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MINI-REVIEW

Towards consensus in acquisition and image analysis of PET and SPECT in the assessment of cardiac sympathetic innervation: a mini-review

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Abstract
In the rapidly evolving field of nuclear medicine, imaging cardiac sympathetic innervation using both conventional nuclear medicine and PET tracers is a small but growing field of interest. Recent larger clinical trials have underlined the importance of imaging cardiac sympathetic innervation as well as the consequences of low regional tracer accumulation for patient outcomes. New developments have resulted in the introduction of novel PET tracers with high clinical potential, especially for imaging centers without an on-site cyclotron. Despite the generated guidelines, especially on MIBG scintigraphy, widespread compliance with standardization efforts for cardiac sympathetic innervation imaging has not been yet achieved. Compliance with standardization of imaging acquisition and data analysis is crucial to move forward towards refinement of clinical guidelines.

Keywords Cardiac sympathetic innervation · MIBG · PET · Methods · Interpretation

Introduction

Disturbances in cardiac sympathetic innervation can be consequence of different pathophysiological mechanisms. Myocardial perfusion abnormalities, such as ischemia and infarction, are the most prevalent causes of impaired cardiac sympathetic innervation. These result in a high risk of developing ventricular dysrhythmias and sudden cardiac death [1, 2]. However, also in non-ischemic cardiomyopathies (e.g., dilated and restrictive cardiomyopathy due to amyloid deposits and infiltration), cardiac sympathetic innervation abnormalities are known to translate into worse clinical outcomes [3, 4].

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Similar to cardiac involvement in systemic amyloidosis, cardiac sympathetic innervation abnormalities can also be a result from systemic synucleinopathy [5]. In Lewy body dementia and Parkinson's disease, α-synuclein aggregates are found in the heart as well as in the brain. As such, cardiac sympathetic innervation imaging enables reliable differentiation between Parkinson's disease from syndromic Parkinsonism (as in multi-system atrophy) [6].

In the rapidly developing field of nuclear medicine, several tracers for cardiac sympathetic innervation imaging have been developed within the last 30 years. In conventional nuclear medicine, the most widely studied tracer is iodine-123-labeled metaiodobenzylguanidine (^{123}I-MIBG), whereas in positron emission tomography (PET), most experience has been obtained using carbon-11-labeled meta-hydroxyephedrine (^{11}C-mHED), which is the chemically preferred description over ^{11}C-mHED. Both these tracers are used to visualize the presynaptic portion of sympathetic innervation. Details on cardiac sympathetic innervation imaging using both ^{123}I-MIBG (in neurodegeneration) and ^{11}C-mHED (in heart failure) are available in reviews published in this issue by Flotats et al. [7] and Popescu et al. [8].

As a complement to the aforementioned reviews, this mini-review addresses the advantages of PET over conventional nuclear medicine, the role of cardiac sympathetic innervation imaging in clinical decision-making, and the

need for improvement of standardization of established techniques.

PET versus SPECT in cardiac sympathetic innervation

In the rapidly evolving field of nuclear medicine, cardiac sympathetic innervation imaging represents a discrete but growing field of interest. Cardiac sympathetic innervation using both conventional nuclear medicine and PET tracers is increasingly investigated, and recently, an overview of the currently available tracers was published in this journal [9].

^{123}I-MIBG is the result of chemical modification of the false neurotransmitter analogue guanethidine and, therefore, an analogue of norepinephrine. The uptake of ^{123}I-MIBG occurs similar to the uptake of norepinephrine: predominantly by a specific uptake system ("uptake-1") and to a much lesser extent, by a non-specific uptake system (passive diffusion, "uptake-2"). Eventually, ^{123}I-MIBG, like norepinephrine, is stored in the granules of the presynaptic nerve terminals. In a non-pathological situation, ^{123}I-MIBG, unlike norepinephrine, is not bound to receptors on the myocyte membrane and does not become catabolized by monoamine oxidase (MOA). Therefore, ^{123}I-MIBG is retained in these granules in healthy subjects [10, 11].

^{11}C-mHED is a PET radiopharmaceutical for imaging cardiac sympathetic innervation. ^{11}C-mHED is derived from the false norepinephrine analogue *metaraminol*, which is taken up by the presynaptic nerve terminals similar to norepinephrine (through an uptake-1 mechanism) [12, 13]. After intravenous injection, ^{11}C-mHED is rapidly cleared from the blood and is taken up by presynaptic nerve terminals. Like ^{123}I-MIBG, ^{11}C-mHED is not metabolized by catechol-*O*-methyl transferase or oxidatively deaminated by MOA. Unlike ^{123}I-MIBG, ^{11}C-mHED rapidly leaks out of the presynaptic vesicles and diffuses into the interstitial space and will dynamically recycle into the neurons again [3]. During increased sympathetic tone, there is an increase in spillover of ^{11}C-mHED from the nerve terminal, leading to a decreased re-uptake [14]. Notably, when released into the synaptic cleft by sympathetic nerve stimulation, both radiopharmaceuticals have no significant postsynaptic effect.

