Myocardial innervation imaging: MIBG in clinical practice

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Short title: Cardiac $^{123}$I-MIBG scintigraphy

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ABBREVIATIONS AND ACRONYMS

ACEi/ARB, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers
ADMIRE-HF, AdreView Myocardial Imaging for Risk Evaluation in Heart Failure
ADMIRE-HFX, extension study of ADMIRED-HF
AF, atrial fibrillation
AL, amyloid light-chain
ATTR, amyloid transthyretin (ATTRv, variant form; ATTRwt, wild-type form)
BNP, B-type natriuretic peptide
CA, cardiac amyloidosis
CAN, cardiac autonomic neuropathy
CCS, chronic coronary syndrome
CI, confidence interval
CRT, cardiac resynchronization therapy
CT, computed tomography
CZT, Cadmium Zinc Telluride
DCM, dilated cardiomyopathy
DLB, dementia with Lewy bodies
DM, diabetes mellitus
EP, electrophysiological
GP, ganglionated plexus
H/M, heart-to-mediastinum
HCM, hypertrophic cardiomyopathy
HF, heart failure
HFrEF, heart failure with reduced ejection fraction
HFS, high-frequency stimulation
HR(V), heart rate (variability)
ICD, implantable cardioverter defibrillator
LBD, Lewy body diseases
LV, left ventricle/left ventricular
LVAD, left ventricular assist device
LVEF, left ventricular ejection fraction
MACE, major adverse cardiac events
MI, myocardial infarction
MIBG, metaiodobenzylguanidine
MRA, mineralocorticoid receptor antagonist
NE, norepinephrine
NET, norepinephrine transporter
NP, natriuretic peptide
NYHA, New York Heart Association
OR, odds ratio
PD, Parkinson’s disease
PV, pulmonary vein
PVI, pulmonary vein isolation
ROI, region of interest
RV, right ventricle/right ventricular
SCD, sudden cardiac death
SGLT2i, sodium glucose cotransporter 2 inhibitors
SHFM, Seattle Heart Failure Model
SPECT, single photon emission computed tomography
TTC, Takotsubo cardiomyopathy
VT, ventricular tachycardia
WR, washout rate

MIBG IMAGING: GENERAL CONCEPTS

A brief history of MIBG
Cardiovascular function continuously adapts to changing demands by means of the autonomic nervous system, which includes the sympathetic and parasympathetic arms, which exert stimulating or inhibitory effects on target tissues. The effects of the sympathetic nervous system are primarily mediated by the release of the neurotransmitter norepinephrine (NE) from presynaptic nerve terminals, and its binding to adrenergic receptors [1]. Around 80-90% of NE released by
sympathetic nerve terminals is re-uptaken into presynaptic nerve terminals through the uptake-1 mechanism, i.e. the NE transporter (NET) [2]. Once inside the nerve terminal, NE is transported into vesicles through vesicular monoamine transporter 2 or is metabolized by monoamine oxidase. The remainder of NE is either be cleared into the circulation or on the postsynaptic side via uptake-2, which transports NE into extraneuronal tissues, such as the heart, where it is metabolized by catecholamine-O-methyl-transferase [3].

In the 1960s, guanethidine was developed as an antihypertensive drug. Guanethidine is transported across the sympathetic nerve membrane by NET and is stored, unmetabolized, in transmitter vesicles, where (at therapeutic concentrations) replaces NE and then inhibits noradrenergic transmission [4]. Combination of a benzyl group and the guanidine group of guanethidine produced metaiodobenzylguanidine (MIBG), which showed a similar affinity and capacity to NE for NET, and is similarly stored into vesicles [5]. Iodination of MIBG with a radioactive isotope enables successful imaging of sympathetic terminals and other neuroectodermally derived cells. The first clinical application of the radiolabeled MIBG with $^{131}\text{I}$ was the visualization of the adrenal medulla and different neural crest-derived tumors such as pheochromocytomas and neuroblastomas [5]. The intense myocardial uptake observed in these studies led to speculate that radiolabeled MIBG with $^{131}\text{I}$ could be used for myocardial imaging. However, due to the suboptimal imaging characteristics of MIBG and a less favorable radiation burden, radiolabeling of MIBG with $^{123}\text{I}$ was preferred for diagnostic purposes. In 1981 Kline et al. used MIBG scintigraphy to image myocardial innervation in 5 healthy subjects, and concluded that MIBG had the potential to provide semiquantitative information on myocardial catecholamine content [6].

