40 Years Anniversary of Cardiac $^{123}$I-mIBG Imaging: State of the Heart

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Accepted: 3 July 2021 / Published online: 3 September 2021 © The Author(s) 2021

Abstract

Purpose of Review This narrative review reflects on the body of evidence on cardiac $^{123}$I-mIBG imaging that has accumulated since the introduction in the late 1970s and focuses on to what extent cardiac $^{123}$I-mIBG imaging has fulfilled its potential in cardiology especially.

Recent Findings In contrast to the linear relationship between $^{123}$I-mIBG-derived parameters and overall prognosis in heart failure, there seems a “bell-shape” curve for $^{123}$I-mIBG-derived parameters and arrhythmic events. In addition, there is a potential clinical role for cardiac $^{123}$I-mIBG in optimizing patient selection for expensive devices (i.e., ICD and CRT). This needs of course to be established in future trials.

Summary Cardiac $^{123}$I-mIBG imaging is, despite the numerous of studies, sometimes mistakenly seen as a nice to have technique rather than a must have imaging modality. Although cardiac $^{123}$I-mIBG imaging has grown and matured over the years, its full clinical potential has still not been tested to the maximum.

Keywords Chronic heart failure · $^{123}$I-mIBG scintigraphy · Heart-to-mediastinum ratio · Washout · Prognosis

Introduction

Meta-iodobenzylguanidine (mIBG), an analog of the false neurotransmitter guanethidine, was developed in the late 1970s as an agent for imaging of the adrenal medulla [1]. However, even in the earliest work with this compound, its potential for use in assessing the autonomic nervous system of the heart in terms of uptake and retention of a norepinephrine (NE) analog was noted [1]. In fact, within months of the first publication of successful $^{131}$I-mIBG adrenal imaging in dogs, animal and human images of the heart were reported [2, 3]. In the latter report, five male volunteers (ages 23–31) underwent a series of images of the chest in the left anterior oblique projection during the first 2 h after administration of 74 MBq of $^{123}$I-mIBG. In all cases, the left ventricular myocardium was visualized by 2 min. These studies mark the start of the odyssey to discover clinical applications for imaging of myocardial sympathetic innervation. In the decade following the initial reports on cardiac $^{123}$I-mIBG imaging, numerous investigators in the United States of America (USA), Europe, and Japan examined the potential of this procedure in a variety of cardiac disease populations.

In contrast to the linear relationship between $^{123}$I-mIBG-derived parameters and overall prognosis in heart failure, there seems a “bell-shape” curve for $^{123}$I-mIBG-derived parameters and arrhythmic events. In addition, there is a potential clinical role for cardiac $^{123}$I-mIBG in optimizing patient selection for expensive devices (i.e., ICD and CRT). This needs of course to be established in future trials.

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Introduction

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(MPI), the large majority of over 800 patients in the study had $^{123}$I-mIBG images that were interpretable for assessment of sympathetic innervation.

The earliest investigations of cardiac $^{123}$I-mIBG imaging relied primarily on qualitative or semi-quantitative measures of uptake, either alone or in combination with MPI studies [5, 10]. However, within a few years, analyses based on pixel- and voxel-based activity determinations on planar and SPECT images were used to characterize neuronal dysfunction associated with various cardiac diseases. In the absence of absolute quantitation techniques, it became common practice to compare heart (H) uptake with activity in adjacent regions such as the lungs (L) and mediastinum (M) [8, 11]. The heart-to-mediastinum (H/M) ratio soon became a commonly used descriptor of cardiac $^{123}$I-mIBG uptake on both planar and SPECT images [7, 8, 12].

Another measure of cardiac adrenergic integrity, $^{123}$I-mIBG washout (WO), was developed as a result of use of multiple time-point imaging during the early investigations of this imaging agent. Calculation of the change in cardiac activity between early (typically 15–30 min post-injection) and late (3–4 h post-injection) images demonstrated a significant difference between normal and abnormal hearts, with more rapid loss of activity associated with disease [7, 11, 13]. The early H/M ratio predominantly reflects the integrity of sympathetic nerve terminals (i.e., number of functioning nerve terminals and intact uptake-1 mechanism (norepinephrine transporter)). The late H/M ratio particularly offers information about neuronal function resulting from uptake, storage, and release. The $^{123}$I-mIBG WO reflects predominantly neuronal integrity of sympathetic tone/adrenergic drive [14].