PET imaging has several advantages over conventional nuclear medicine techniques, the most important being the better spatial resolution: 8–10 mm for conventional nuclear medicine versus approximately 3–4 mm for PET. Another advantage of using PET as the imaging modality over conventional nuclear medicine techniques is the possibility of absolute quantification of tracer uptake. The uptake of ^{11}C-mHED is expressed by the retention index, which is defined as the myocardial activity divided by the integral of the time-activity curve in plasma [15]. Since retention of ^{11}C-mHED is dependent of myocardial perfusion, a nitrogen-13-labeled ammonia (^{13}N-NH_3) PET is always performed before the ^{11}C-mHED acquisition. Distribution of ^{11}C-mHED throughout left ventricular myocardium in healthy normal individuals is regionally homogeneous with high uptake in all myocardial segments [16]. Therefore, the PET tracer ^{11}C-mHED is an attractive non-invasive method to quantify the activity and distribution of sympathetic innervation.

Performing head-to-head comparisons within the same patient cohort would provide insights into which modality outperforms the other. However, these comparisons between ^{123}I-MIBG and ^{11}C-mHED for cardiac sympathetic innervation in humans are rather scarce. In patients with left ventricular dysfunction, defect size (defined as < 60% of maximum) assessed with ^{123}I-MIBG scintigraphy and ^{11}C-mHED PET are closely correlated: $r=0.88$ based on late heart-to-mediastinum ratio [17]. Since ^{123}I-MIBG scintigraphy underestimates the tracer uptake in septal and inferior wall segments, this modality overestimates defect size in those areas compared to ^{11}C-mHED. The inferior to inferoapical (or even inferolateral) defect in ^{123}I-MIBG accumulation is probably not a consequence from heart failure, since the same distribution is found in healthy controls [18]. At present, the explanation for this defect has not been fully elucidated, but may be caused by the so-called liver–heart artifact and filtered back projection algorithm. Therefore, it is likely that ^{11}C-mHED outperforms ^{123}I-MIBG in the assessment of regional cardiac sympathetic innervation abnormalities. Despite the advantage of ^{11}C-mHED over ^{123}I-MIBG in tracer uptake quantification, ^{11}C-mHED does not provide in washout kinetics, in contrast to ^{123}I-MIBG. To overcome the challenges of applying ^{11}C-labeled PET sympathetic innervation imaging radiotracers, an ^{18}F-labeled benzylguanidine [^{18}F-*N*-(3-bromo-4-(3-fluoro-propoxy)-benzyl)-guanidine (^{18}F-LMI1195)] was developed resembling the structure of ^{123}I-MIBG with the additional benefit of high-sensitivity PET imaging and the extended half-life of ^{18}F. ^{18}F-LMI1195 has similar binding affinity and transport kinetics to endogenous norepinephrine [19] and similar tracer kinetics to ^{123}I-MIBG [20, 21]. These initial clinical studies also showed excellent image quality of ^{18}F-LMI1195, which was superior to ^{123}I-MIBG and equal to ^{11}C-mHED [22]. Future studies are needed to assess the potential of MIBG-like PET tracers in the evaluation of PET-derived washout kinetics.

The role of cardiac sympathetic de-innervation in clinical decision-making

There is increasing evidence that a diminished cardiac ^{123}I-MIBG uptake and ^{11}C-mHED retention are associated with worse clinical outcome in patients with ischemic and non-ischemic cardiomyopathies (especially dilated cardiomyopathy) [23–25]. The ADMIRE-HF trial showed that low late heart-to-mediastinum ratio (HMR) was associated with a higher incidence of appropriate implantable cardioverter–defibrillator (ICD) discharges as well as with the composite end-point consisting of progression of heart failure, ventricular arrhythmia, and sudden cardiac death. Unfortunately, a meta-analysis of 600 + heart failure patients could not identify a low HMR as an independent prognostic factor for the development of ventricular arrhythmia [26]. However, in transthyretin-derived cardiac amyloidosis, multivariate analyses did reveal that a low late HMR is as an independent prognostic marker for 5-year mortality [4]. Despite the evidence for dichotomizing late ^{123}I-MIBG HMR to predict survival, survival rates are linearly correlated with decreasing late ^{123}I-MIBG HMR. This dichotomizations may have limitations, since the presence of both intra- and inter-observer variabilities in drawing the regions-of-interest. This uncertainty results in a 'measurement grey zone' with potentially important consequences for both treatment and prognosis [27].

Decreased cardiac ^{11}C-mHED retention is inversely related to severity of heart failure symptoms in patients with dilated cardiomyopathy and associated with an increased risk of ventricular arrhythmia in patients with ischemic cardiomyopathy.