**BASIC INFORMATION FOR CLINICIANS**

Usually, MIBG is administered intravenously after blockade of thyroid uptake of free $^{123}\text{I}$ through either 500 mg potassium perchlorate or 200 mg potassium iodide (10% solution), although this
could be omitted considering that $^{123}$I is a gamma emitter with a short half-life [7]. A standard dose is 185 MBq for cardiac imaging, corresponding to an effective dose of 2.4 mSv in adults [8]. The administered dose of MIBG can be down to 55-111 MBq when using the new gamma cameras.

MIBG is internalized by presynaptic nerve endings of postganglionic neuronal cells through NET. A 15% energy window is usually used, centered on the 159-keV $^{123}$I photopeak. Anterior planar images are obtained 15 minutes (early) and 4 hours (late) after injection and stored in 128*128 or 256*256 matrixes with standard single photon emission computed tomography (SPECT) camera. Because MIBG is primarily secreted via the kidneys, patients are encouraged to void frequently to facilitate rapid excretion of the tracer [7]. Importantly, differences in the rate of renal excretion did not contribute to variability in mediastinal and myocardial counts between early and late planar MIBG images [9].

The commonly evaluated parameters on MIBG scintigraphy are the heart-to-mediastinum (H/M) ratio and washout ratio (WR). On anterior planar images, regions of interest (ROIs) are drawn over the heart (H) and the mediastinum (M). The average counts in each ROI are obtained, and the H/M ratio is calculated. The WR is calculated as the difference between the early and late H/M, as a percentage of the early H/M, or by computing the actual myocardial counts during the early and late phases:

$$\left\{ \frac{\text{early } H - \text{early } M}{\text{early } H - \text{early } M} - \frac{\text{late } H - \text{late } M}{\text{early } H - \text{early } M} \right\} \times 100$$

This calculation must be corrected for decay to the moment of early acquisition.

The early H/M probably reflects the integrity of presynaptic nerve terminals and NET function. The late H/M combines information on neuronal function from uptake to release through the storage vesicle at the nerve terminals. The WR is an index of the degree of sympathetic drive. Therefore, increased sympathetic activity is associated with high WR and low myocardial MIBG delayed uptake. Reference values have been identified in the Japanese Society of Nuclear Medicine normal database: early H/M, average 3.1, range 2.2-4.0; late H/M, average 3.3, range 2.2-4.4; WR, average
Early and late H/M decrease with age even in normal subjects, while WR is not affected by age [11].

The use of cardiac SPECT may provide information on regional MIBG distribution. SPECT images can be acquired after planar images with early and delayed acquisition. A tomographic reconstruction is performed, and correction for scatter or tissue attenuation may be applied. MIBG distribution in the SPECT study is similar to that of perfusion imaging tracers, but the inferior accumulation is relatively lower in an MIBG study, particularly for aged individuals [12]. Myocardial regions displaying no uptake of MIBG can still be viable, as demonstrated by perfusion imaging with a tracer such as $^{99m}$Tc-tetrofosmin.

Several drugs are known, or may be expected, to interfere with organ MIBG uptake. In a review of the literature on drug interactions with MIBG uptake, the only medications for which level of evidence was judged high were labetalol and reserpine. Level of evidence was judged medium for tricyclic antidepressants, calcium channel blockers, and antiarrhythmics (specifically amiodarone). Evidence was judged sufficient to recommend withholding labetalol and the tricyclic antidepressants prior to cardiac MIBG imaging, and to suggest consideration of withdrawal of sympathomimetic amines and serotonin-norepinephrine reuptake inhibitors [13]. On the contrary, cardiac MIBG imaging can be performed in patients on beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEi/ARB) [14]. Withdrawal of beta-blockers (with the possible exception of labetalol), ACEi/ARB, or other HF medications is then not required [7]. Conversely, food containing vanillin and catecholamine-like compounds (such as chocolate) should be avoided as they may interfere with MIBG uptake [7].

POTENTIAL CLINICAL APPLICATIONS OF MYOCARDIAL INNERVATION IMAGING

Heart failure
Despite considerable advances in drug and device treatment, heart failure (HF) still represents a significant cause of morbidity and mortality, and its epidemiological burden is bound to increase in the next years. HF is by far the condition most intensely studied through MIBG imaging, given the crucial pathogenetic role of sympathetic overactivity in HF with reduced ejection fraction (HFrEF). As of September 2020, a search for “MIBG” and “heart failure” on Pubmed yields 556 papers, with a progressive increase in publications since the ‘80s. Many of these papers focused on the role of MIBG imaging for risk stratification, and on patients with HFrEF, considering heterogeneous endpoints, but usually cardiac death or major cardiac events.