As experience with $^{123}$I-mIBG cardiac imaging increased, the number of patients studied became sufficient to allow assessment of the prognostic significance of the findings on these studies over time. The first major report, published in 1992, used multivariate stepwise regression discriminant analysis to demonstrate that the H/M ratio was a stronger predictor of survival probability than other indices (x-ray cardiothoracic ratio, echographic end-diastolic diameter, and radionuclide left ventricular ejection fraction) in patient with cardiomyopathy followed for 1–27 months [15]. This observation has since been confirmed in multiple subsequent retrospective and prospective studies, some of which are described later in this review. There is now 30 years of evidence of the prognostic value of $^{123}$I-mIBG cardiac imaging, particularly in patients with ischemic and non-ischemic heart failure. More generally, cardiac $^{123}$I-mIBG imaging has been established as a highly reproducible [16–18] and feasible technique to evaluate and assess any disease that results in autonomic dysfunction affecting the heart.

### Cardiac $^{123}$I-mIBG Imaging Acquisition and Analyses

Both planar and SPECT cardiac $^{123}$I-mIBG imaging have been widely used to evaluate global and regional cardiac sympathetic function. A standard dose of $^{123}$I-mIBG varies among countries: 111 MBq in Japan, 185 MBq in Europe, and 370 MBq in the USA. After administration of $^{123}$I-mIBG early (15–30 min) and late (3–4 h), images are acquired using a gamma camera equipped with a low-energy (LE) or medium-energy (ME) collimator. Typical acquisition conditions for planar and SPECT images are summarized in Table 1. Among several quantitation methods, the H/M ratio and $^{123}$I-mIBG WO has been most widely used in cardiology and neurology applications. This method is based on a simple ratio of average counts (count/pixel) of the heart and mediastinum [19••]. The regions of interest (ROI) are set as a cardiac contour, ellipsoid or circle on the heart and a fixed rectangular shape on the upper mediastinum [16, 20, 21] (Figure 1). There are variations to the WO (%) calculation using the myocardial count densities only, requiring a time-decay correction (factor of 1.21*), without (B) or with background correction (C):

\[
\text{(A) WO} = \left( \frac{\text{early H/M ratio} - \text{late H/M ratio}}{\text{early H/M ratio}} \right) \times 100
\]

\[
\text{(B) WO} = \left( \frac{\text{early H} - \text{[late H]} \times 1.21}{\text{early H}} \right) \times 100
\]

\[
\text{(C) WO} = \left( \frac{\text{[early H-early M]} - \text{[late H-late M]} \times 1.21}{\text{[early H-early M]}} \right) \times 100
\]

\* = $^{123}$I decay correction for 3 h and 45 min (1: 0.8213).

Normal ranges for H/M ratios and WO have been derived from normal databases to standardize definition of abnormal thresholds for various camera-collimator types and possibly for different populations. Japanese normal databases have defined the normal ranges of early (20 min) and late H/M ratios (3 h) of 2.2–4.0 and 2.3–4.4, respectively. Upper limit of $^{123}$I-mIBG WO is 34% if calculated by heart count with background and time-decay corrections (equation C) and 14% if calculated by the formula in equation A [22, 23].

Compared with the H/M ratio derived from two-dimensional planar images, the results of three-dimensional imaging using SPECT provide a more complete understanding of global innervation. The SPECT acquisitions are comparable with MPI. Analysis can be performed similar to the 17-segment/5-point model used for MPI [24]. An example is shown in Figure 2.

A normal database for $^{123}$I-mIBG SPECT imaging has also been developed by the Japanese Society of Nuclear Medicine working group [22]. Although this specific database cannot be applied to patients with markedly impaired cardiac
sympathetic activity, use of such standard databases facilitates evaluation of $^{123}$I-mIBG images. Without access to these databases, careful visual evaluation is essential, incorporating the specific distribution patterns of cardiac $^{123}$I-mIBG. Furthermore, comparison of cardiac SPECT $^{123}$I-mIBG images with MPI can also be useful in specific cardiac pathologies such as ischemic heart disease. However, the combined assessment of myocardial innervation and perfusion has not been gained wide implementation, possibly due to relatively higher radiation exposure and long acquisition time. In the last two decades, solid-state cardiac cameras with CTZ detector have been developed that allow the assessment of myocardial innervation and perfusion in a single imaging session with limited radiation exposure and acquisition time [25, 26].

Standardization

Although a large number of studies on planar $^{123}$I-mIBG assessed cardiac sympathetic activity have been published, methodological and analytical limitations have hampered wide-scale clinical implementations of cardiac $^{123}$I-mIBG scintigraphy and also hampered comparison between different institutions. Moreover, most of these data are acquired from single center experiences and do not necessarily allow extrapolation of the obtained results to other institutions. Essential for large-scale implementation of cardiac $^{123}$I-mIBG imaging is adequate reproducibility, standardization, and validation as suggested by Flotats et al. [19]. Furthermore, the American

Table 1. Recommended cardiac $^{123}$I-mIBG imaging acquisition conditions.