Besides global tracer accumulation, the size of a regionally diminished cardiac tracer accumulation (defined as < 60% of maximum) has been studied in relation with clinical outcome. A prospective multicenter center identified defect size as the only independent prognostic factor for ventricular arrhythmia in patients with ischemic cardiomyopathy [28]. In addition, in patients who underwent ICD implantation due to (non-)ischemic cardiomyopathy, a large late ^{123}I-MIBG sized defect was an independent prognostic predictor of appropriate ICD discharge and sudden cardiac death [29]. Although in another study, neither late HMR nor ^{123}I-MIBG defect size was associated with appropriate ICD therapy, the combination of late HMR and LVEF was significantly associated with the absence of appropriate ICD discharge [30]. In addition, comparable results were presented in the PAREPET trail using ^{11}C-mHED for cardiac sympathetic innervation imaging [23]. PET-derived defect size was considered to be the only independent predictive marker for sudden cardiac death [23]. Based on these findings, future studies should focus on cost-effectiveness of ICDs in patients with ischemic cardiomyopathy. Despite that ICD is the most effective treatment option to prevent death from ventricular arrhythmia and superior compared to the use of anti-arrhythmic drugs alone [31, 32], not all patients eventually suffer from ventricular arrhythmia. In fact, it seems that only a minority of patients (approximately 30%) benefit from prophylactic ICD treatment.

Cardiac resynchronization therapy (CRT) is a potential treatment option for patients with heart failure (HF), particularly in those with a left ventricular ejection fraction (LVEF) < 35%, a wide QRS complex (≥ 150 ms), and a New York Heart Association (NYHA) class of II–IV [31]. CRT has been shown to improve HF symptoms and reduce hospitalizations and life-threatening arrhythmias in some patients [33]. However, about one-third of patients receiving CRT do not respond to therapy. In a case series ($n = 10$), patients with dilated cardiomyopathy and moderate severity HF (LVEF ≤ 35%; NHYA II–III) underwent ^{11}C-mHED PET imaging prior to and early (1 week, respectively, 3 months) after CRT implantation [34]. Patients that responded to CRT therapy (reduction in left ventricle end systolic volume of ≥ 15% at the 3-month follow-up) had higher ^{11}C-mHED SUVs and less regional heterogeneity in tracer uptake at baseline compared to non-responders.

Therefore, future studies should focus on: (1) the need for additional therapy in patients with larger innervation defect sizes to decrease the risk of sudden cardiac death; (2) confirmation that patients with a small sized defect on either ^{123}I-MIBG or any PET tracers are likely to benefit from postponing ICD implantation; and (3) better identification of those patients who will benefit from CRT.

Improvements in standardization of acquisition and analysis

With the recent introduction of new and improved tracers for cardiac sympathetic innervation, there is an increasing demand for standardization of both image acquisition and analysis. Imaging cardiac sympathetic innervation has been reported to have potential in clinical decision-making, especially regarding the identification of those patients who will benefit from ICD implantation. However, this potential may not proceed into incorporation to the guidelines as long as there is heterogeneity in image acquisition and data analysis [35]. Despite proposed standardization for ^{123}I-MIBG imaging, substantial differences in late HMR and washout have been reported due to unaddressed heterogeneity in imaging acquisition and semi-quantitative calculations, respectively. In particular, both early and late HMR are vendor dependent and are determined by the choice for either low-energy or medium-energy collimators [36]. HMRs determined on

images acquired with low-energy collimators are generally lower than those acquired with medium-energy collimators [36]. Although the use of medium-energy collimators is preferred, many studies report image acquisition using low-energy collimators, and conversion algorithms have been published to overcome these differences [37, 38]. In addition, meta-analyses of data from larger prospective studies using these conversion factors in the evaluation of outcome parameters are now being published. Especially, in discriminating dementia with Lewy bodies from Alzheimer's disease, the conversion factors were used to re-assess ^{123}I-MIBG HMR [39]. In addition to these conversion factors, cross-calibration phantom studies have been performed in both Japan and Europe, to convert clinically established HMR into standardized HMR [40, 41]. Very recently, recalculation of previously published ^{123}I-MIBG HMR and washout data was used to validate a 2-year mortality risk model in patients with chronic heart failure [42]. The model showed a good correlation with actual cardiac mortality, but underestimated cardiac mortality for the quartile of patients with the highest risk of cardiac death. Data from these cross-calibration studies may also be helpful in comparing future multicenter ^{123}I-MIBG databases [43].

Finally, comparison of results from different studies would benefit from robust software applications for analysis of both PET and ^{123}I-MIBG-based data. At present, there is no dedicated application for quantification of cardiac sympathetic function available.

Conclusions

Imaging cardiac sympathetic innervation is a small but growing field of interest. It has a large potential in clinical decision-making, particular in risk stratification to define patients that would benefit from ICD therapy or in predicting the response to CRT in HF patients with reduced LVEF. Compliance to standardization of imaging acquisition and data analysis is needed to move forward towards incorporation into clinical guidelines.

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Compliance with ethical standards

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