Myocardial denervation has been consistently associated with a worse prognosis in patients with HF. For example, the mean H/M ratio in patients who died was typically 0.2-0.3 lower than in those who survived. Meta-analyses of published studies reported pooled hazard ratios of late H/M for cardiac death of 1.82 (95% confidence interval [CI] 0.80-4.12; p=0.15) and 1.98 for cardiac events (1.57-2.50; p<0.001) [15], and that a low H/M (with threshold ranging from 1.5 to 1.89) denoted a 5-fold higher risk of cardiac death (odds ratio [OR] 5.2, 95% CI 3.1-5.7) [16]. Furthermore, MIBG uptake was an independent and stronger predictor of mortality than late H/M [17], and a high washout rate (WR) (from 38% to 53%) was also associated with lethal events with a pooled odds ratio of 2.8 (95% CI 1.6-5.0) [16]. The H/M or WR emerged as independent predictors of adverse events from LVEF, New York Heart Association (NYHA) class, and natriuretic peptides (NPs) [18].

The results of the largest prospective trial examining the prognostic significance of MIBG imaging in HF were published in 2010. The AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study enrolled 961 patients with stable HF, LVEF ≤35%, NYHA class II-III symptoms, and on guideline-recommended medical therapy [19]. Patients with a ventricular pacemaker that routinely functioned or had received defibrillation (either external or via an ICD), anti-tachycardia pacing, or cardioversion for ventricular arrhythmias were excluded [20]. Patients had a mean LVEF of 27%, and 66% of them were adjudicated as having ischemic HF.
Over a mean follow-up of 17 months, 237 subjects (25%) experienced events (cardiac death, life-threatening arrhythmias or NYHA class progression), of which only 25 occurred in the 201 subjects with a late H/M ≥1.60 (chosen as the lower limit of normal). Two-year event rate was 15% in patients with H/M ≥1.60 and 37% in those with H/M <1.60. The H/M, LVEF, B-type NP (BNP), and NYHA class were independent predictors of outcome [19]. Post-hoc analyses of ADMIRE-HF and its extension study (ADMIRE-HFX) showed that the H/M retains its prognostic validity regardless of the intensity of treatment (based upon range of dosage) using ACEi/ARBs, beta-blockers, and MRAs) [21], and that the H/M independently predicts all-cause mortality over a median of 24 months [22]. Furthermore, adding the H/M to a well-established Seattle HF Model (SHFM) resulted in improved risk stratification, particularly in the highest-risk SHFM subset [23].

Future studies could usefully investigate the prognostic performance of MIBG imaging in patients with HFrEF receiving sacubitril/valsartan and/or sodium glucose cotransporter 2 inhibitors [SGLT2i], the added value of SPECT to planar scintigraphy and MIBG imaging over techniques such as cardiac magnetic resonance, and the possible role of MIBG imaging for the selection of candidates to cardiac resynchronization therapy (CRT), left ventricular assist device (LVAD), or heart transplantation) [23].

The degree of cardiac sympathetic stimulation, as evaluated through the WR, yielded additive prognostic significance for fast ventricular arrhythmias to other measures of autonomic dysfunction (MIBG findings, heart rate variability [HRV] on 24-hour ECG Holter monitoring and baroreflex sensitivity) over a mean of 32 months [24]. Moreover, the presence and extent of an innervation/perfusion mismatch, i.e. denervated but still viable areas, has been consistently associated with increased arrhythmogenicity. For example, in a cohort of 17 patients with implantable cardiac defibrillators (ICDs), the combined assessment of innervation/perfusion mismatch and HRV allowed correct identification of patients at high and low risk for potentially fatal arrhythmias [25]. The added value of a dual isotope SPECT protocol (to assess innervation and perfusion) over a simple innervation imaging was questioned by a study on 116 HF patients referred
to defibrillator implantation for primary or secondary prevention, the extent of late MIBG SPECT defects predicted appropriate ICD discharges and cardiac death over 23±15 months, independent from an innervation/perfusion mismatch score [26]. Conversely, perfusion SPECT might hold additive prognostic significance to a global assessment of myocardial innervation by planar MIBG scintigraphy. In a cohort of 60 ICD patients followed for a mean of 29 months, patients with impaired MIBG uptake (H/M <1.9) and \(^{99m}\)Tc-tetrofosmin defect score >12 had a significantly greater event rate (94%) than the group with impaired MIBG uptake and preserved \(^{99m}\)Tc-tetrofosmin uptake [45%; p<0.05] and the group with preserved uptake of both agents (18%) [27].