| Pre-test treatment | Medications: discontinue medications to interfere norepinephrine uptake | Thyroid blockade: (optional; may not necessarily be used) |
|--------------------|-----------------------------------------------------------------------|--------------------------------------------------------|
| Administration dose | 111–370 MBq (3–10 mCi)                                                 |                                                        |
| Timing of acquisition | 15–30 min (early) and 3–4 h (late) post-injection                     |                                                        |
| Planar image       | At least anterior image                                                | 128 × 128 or 256 × 256 matrix                          |
|                    | 5–10 min                                                              | LE or ME collimators (standardization recommended)      |
| SPECT image        | 64 × 64 matrix                                                        | 3–6-degree step, 30 s per projection*                   |
|                    | 180- or 360-degree rotation                                           |                                                        |
|                    | *Total acquisition time adjusted for 20–30 min with Anger camera, and 10 min with cardiac CZT camera |
Figure 2. Example of late $^{123}$I-mIBG SPECT imaging. On the left, the conventional short, vertical, and horizontal axis; in the middle, the corresponding 17-segment model polar map, and on the right, a 3D reconstruction. There is impaired regional $^{123}$I-mIBG uptake in the inferior wall from the myocardial base until the apex with extension to both inferoseptal and inferolateral regions.

Society of Nuclear Cardiology (ASNC) recommends locations of heart (heart shape) and mediastinum ($7 \times 7$ pixels) [27], and Japanese semi-automatic software (smartMIBG) uses a template of circular cardiac region and rectangular mediastinal region ($30\%$ of the mediastinal height, and $10\%$ of the width) [28].

Due to a non-negligible fraction of scatter and collimator septal penetration from $^{123}$I high-energy photons, variation in H/M ratio have been problematic, particularly when results from LE and ME collimators were mixed [29]. Among several methods applied, a calibration phantom-based correction method for different collimator and gamma cameras has been successfully used in Japan and partly in Europe (Table 2) [21, 32, 33••]. This cross-calibration of H/M ratio enables a better comparison between institutions and unifies H/M ratios among various institutions in multicenter studies, which is important for identifying appropriate thresholds for differentiating high- and low-risk patients.

The Diagnostic and Prognostic Role of Cardiac $^{123}$I-mIBG Imaging

Since its introduction, cardiac $^{123}$I-mIBG imaging has been shown to be an important predictor for many cardiac diseases.

Although most cardiac $^{123}$I-mIBG imaging studies evaluated chronic heart failure (CHF) populations, there is also evidence that cardiac $^{123}$I-mIBG imaging has a prognostic role in other cardiac diseases, such as atrial fibrillation, hypertrophic cardiomyopathy, and chemotherapy-induced cardiac toxicity. Cardiac $^{123}$I-mIBG imaging seems also helpful in the diagnosis for some neurology diseases. This paragraph will discuss the role of cardiac $^{123}$I-mIBG imaging in cardiac diseases with a focus on CHF. Furthermore, its role as a diagnostic tool in neurology will be discussed.

Cardiac $^{123}$I-mIBG Imaging in CHF

Since the first study [15] in the early 1990s, a number of small prospective and retrospective studies have confirmed that myocardial $^{123}$I-mIBG parameters in CHF patients are independent predictors of cardiac events (i.e., progression of HF, arrhythmia, and cardiac death) [14, 34–36]. Patients with impaired myocardial $^{123}$I-mIBG parameters (i.e., reduced late H/M ratio and increased $^{123}$I-mIBG WO) had a worse prognosis compared with those with relatively preserved parameters. In 2010, the ADMIRE-HF study, a large prospective multicenter study, confirmed the prognostic value of cardiac $^{123}$I-mIBG scintigraphy [30]. This study included 961 CHF patients with New York Heart Association

Table 2. Typical conversion coefficients and examples of thresholds for the most used collimator types in clinical practice.

| Collimator | Conversion coefficient | H/M = 1.6* with LEHR collimator | H/M = 2.2* with MEGP collimator |
|------------|------------------------|--------------------------------|--------------------------------|
| LEHR       | 0.55                   | 1.60                           | 1.75                           |
| LEGP       | 0.60                   | 1.65                           | 1.82                           |
| LME        | 0.83                   | 1.91                           | 2.13                           |
| MEGP       | 0.88                   | 1.96                           | **2.20**                       |
| MELP       | 0.90                   | 1.98                           | 2.23                           |

