberne HJ.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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This study is not associated with any thesis or dissertation work.

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