We are not aware of studies evaluating whether MIBG imaging can inform the decision as to whether an ICD should be implanted in borderline cases (for example, in patients with non-ischemic etiology and LVEF approaching the 35% threshold), or can help predict response to CRT.

The increased circulating NE levels commonly seen in patients with HF and the poor prognosis of individuals with particularly high NE levels are associated with a decreased responsiveness of the heart to adrenergic stimulation and downregulation of cardiac beta-receptors. The prognostic benefit of beta-blockers in HFrEF can be partially attributed to an improvement in cardiac sympathetic function. Imaging of myocardial sympathetic innervation provides a means to judge the recovery of this regulatory system in HF patients receiving standard-of-care medical therapy [28], CRT or LVAD [29].

Beneficial effects on cardiac sympathetic innervation have been reported after the start of HF treatment [30,31], in agreement with the prognostic benefit from these medications in HFrEF. Conversely, patients whose cardiac sympathetic innervation does not recover or even worsens on HF therapy have a worse prognosis, as indicated in a cohort of 74 patients with LVEF <45%. During follow-up, there were 12 deaths and 11 other adverse outcomes. Although there was no difference in the mean H/M at baseline between subjects who did and did not survive, 92% of those who died showed a decrease in H/M between the two MIBG studies. The change in MIBG uptake
was a better predictor of adverse long-term outcome than baseline NE or BNP or their changes over 6 months [32].

Open questions:

1. can MIBG be routinely used to select best candidates for ICD?
2. which is the impact of the novel therapeutic options for HFrEF on MIBG findings (most notably SGLT2i)?
3. can MIBG imaging help identify patients with a poor response to the standard combination of ACEi/ARB, beta-blocker, and MRA, and who could then benefit most from the switch to sacubitril/valsartan or other therapies?
4. can serial MIBG examinations better characterize the response to CRT, beyond QRS duration and changes in LV volumes and function?
5. can MIBG imaging identify patients with HFpEF and deranged sympathetic cardiac innervation, who could have a prognostic benefit from a therapy with beta-blockers?

**Ischemic heart disease**

**Chronic coronary syndrome**

Several studies on chronic coronary syndrome (CCS) have focused on the specific disease entity known as vasospastic angina, where coronary vasospasm causes a transient ischemia in the corresponding vascular territory, leading to MIBG defects that persist even when perfusion is restored. Conflicting results have been reported on WR values, as a lower WR was associated with diagnosis of vasospastic angina [33], but a higher WR with an increased risk of recurrent events [34]. Additionally, areas of defective MIBG uptake were found in patients with silent myocardial ischemia [35].

**Myocardial infarction**

Following the acute phase of myocardial infarction (MI), patients can undergo MIBG imaging to assess the consequences of the ischemic insult on sympathetic nerve terminals. Small-caliber,
unmyelinated fibers are more susceptible to ischemia than cardiomyocytes, resulting in fiber dysfunction (stunning) or death [36]. The area of defective MIBG uptake is larger than the perfusion defect, and the innervation defects persist after revascularization [37]. The resulting innervation/perfusion mismatch may predispose to ventricular arrhythmias [38], as demonstrated by the fact that the degree of perfusion/innervation mismatch is significantly correlated with the site of earliest activation in ventricular tachycardias (VT) [39].

A recovery from stunning and/or some degrees of reinnervation are believed to occur given that a normal MIBG uptake was found 14 weeks after MI in dogs [40], and MIBG uptake in the peri-infarcted area increased over 12 months in humans [41]. Patients with a recent MI (<14 days) also demonstrated a faster myocardial MIBG washout than normal subjects, in the whole heart as well as in the remote myocardium, denoting an increased sympathetic stimulation that might contribute to post-MI remodeling [42].