LEHR, low-energy, high-resolution collimator; MEGP, medium-energy general purpose collimator. Thresholds of 1.6 and 2.2 are derived from ADMIRE-HF [30••] and Japanese multicenter study of dementia with Lewy bodies [31], respectively.
(NYHA) functional class II or III HF, LVEF ≤ 35%, and optimized medical therapy (OMT). Late H/M ratio, as a dichotomous variable with a predefined cut-off of 1.6 using a LEHR collimator, was a prognostic predictor independent from other markers, such as brain natriuretic peptide (BNP) and LVEF. The risk of event occurrence was significantly higher in patients with late H/M < 1.6, with a 2-year event rate of 38% (p < 0.001). Moreover, the 2-year death rate, whether cardiac or all-cause, decreased linearly with increased late H/M ratio, dropping from 20% with late H/M ratio < 1.1 to none with late H/M ratio ≥ 1.8. Since the ADMIRE-HF study, a late H/M ratio cut-off of 1.6 became an accepted cut-off to discriminate low- and high-risk patients. However, this cut-off point is based on LEHR collimator use only. Therefore, for institutions using other types of collimators than a LEHR collimator, the cut-off value should be corrected using the above described cross-calibration phantom [21, 32, 33] (Table 2). A meta-analyses including individual patient and original image data of 636 CHF patients retrieved from 6 studies from USA and Europe showed that the late H/M ratio is not only useful as a dichotomous predictor of events (i.e., high vs. low risk) but also has prognostic implication over the full range of the outcome value for all event categories except ventricular arrhythmias [37]. The latter is interesting as there are also some smaller studies suggesting an association between increased cardiac sympathetic activity and arrhythmic events or appropriate implantable cardioverter defibrillator (ICD) therapy [38–40]. In a prospective study including 116 CHF patients, eligible for ICD implantation for both primary and secondary prevention of sudden cardiac death (SCD), 123I-mIBG 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-year follow-up was significantly higher when a relatively large 123I-mIBG SPECT defect (median summed defect score (SDS) > 26) was present. In another small study including 27 CHF patients referred for ICD implantation patients with fatal arrhythmia and SCD had lower late H/M ratios and higher 123I-mIBG SPECT SDS compared to those without an arrhythmic event [38]. Except from these small studies, a (linear) relation between 123I-mIBG scintigraphy findings and the occurrence of fatal arrhythmic events is lacking. One explanation could be the heterogeneity of the studied populations including ischemic vs. non-ischemic HF and primary vs. secondary prophylactic ICD implantation.

Currently, there is an international effort to better understand the relation between cardiac 123I-mIBG findings and the occurrence of fatal arrhythmic events. Cardiac sympathetic hyperactivity is an important factor in the occurrence of ventricular arrhythmias in patients with a reduced LVEF. In these patients, ventricular arrhythmias develop in relation to enhanced automaticity, triggered automaticity, and re-entrant mechanisms. These mechanisms are enhanced by release of NE [41]. In addition, non-uniform denervated myocardium in infarct tissue can be hypersensitive to NE. Especially the border zone of infarct tissue with viable myocardial tissue is predisposed to develop re-entrant circuits. This mechanism is most likely triggered by the fact that sympathetic nerve fibers are more susceptible to ischemia than myocytes, thereby causing a disbalance between still viable but partly denervated and normal myocardium [42, 43]. Interestingly, a multicenter study including 135 stable CHF subjects (age 64.5 ± 9.3 years, 79% male, LVEF 25 ± 6%) referred for prophylactic ICD implantation showed that in contrast to the linear correlation between 123I-mIBG scintigraphy findings by using standardized H/M ratio and the overall prognosis in CHF, there seems to be a “bell-shape” relation between 123I-mIBG scintigraphy findings and the occurrence of appropriate ICD therapy (i.e., fatal arrhythmia) [44••]. Figure 3 shows the combined endpoint (i.e., appropriate ICD therapy, progression of HF, SCD, and death due to terminal HF) in relation to standardized late H/M ratio. Patients with intermediate late H/M ratios (range 1.40–2.10) were more likely to have appropriate ICD therapy compared to patients with low and high late H/M ratios. These findings are in line with previous findings of Agostini et al. [14]. Arrhythmia occurred in CHF patients with an intermediate late H/M ratio between 1.46 and 2.17. In addition, Travin et al. concluded that the presumption of a monotonic increase in risk of an arrhythmic event with increasing 123I-mIBG SPECT defects may not always be correct [45]. This conclusion was based on the observation that in 471 ischemic CHF patients, those with intermediate defects on 123I-mIBG SPECT summed score appeared to be at the highest risk for cardiac events. The results of previous studies with a “bell-shaped” curve [14, 44–46] for the late H/M ratio or 123I-mIBG SPECT summed score of in relation to ventricular arrhythmia or appropriated ICD therapy underline the previous described hypothesis of the occurrence of ventricular arrhythmias. More importantly, these studies suggest that cardiac 123I-mIBG imaging could play a role in patient selection for an expensive disease-modifying therapy such as ICD implantation.