Ischemic heart failure

Many studies on the prognostic value of MIBG imaging in HF included a significant number of patients with ischemic etiology [19], while patients with ischemic HF have been less often specifically evaluated. Cardiac sympathetic nerve activity became progressively more altered in parallel with HF severity regardless of the underlying etiology [43], and late H/M was the strongest independent predictor of cardiac death in patients with LVEF <40% and either ischemic or non-ischemic etiology, with a lower best cut-off in those with ischemic HF (1.50 vs. 2.02) [44]. In a study on 50 patients with a history of MI and LVEF ≤40% referred to electrophysiological (EP) testing because of syncope or non-sustained VT, late H/M did not differ significantly between patients with inducible sustained ventricular tachyarrhythmias, while a 4-hour regional defect score ≥37 yielded a sensitivity of 77% and specificity of 75% for predicting a positive EP results [45]. The notion that larger regional defects are associated with an increased risk of arrhythmias was supported by a study on patients evaluated before ICD implantation for primary (89%) or secondary
prevention (11%) [26]. The late MIBG defect score was an independent predictor of both appropriate ICD discharge and cardiac death over 23±15 months. Furthermore, patients with a large late MIBG SPECT defect (summed score >26) showed significantly more appropriate ICD therapy (52% vs. 5%, p<0.01) and appropriate ICD therapy or cardiac death (57% vs. 10%, p<0.01) than patients with a small defect (summed score ≤26) at 3-year follow-up. An innervation/perfusion mismatch score was a univariate, but not an independent predictor of both endpoints [26]. In a very recent study on patients with ischemic HF (mean follow-up of 18 months), those receiving an ICD for secondary SCD prevention had significantly larger perfusion and innervation defects, while the imaging results could not predict patients with appropriate ICD therapy among patients with ICD implants for primary prevention [46]. Finally, innervation and perfusion defects were evaluated also as predictors of response to catheter ablation of ventricular arrhythmias in patients with prior MI and low LVEF. Perfusion/innervation mismatch in a specific LV zone was an independent predictor of local abnormal ventricular activity on electroanatomic mapping, and a significant reduction in the perfusion/innervation mismatch score after ablation predicted a reduction of the arrhythmic burden [47].

Take-home message:

1. A quite limited number of studies have evaluated MIBG imaging in patients with ischemic heart disease (from CCS to ischemic HF), and the evidence is quite fragmentary.
2. Myocardial ischemia causes enduring innervation defects, areas of innervation/perfusion mismatch are pro-arrhythmogenic in the post-MI setting,
3. Larger regional defects of MIBG uptake predict cardiac death and appropriate ICD discharge in ischemic HF.

Ventricular arrhythmias and prediction of sudden cardiac death in genetic disorders
The evaluation of the integrity of cardiac sympathetic innervation by MIBG scintigraphy has been long proposed as a valuable method to stratify the risk of ventricular arrhythmias (VA) and sudden cardiac death (SCD) in patients with structural heart diseases with a genetic etiology, or arrhythmogenic disorders not associated with functional and anatomic changes detectable by conventional techniques.

Idiopathic dilated cardiomyopathy

In patients with idiopathic dilated cardiomyopathy (DCM), MIBG washout was correlated with baseline LV function, and the late H/M with contractile reserve on atrial pacing [48] or contractility during dobutamine stress testing [49]. Furthermore, the late H/M emerged as the most powerful independent predictor of cardiac death in patients with DCM [44]. In another small study, a mismatch between regional innervation and perfusion was associated with a higher risk of VT [50]. These findings have not been replicated, despite their potential relevance to select patients for defibrillator implantation or to guide ablation procedures.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disorder, and an important cause of SCD. Preliminary results indicated an important role of cardiac sympathetic nervous innervation in LV function at baseline (HCM patients with systolic dysfunction had a significantly lower early MIBG uptake than controls with a WR decrease from normal to abnormal EF) and during exercise, even if it remains to be established if MIBG scintigraphy can predict the deterioration of cardiac function or other outcomes, most notably SCD.

Takotsubo cardiomyopathy
Takotsubo cardiomyopathy (TTC) is a condition where the heart takes on the appearance of a Japanese octopus fishing pot, and symptoms and signs of MI coexist with no demonstrable coronary artery stenosis or spasm. LV function can be remarkably depressed, but usually recovers within a few weeks. A sudden surge in sympathetic activity is considered as a crucial determinant of disease in TTC. A demonstration of adrenergic hyperactivity in TTC came from a study where $^{123}$I-mIBG planar scintigraphy was performed during the subacute phase (median of 8 days after coronary angiography). Patients (n=32) displayed a lower late H/M and increased WR than control subjects with acute coronary syndrome. Decreased cardiac MIBG uptake was attributed to inhibited MIBG reuptake by high epinephrine levels in the synaptic cleft and/or NET downregulation. Adrenergic overactivity resolved over time, as demonstrated by late H/M and WR values after a median of 109 days [51].

The relationship among sympathetic innervation, myocardial perfusion and glucose metabolism in TTC was evaluated by MIBG gated SPECT, $^{99m}$Tc-tetrofosmin or $^{201}$Tl gated SPECT and $^{18}$F-FDG gated positron emission tomography (PET), respectively [52]. Dysfunctional LV segments were found to have a normal perfusion but reduced innervation and glucose metabolism. These last alterations recovered slowly than LV motion [52]. The role of MIBG imaging for patient characterization and risk prediction after the acute phase remains to be characterized, while there is probably no room for improvement of the diagnostic workup [53].

**Anthracycline cardiotoxicity**

Among antineoplastic regimens, anthracyclines carry a particularly high risk of cardiotoxicity [54]. Anthracyclines cause abnormalities in myocardial adrenergic function that precede LVEF decline and overt HF. In animal studies, MIBG uptake in myocardial adrenergic neurons was reduced in a dose-dependent way [55], and MIBG imaging proved superior to echocardiography, plasma NE and cardiomyocyte staining in the early detection of doxorubicin-induced cardiotoxicity [56]. A dose-dependent decrease in MIBG uptake prior to LVEF deterioration was confirmed in humans. In
patients with previous exposure to anthracycline-containing chemotherapy regimens, late H/M displayed an inverse correlation with global longitudinal strain [57], but damage to adrenergic myocardial neurons seemed to persist even in patients recovering from LV dysfunction [58]. At present, the most promising application of MIBG imaging in this setting is early diagnosis of anthracycline cardiotoxicity, but further comparisons with alternative approaches such as speckle tracking echocardiography or high-sensitivity troponins are warranted.

Heart transplantation

During heart transplantation, postganglionic sympathetic nerve fibers of the donor heart are surgically interrupted, resulting in complete denervation [59]. The denervated heart early after transplantation is a useful model to test the specificity of neuronal imaging agents, as no cardiac uptake should be detected in this condition [60]. Sympathetic reinnervation after transplantation was first reported in animal models [61], and then in human patients evaluated with MIBG SPECT as well as with PET tracers [62,63]. For example, 48% of 23 patients evaluated 1-2 years after transplantation showed a cardiac uptake [60], and reinnervation starts from basal segments, anterior and septal walls [62,63]. Areas of reinnervated myocardium have improved blood flow regulation, energy substrate use, cardiac performance, and exercise capacity [64], but the relationship between reinnervation and patient survival is uncertain [65].

Cardiac amyloidosis

Systemic amyloidoses are characterized by the extracellular accumulation of misfolded proteins into the beta-sheet configuration, leading to tissue damage. The two most common forms are amyloid light-chain (AL) and transthyretin amyloidosis (ATTR), the latter due to the deposition of either normal (wild-type ATTR, ATTRwt) or mutated TTR molecules (variant ATTR, ATTRv) [66-68]. The heart is the organ most commonly affected in ATTRwt and one of the main sites of light-chain deposition; furthermore, different mutations in the TTR gene have been associated with a
prevalent involvement of the heart or the peripheral nervous system. Manifestations of cardiac amyloidosis (CA) include left ventricular pseudohypertrophy and conduction disturbances. Clinical evidence of autonomic dysfunction is quite common in ATTRv and AL amyloidosis, but not in ATTRwt. Sudden cardiac death has a high incidence and may result from tachyarrhythmias, but more often from electromechanical dissociation or arrhythmias not amenable to defibrillator therapy [66-68].

MIBG scintigraphy may allow to assess myocardial innervation in CA [69]. Carriers of TTR gene mutations (n=31) displayed a reduced late H/M (<1.85) in 48% of cases, half of whom had a normal diphosphonate scan, and all the subjects with a normal H/M had a normal \(^{99m}\text{Tc}\)-DPD scan. In the whole cohort (carriers or patients with overt ATTRv, n=75), DPD scan was negative in all patients with normal MIBG scan except for 2 patients [70]. Therefore, sympathetic denervation may be an early marker of cardiac disease in ATTRv, and could be considered as a screening tool for cardiac involvement in TTR gene carriers.