Cardiac resynchronization therapy (CRT) is another disease-modifying therapy in selected CHF patients (QRS ≥ 150 msec, LVEF ≤ 35%, and NYHA class ≥ 2) [47]. However, one-third of these CHF patients does not benefit from CRT. Scholten et al. reviewed 9 small studies that evaluated CRT and 123I-mIBG assessed cardiac innervation [48]. The authors concluded that the lack of uniformity in acquisition protocols, especially collimator use, and the variation in criteria used to define response to CRT impair any direct comparison between the available studies. However, in all available studies, cardiac 123I-mIBG scintigraphy showed positive changes in cardiac sympathetic activity in responders to CRT. Furthermore, cardiac 123I-mIBG scintigraphy seems to be promising in identifying CHF patients who do not benefit from CRT. This was confirmed...
by the single center BETTER-HF study (n = 121) that showed that late H/M ratio was an independent predictor of CRT response defined as LV remodelling with 15% reduction of LVESV (regression coefficient 2.906, 95% CI 0.293–3.903, \(p = 0.029\)). However, extrapolation of these data to other institutions is hampered by the lack of uniform CRT response criteria and different collimator use. To overcome the issues of different collimator use, recently, a multicenter study including 78 CHF subjects referred for CRT implantation evaluated cardiac 123I-mIBG scintigraphy in relation to response to CRT by using standardized H/M ratio [49]. The results showed that early and late H/M ratios were independent predictors of CRT response when improvement of LVEF was used as measure of response. Therefore, cardiac 123I-mIBG scintigraphy maybe used as a tool to selection of subjects that might benefit from CRT.

**Cardiac 123I-mIBG Imaging in Atrial Fibrillation**

Although cardiac 123I-mIBG imaging has mainly focussed on CHF, there is also some evidence that cardiac 123I-mIBG imaging has prognostic value in subjects with atrial fibrillation. Akutsu et al. showed in 98 patients with idiopathic paroxysmal atrial fibrillation and preserved LVEF (i.e., > 50%) that a lower late H/M ratio (HR 3.44 [CI 1.9–6.2], \(p < 0.0001\)) and lower LVEF (HR 1.04 [CI 1.01–1.08], \(p = 0.014\)) were the independent predictors of the transit from paroxysmal atrial fibrillation to permanent paroxysmal atrial fibrillation [50]. This finding further stresses the relation between autonomic imbalances and the occurrence of arrhythmias.

**Cardiac 123I-mIBG Imaging in Hypertrophic Cardiomyopathy**

Since the introduction of cardiac 123I-mIBG imaging, it has been demonstrated that cardiac sympathetic activity is impaired in hypertrophic cardiomyopathy (HCM). Not only serum levels of NE are increased [51–53], but also late H/M ratio is decreased and 123I-mIBG WO is increased [54–56]. Some of these studies demonstrated that 123I-mIBG WO correlates with the severity of myocardial hypertrophy [54, 55]. Pace et al. evaluated in patients with HCM (n = 11) late H/M ratio and 123I-mIBG WO in relation to LVEF and perfusion [57]. 123I-mIBG WO showed a positive relation with LVOT obstruction (\(r = 0.84, p < 0.001\)) and septum thickness (\(r = 0.76, p < 0.01\)), suggesting that cardiac sympathetic activity correlates to the degree of septal hypertrophy and consequently LVOT obstruction in HCM. Furthermore, late H/M ratio increases and 123I-mIBG WO decreases in the months following septal ablation which results in LVOT obstruction reduction [58]. In patients with HCM, congestive HF as a result of LV dilatation and dysfunction is an important predictor of SCD [59–61]. However, clinical tools for predicting the onset of CHF in HCM are limited. A small study including 84 HCM patients demonstrated that cardiac 123I-mIBG imaging could be useful in predicting the onset of congested HF in these patients [62]. During a follow-up of 9–86 months, the prevalence of HF was 0% in patients with late H/M ratio > 2.11, 3.3% in patients with late H/M ratio 1.86–2.11, and 55.0% in patients with late H/M ratio < 1.86. Multivariate
analysis showed that late H/M ratio and LV fractional shortening were significant predictors of congested HF in HCM.

**Cardiac ¹²³I-mIBG Imaging in Oncology Cardiotoxicity**

Chemotherapy-related cardiac dysfunction is one of the most notorious side effects of anticancer treatment, occurring in approximately 10% of patients [63]. Anthracyclines are the cornerstone in the treatment of numerous hematological and solid tumors. In a large meta-analysis pooling data from 18 studies involving almost 50,000 patients treated with anthracyclines, the incidence of clinically overt and subclinical cardiotoxicity was reported in 6.3% and 17.9% of patients, respectively [64]. Mechanisms for development of cardiotoxicity involved may include free radicals, myocyte death due to calcium overload, and altered adrenergic function. Dos Santos et al. evaluated in 89 patients the late cardiotoxicity involved may include free radicals, myocyte death due to calcium overload, and altered adrenergic function. Dos Santos et al. evaluated in 89 patients the late cardiotoxic effect of anthracyclines by assessing sympathetic activity with cardiac imaging [65]. Although patients treated with anthracyclines had a reduction in LVEF compared to controls, there was no difference in ¹²³I-mIBG-derived parameters. However, cardiac ¹²³I-mIBG imaging seems sensitive enough to detect alterations in innervation before left ventricular dysfunction occurs. Another study evaluated the correlation between ¹²³I-mIBG assessed cardiac sympathetic activity and echocardiography assessed global longitudinal strain (GLS), global radial strain, (GRS) and biomarkers [66]. The parameters found as the most robust were late H/M ratio and ¹²³I-mIBG WO. Nevertheless, it is important to emphasize that there was a significant correlation between H/M ratio and GRS.

All these preliminary data suggest that it seems feasible to assess cardiotoxicity with cardiac ¹²³I-mIBG imaging. Furthermore, cardiac ¹²³I-mIBG imaging in combination with parameters of LV impairment seems to be promising for routine clinical use in these oncology patients.

**Cardiac ¹²³I-mIBG Imaging in Specific Neurology Diseases**

To understand the pathophysiology in different neurogenerative diseases, cardiac ¹²³I-mIBG imaging has been useful. Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant neurogenetic disorder with often autonomic nervous system dysfunction. Cardiac ¹²³I-mIBG imaging revealed that compared to Parkinson’s disease, the cardiac innervation in SCA2 is less impaired [67]. Huntington’s disease (HD) is also an autosomal dominant neurodegenerative disorder with potential cardiac manifestation of severe autonomic dysfunction, including tachycardia, arrhythmia, and SCD. Recently, Assante et al. demonstrated that ¹²³I-mIBG assessed cardiac innervation was preserved in patients with HD, suggesting that cardiovascular dysfunction might be mainly due to impairment of brain areas associated with the regulation and modulation of the heart function [68].

Not only is cardiac ¹²³I-mIBG imaging helpful in better understanding the pathophysiology of some neurodegenerative diseases, but it is also useful in daily clinical practice. Reduced cardiac uptake in ¹²³I-mIBG scintigraphy is considered as a biomarker of Lewy body diseases including dementia with Lewy bodies, Parkinson’s disease, and pure autonomic failure [69–71]. The diagnostic thresholds for late H/M ratio were reported as 2.2 (standardized to the ME collimator condition) for dementia with Lewy bodies [31] and 1.77 (not standardized) for Lewy body diseases including Parkinson’s disease (see Table 2 for conversion) [72]. In Japan, cardiac ¹²³I-mIBG scintigraphy was approved and reimbursed for any cardiac diseases since 1992, and additionally approved by social insurance for Parkinson’s disease and dementia with Lewy bodies in 2012 [20]. Total number of all cardiac SPECT imaging is around 250,000 per year and the number reached plateau or slightly decreased currently. However, in contrast to USA and Europe, the number of cardiac ¹²³I-mIBG scintigraphy is increasing in Japan and reached approximately 50,000 studies per year, in which 2/3 are estimated to be performed for neurology purposes (Figure 4). Although ¹²³I-Ioflupane has been approved worldwide for Parkinson’s disease, parkinsonism, and dementia, the indications of ¹²³I-Ioflupane are mainly for the differentiation of neurodegenerative and non-neurodegenerative such as essential tremor and drug-induced parkinsonism. Cardiac ¹²³I-mIBG imaging can differentiate Parkinson’s disease from various types of Parkinson’s syndrome, whereas activity is decreased on images of both Parkinson’s diseases and syndrome with ¹²³I-Ioflupane. Therefore, it has been recognized that clinical roles for diagnosis are different between ¹²³I-mIBG and ¹²³I-Ioflupane. Although the role of imaging might be limited for patients with typical neurological symptoms and signs, the ability to accurately diagnose borderline cases remains a challenge even for neurologists. Whether such clinical experiences of combined use of ¹²³I-mIBG and ¹²³I-Ioflupane for neurodegenerative diseases and dementia can be extrapolated to other countries need to be further investigated. However, the practical role of cardiac ¹²³I-mIBG imaging for neurology purposes should be emphasized.