A combined assessment of innervation, amyloid burden (with \(^{99m}\text{Tc}\)-hydroxymethylene diphosphonate - \(^{99m}\text{Tc}\)-HMDP), and perfusion (\(^{99m}\text{Tc}\)-tetrofosmin) with a Cadmium Zinc Telluride (CZT) camera was performed only in patients with ATTRwt, in a small study (n=15), reporting a cardiac sympathetic denervation more evident in the inferior and septal regions. Although the same regions displayed a severe amyloid burden, the accumulation of amyloid fibers was more intense and extended to all other LV regions. Similarly, myocardial hypoperfusion was less intense than amyloid deposition, with a similar spatial distribution than denervation [71]. These results are in agreement with the notion that myocardial sympathetic denervation is not a prominent feature of ATTRwt and develops in a much later stage than amyloid deposition, contrary to ATTRv.

In summary, very fragmentary data are available on MIBG imaging in CA, with some evidence of a role for early diagnosis in ATTRv. SPECT imaging deserves consideration in future studies, exploring for example the patterns of myocardial denervation, their relationship with outcome, and the changes in response to novel therapies such as tafamidis.
**Atrial fibrillation**

Abnormal activity of the intrinsic cardiac autonomic nervous system seems to play an important role in the initiation and maintenance of atrial fibrillation (AF). For example, in patients with first occurrence of paroxysmal AF, a reduced late H/M predicted the development of permanent AF during a 4-year mean follow-up [72], and a high WR (calculated in a stable sinus rhythm condition 5 days after pulmonary vein isolation (PVI) independently predicted AF relapses during a mean of 14 months in patients with paroxysmal or permanent AF [73]. Furthermore, the presence of regional innervation defects after PVI on MIBG SPECT images was associated with an increased risk of AF relapses over a 6-month follow-up (40% vs. 17% of patients) [74].

The cardiac autonomic system includes thousands of neurons located in ganglionated plexuses (GPs) in the epicardial fat pads that project axons to widespread regions of the heart. Four of the 7 main GPs are located around the pulmonary veins, and the results of PVI by radiofrequency pulses may depend on effective destruction of these GPs. The standard approach to localize the GPs is to apply high-frequency stimulation to the presumed GP areas to elicit atrioventricular blocks, but this method has low specificity and sensitivity, is invasive and time-consuming [75]. MIBG imaging has been recently used to localize GPs. Stirrup et al. defined a high-resolution CZT SPECT/computed tomography (CT) protocol to identify GPs, which measure 5-10 mm, with good accuracy and reproducibility when compared to high-frequency stimulation (HFS) [76]. Left atrial innervation imaging by SPECT might replace or integrate invasive HFS in the identification of GPs, thus refining the planning of the ablation procedure. Moreover, MIBG SPECT represents an innovative tool to assess the extent of left atrium denervation and the dynamics of reinnervation after PVI, which might help predict AF recurrences [77].

**Diabetes mellitus**
Diabetes mellitus (DM) is the most common endocrine disease and one of the main determinants of morbidity and mortality worldwide. Long-term complications of DM include macrovascular disease, manifesting as coronary or peripheral artery disease, and microvascular damage to the retina, kidneys, and nerves. Diabetic neuropathies are a heterogeneous group of diabetic complications that affect different parts of the peripheral nervous system. Cardiac autonomic neuropathy (CAN) results from damage to the autonomic fibers innervating the heart and blood vessels, which impairs heart rate (HR) control and vascular dynamics. Clinical manifestations include resting tachycardia, inadequate increases in cardiac output during exercise, orthostatic hypotension, and asymptomatic ischemia or infarction. In a retrospective cohort of 144 patients with type 2 DM, reduced late H/M (<1.7) independently predicted all-cause mortality over 7.2±3.2 years, and the combination of reduced late H/M and low HRV independently predicted cardiac events (arrhythmias, HF or MI), as well as all-cause mortality [78]. Therefore, the H/M, either alone or integrated with other measures of CAN, holds prognostic significance in patients with DM. We are not aware of studies investigating the prognostic value of MIBG SPECT, and no conclusive demonstration has been provided that a more intensive glycemic control can improve cardiac MIBG uptake.

**Parkinson’s disease and related disorders**

Parkinson’s disease (PD), dementia with Lewy bodies (DLB) and pure autonomic failure are referred to as “Lewy body diseases (LBD)” because they share the presence of Lewy bodies (cytoplasmic inclusions containing alpha-synuclein protein aggregates) in neurons. The main clinical application of cardiac MIBG scintigraphy in patients with PD is currently the differential diagnosis between PD and other parkinsonisms with high sensitivity and specificity [79].