**Risk Models Using Cardiac ¹²³I-mIBG Imaging**

CHF is the only cardiovascular disease with both growing incidence and prevalence [73]. As a consequence, the medical costs for HF will increase. Therefore, there is a need for more precise patient-tailored risk stratification in order to achieve a more (cost)effective management of patients with CHF. To enhance the utility of risk markers, a large number of scintigramultivariate risk models have been developed in the
past decades [74–77]. However, the clinical use of these models remains limited. Based on a multicenter Japanese cohort study \((n = 933)\), a risk model was developed for predicting 5-year cardiac mortality in CHF patients [78]. Parameters used in this model include age, gender, NYHA functional class, and LVEF. By adding late H/M ratio to the net reclassification improvement, analysis for all subjects was 13.8% \((p < 0.0001)\) and its inclusion was most effective in the downward reclassification of low-risk patients. Based on 2- and 5-year risk models using 4 variables (NYHA class, age, LVEF, and late H/M ratio), mortality risk charts for CHF patients have been developed [79•].

Recently, a redefined risk model using machine learning has been developed for predicting 2 years risk of life-threatening arrhythmia and HF death [80•]. In total, 13 variables were used including age, gender, NYHA functional class, LVEF, and late H/M ratio. An example is shown in Figure 5. The probability of HF death significantly increased as late H/M ratio decreased when variables were combined. However, the probability of arrhythmic events was maximal when late H/M ratio was intermediate. This is in line with previously described studies showing a “bell-shaped” curve of arrhythmic events in relation to \(^{123}\)I-mIBG-derived parameters [44–46]. Furthermore, cardiac \(^{123}\)I-mIBG scintigraphy for a better selection of ICD candidates seems to be cost-effective [81]. In a cost-effectiveness model, screening was associated with a reduction in ICD implantation by 21%, resulting in a number needed to screen to prevent 1 ICD implantation of 5. Consequently, costs per patient were reduced by US$5500 and US$13,431 over 2 and 10 years, respectively, in comparison with no screening. Use of cardiac \(^{123}\)I-mIBG scintigraphy screening resulted in losses of 0.001 and 0.040 life-years, respectively, over 2 and 10 years. These findings are encouraging in better discriminating those who benefit from those who do not benefit from ICD implantation. However, larger studies are necessary to further define the role of cardiac \(^{123}\)I-mIBG imaging in patient selection for ICD implantation.

**Why Has Cardiac \(^{123}\)I-mIBG Imaging not Fulfilled Its Clinical Potential?**

Many factors contribute to the eventual success (or failure) of a new nuclear imaging agent. Among these are the following: the quality of the efficacy evidence, including the ability to confirm the new findings using existing established methods; widespread availability of the agent from commercial suppliers; ease of use of the agent with existing imaging equipment; and price in relation to levels of reimbursement from government and private insurers. While early evaluations of many new diagnostic radio-pharmaceuticals are in small investigator-initiated studies, commercialization typically requires larger, sponsored multicenter trials to support submissions to pharmaceutical regulatory agencies for marketing approval in various countries. This latter process, which is often both lengthy and expensive, sometimes results in judgment errors that adversely affect one or more of the success factors noted above.

It is instructive to compare the early time courses of cardiac \(^{123}\)I-mIBG imaging in oncology and cardiology, considering that the initial work in both areas occurred at about the same time. Although both early \(^{123}\)I-mIBG imaging oncology and cardiology studies were investigator-designed and executed, the former benefited from meeting an unmet medical need for a reliable diagnostic procedure for rare neural crest tumors such as pheochromocytoma and neuroblastoma [2, 82]. In cardiology, although the physiological association between myocardial \(^{123}\)I-mIBG uptake and NET-mediated sympathetic neuron function was established in early studies [83,84], there was neither a direct anatomical correlate for the new imaging findings nor a specific therapeutic action that could be taken in response. While \(^{123}\)I-mIBG imaging...
results were being used by oncologists in the mid-1980s in clinical management of patients with pheochromocytoma and neuroblastoma, cardiologists considered $^{123}$I-mIBG findings interesting but of uncertain utility.

During the past 30 years, hundreds of studies using cardiac $^{123}$I-mIBG imaging, both planar and SPECT, have been published [20, 85]. Three broad categories of studies, diagnostic, response to therapy, and prognostic, are of particular relevance to the degree of clinical utilization of the procedure.

Analogous to most other diagnostic radiopharmaceuticals (including $^{123}$I-mIBG for oncology), the most consistent growth area for $^{123}$I-mIBG cardiology use has been as a diagnostic agent. In both Europe and Japan, the majority of cardiac $^{123}$I-mIBG imaging studies are performed for evaluation of patients with neurologic disorders such as Parkinson’s disease and Lewy body disease, which can cause extensive cardiac dysinnervation. The high sensitivity and specificity of a simple discrimination between preserved and significantly decreased cardiac innervation is the primary reason cardiac $^{123}$I-mIBG imaging has been incorporated into clinical practice [86, 87]. The irony is that it is usually neurologists, not cardiologists, who order the study. In the USA, where $^{123}$I-mIBG is not indicated for neurological imaging, these procedures are rarely performed.

Neither the numerous studies showing changes in cardiac $^{123}$I-mIBG imaging findings as a measure of response to heart disease therapy [49, 88] nor the enormous number of outcome studies documenting the prognostic significance of myocardial $^{123}$I-mIBG uptake in HF and other chronic heart conditions [30, 37, 89, 90] has convinced cardiologists of the value and relevance of the procedure in routine clinical practice. This reflects a fundamental reality in cardiology: in a guidelines-driven field, prognostic information that does not change management is of little value. The difference between a predicted 2% and 10% annual mortality risk may be statistically significant, but if it reflects underlying disease that is already being treated in accordance with current guidelines, the information will be unlikely to change how the cardiologist treats the patient. Even if this same example was converted to risk for SCD in a patient eligible for an ICD, almost all cardiologists would adhere to the guidelines even if $^{123}$I-mIBG imaging suggested the patient’s true arrhythmic event risk was extremely low [90]. Currently, there are no randomized clinical trials that demonstrated that cardiac $^{123}$I-mIBG-guided therapy improves CHF patient outcomes, and without such data, clinical cardiologists have little incentive to order the scans. There is no substitute for prospective trial data that demonstrates patient benefit from the information provided by the diagnostic imaging procedure.

In recent years, clinical use of cardiac $^{123}$I-mIBG imaging has also been affected by the perception that the method is outdated in comparison with other technologies. Whether it is the continued reliance on planar imaging and the rudimentary quantification of the heart/mediastinum ratio in a field now dominated by quantitative tomographic techniques, the limited image quality of even the best $^{123}$I-mIBG SPECT study compared with PET scans using agents such as $^{11}$C-HED [91] or $^{18}$F-Flubrobenguane [92], or the advancements in other imaging and invasive cardiac mapping technologies [93, 94], convincing cardiologists to use cardiac $^{123}$I-mIBG imaging is challenging. Eventual approval of a cardiac PET agent capable of quantifying sympathetic innervation will probably make this challenge even more daunting. Except in locations where $^{123}$I-mIBG is relatively inexpensive and can be used as a binary diagnostic test agent, it seems unlikely there will be significant growth in $^{123}$I-mIBG imaging procedure volume in the foreseeable future.

However, given the increasing medical costs associated with HF, a better selection of patients for expensive therapy such as devices (i.e., ICD and CRT) is mandatory. The current selection criteria fail to make a proper selection of patients that benefit from these devices. If there is a potential clinical role for cardiac $^{123}$I-mIBG imaging in CHF, it will be in guiding the selection of these HF patients. Although currently available data show promising result for cardiac $^{123}$I-mIBG imaging, none of these studies was designed to demonstrate that $^{123}$I-mIBG-guided findings can be used to improve patient outcomes (analogous to standard randomized double-blind therapy trials).

**Conclusion**

Cardiac $^{123}$I-mIBG imaging is a widely available non-invasive modality to assess cardiac sympathetic activity. Over the past 4 decades, cardiac $^{123}$I-mIBG imaging has been established to evaluate the prognosis, especially in CHF and diagnosis in specific neurological diseases. Standardization, especially among various gamma camera-collimator combinations, is important for identifying appropriate thresholds for adequate risk stratification. In contrast to the linear relationship between $^{123}$I-mIBG-derived parameters and the overall prognosis in CHF, there seems a “bell-shape” curve for $^{123}$I-mIBG-derived parameters and fatal arrhythmias. These new insights could be helpful in
patient selection for expensive therapy such as devices (i.e., ICD and CRT). However, none of the previous studies were designed to demonstrate that $^{123}$I-mIBG-guided findings can be used to improve patient outcomes. Therefore, except from Japan, cardiac $^{123}$I-mIBG imaging has not widely been accepted as clinical tool. So, future trials are essential to address this topic and will help in establishing clinical acceptance of the robust non-invasive imaging tool that cardiac $^{123}$I-mIBG imaging is.

**Abbreviations** $^{123}$I-mIBG, $^{123}$I-meta-iodobenzylguanidine; CHF, Chronic heart failure; CRT, Cardiac resynchronization therapy; ICD, Implantable cardioverter-defibrillator; H/M ratio, Heart-to-mediastinum ratio; LVEF, Left ventricular ejection fraction; MPI, Myocardial perfusion imaging; NE, Norepinephrine; SCD, Sudden cardiac death; WO, Washout

**Declarations**

**Conflict of Interest** D.O. Verschure reports personal fees from Astra Zeneca and personal fees from Novartis. A.F. Jacobson was an employee at GE Healthcare during the conduct of the original ADMIRE-HF study. K. Nakajima has collaborative research works with FUJIFILM Toyama Chemical, Co, Ltd, Japan. H.J. Verberne declares that he has no conflict of interest.

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