**FUTURE PERSPECTIVES**
The main applications of MIBG and SPECT for cardiac sympathetic imaging are recapitulated in the Summary Table. One of the possible causes why MIBG cardiac imaging has not been widely adopted in clinical practice, even for the characterization of patients with HF, is the fact that acquisition protocols remain quite heterogeneous in terms of tracer doses, timing of acquisition, ROI drawing, and use of LE instead of ME collimators, despite a proposal for standardization [7]. Lack of standardization is likely a major source of heterogeneity among study results, and may help explain why this technique has not gained widespread adoption in clinical practice, and has not entered even HF guidelines in spite of the evidence that MIBG holds prognostic significance in this condition. The only exception is a guideline by the Japanese Circulation Society Joint Working Group, which includes a class I recommendation for MIBG imaging for the assessment of severity and prognosis of HF [80]. A standardized approach to MIBG acquisition, possibly stimulated by novel and updated recommendations, can then be envisaged. The strengths of MIBG imaging, i.e. the fact that early and late acquisitions are relatively rapid, radiation exposure is limited (with an effective dose of less than 1 mSv when using CZT cameras), results are not influenced by most therapies, contraindications are limited to known hypersensitivity to MIBG or MIBG sulphate, and adverse effects are very rare [7], should be emphasized. Furthermore, the role of regional characterization through MIBG SPECT deserves further consideration as a tool to capture early stages of myocardial denervation, possibly missed by planar scintigraphy, or to identify regions of innervation/perfusion mismatch when combined with perfusion SPECT. The latest developments in SPECT imaging, namely the CZT technique and digital detector-based SPECT/CT, can also obviate the need for ME collimators. PET imaging of cardiac sympathetic innervation has many advantages over MIBG SPECT, including a greater spatiotemporal resolution and well-validated attenuation correction, the availability of many tracers that allow to explore both pre- and post-synaptic terminals, and the possibility of quantitative tracer uptake [1]. On the other hand, the need for an on-site cyclotron for all $^{11}$C-labelled tracers will greatly limit the applicability of PET in current clinical practice, and prompts a search for the settings where it can be replaced by MIBG SPECT.
### Summary Table. 

\( ^{123} \text{I-MIBG} \) imaging and cardiac disease: evidence from clinical studies.

|                          | Diagnosis (early diagnosis or differential diagnosis) | Risk stratification | Patient management (planning or monitoring of drug/device therapy, follow-up) |
|--------------------------|------------------------------------------------------|---------------------|--------------------------------------------------------------------------------|
|                          | Planar scintigraphy | SPECT               | Planar scintigraphy | SPECT | Planar scintigraphy | SPECT |
| Heart failure            | -                     | -                   | +++                 | ++    | +                   | -     |
| Ischemic heart disease   |                        |                      |                     |       |                     |       |
| Chronic coronary syndrome| +                     | +                   | -                   | -     | -                   | -     |
| Myocardial infarction    | -                     | -                   | +                   | +     | -                   | -     |
| Ischemic heart failure   | -                     | -                   | +                   | +     | -                   | -     |
| Ventricular arrhythmias  |                        |                      |                     |       |                     |       |
| and prediction of sudden |                        |                      |                     |       |                     |       |
| cardiac death in genetic |                        |                      |                     |       |                     |       |
| disorders                |                        |                      |                     |       |                     |       |
| Idiopathic DCM           | -                     | -                   | +                   | +     | -                   | -     |
| HCM                      | -                     | -                   | -                   | -     | -                   | -     |
| Condition                                      | ++ | +  | -  | -  | -  | -  | -  | -  |
|-----------------------------------------------|----|----|----|----|----|----|----|----|
| Takotsubo cardiomyopathy                      | -  | -  | -  | -  | -  | -  | -  | -  |
| Anthracycline cardiotoxicity                  | +  | -  | -  | -  | -  | -  | -  | -  |
| Heart transplantation                         | -  | -  | -  | -  | -  | -  | -  | -  |
| Cardiac amyloidosis                           | -  | +  | -  | -  | -  | -  | -  | -  |
| Atrial fibrillation                           | -  | -  | -  | -  | -  | -  | -  | +  |
| Diabetes mellitus                             | -  | -  | -  | -  | -  | -  | -  | -  |
| Parkinson’s disease and related disorders     | +  | -  | -  | -  | -  | -  | -  | -  |

+++, evidence from multiple clinical studies; ++, evidence from a small number of studies; +, evidence from one or very few studies; -, no clear evidence from published studies.
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