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SYSTEMATIC REVIEW

Assessment of myocardial sympathetic innervation by PET in patients with heart failure: a review of the most recent advances and future perspectives

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Abstract

Purpose Life-threatening ventricular arrhythmias (VA) are a major cause of death in patients with congestive heart failure (HF). Among various factors, the sympathetic nervous system may give rise to VA in several pathophysiological pathways due to an impaired function of presynaptic sympathetic nerve terminals. Positron emission tomography (PET) with labeled catecholamine analogues represents a reliable tool to assess the sympathetic innervation activity. This review aims at summarising the most relevant and recent literature findings on the current role of PET in the evaluation of cardiac sympathetic activity in patients with heart failure.

Methods and Results A comprehensive literature search strategy using PubMed databases was carried out looking for articles on the role of Positron emission tomography/Computed Tomography (PET/CT) in the assessment of myocardial sympathetic innervation in patients with heart failure. The literature search limited to the last 5 years retrieved 40 papers. Most of the papers dealt with PET studies with ^{11}C-HED. 19 pre-clinical, first-in-human and clinical studies highlighting the current role of PET and future perspectives resulted eligible for inclusion in the present review.

Conclusion The assessment of myocardial sympathetic activity in patients with heart failure with PET will play a pivotal role in clinical practice. Its capability to predict the occurrence of life-threatening VA and the effectiveness of resynchronization therapy makes this technique ideal in the era of personalized medicine.

Keywords Positron emission tomography · Myocardial sympathetic innervation · Heart failure

Introduction

Life-threatening ventricular arrhythmias (VA) are a major cause of death in patients with congestive heart failure (HF). Although impaired left ventricular ejection fraction (LVEF) remains the primary criterion for implantable cardioverter-defibrillator therapy to prevent sudden cardiac death, it still has low sensitivity and specificity for the population at risk [1].

As such, it is mandatory to identify other variables with prognostic value to predict the occurrence of VA.

The sympathetic nervous system may give rise to VA through several pathophysiological pathways including increased global sympathetic activity and regional cardiac sympathetic denervation resulting from ischemia, hibernation, or infarction [2]. In fact, an impaired function of presynaptic sympathetic nerve terminals is considered to reflect impaired reuptake and thus impaired removal of the neurotransmitter from the synaptic cleft [3], resulting in overexposure of the myocardium to catecholamines and in a pre/post-synaptic signaling imbalance [4].

Radionuclide imaging techniques, with Single-Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) imaging, using radiolabeled catecholamines, have been successfully used to identify global and regional impairments of sympathetic nerve terminals in the myocardium and their contribution to disease development and progression.

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The most widely available tracer to assess cardiac sympathetic innervation using SPECT imaging is currently Iodine-123-labeled metaiodobenzylguanidine (^{123}I-MIBG) [5–7]. Many studies have demonstrated that cardiac uptake of ^{123}I-MIBG is reduced in individuals with heart failure and indicate that ^{123}I-MIBG can be used as an independent predictor of heart failure progression and cardiac mortality [7–9]. Unfortunately, ^{123}I-MIBG imaging suffers from evident limitations, mainly due to the fact that its main prognostic parameters, i.e., the heart-to-mediastinum ratio and the cardiac washout rate, are generally derived from planar scans of the chest, thus allowing only a semiquantitative evaluation of the global activity of sympathetic innervation [10]. Hence, PET may be a preferred technique, able to provide also a regional evaluation of the cardiac sympathetic innervation activity, which is considered to have a higher impact on clinical practice [11].

We present here the most relevant and recent literature findings, highlighting the current role of PET in the evaluation of cardiac sympathetic activity in patients with heart failure.

Materials and methods

Search strategy

A comprehensive literature search strategy using PubMed databases was carried out looking for articles on the role of Positron emission tomography/Computed Tomography (PET/CT) in the assessment of myocardial sympathetic innervation in patients with heart failure. The string used for the search included a combination of the terms: 'myocardial sympathetic innervation', 'heart failure', 'myocardial PET imaging', 'radiolabeled catecholamines', '^{11}C-hydroxyephedrine', 'sudden cardiac death', 'regional denervation', 'myocardial infarction'. The search was extended to all radiopharmaceuticals tracing myocardial sympathetic innervation. The search was updated until October 2017 and was limited to the previous 5 years, taking into consideration only original papers published in English. The reason for this choice is that the large amount of references suggested limiting the search to the most recent findings, which were nevertheless reported in relation to previously published material. The references of the retrieved articles were also checked so as not to miss important clinical studies.

Review articles, articles not in the field of interest, single/double case reports, and commentaries were excluded. Papers on future perspectives in the field and experimental data were also considered eligible.

Study selection

Only original articles were selected in the systematic review according to the following inclusion criteria: a) evaluation of the role of PET in the assessment of cardiac sympathetic innervation in patients with heart failure and b) a minimum sample size of ten patients (in order to minimize the publication bias). Two researchers (C.E.P. and F.C.) independently reviewed the titles and the abstracts of the retrieved literature, selecting relevant articles according to the inclusion criteria mentioned above. Disagreements were resolved in a consensus meeting.

Results

The initial literature search revealed 142 papers published in the past 25 years. From a first check, considering only the articles of the previous 5 years, 40 out of 142 articles were selected. Applying the selection criteria, 21 of the 40 papers were excluded (11 reviews, 5 commentaries and letters, 5 papers not relevant for the aim of the study). Finally, 19 articles resulted eligible for the inclusion in this review. Specifically, 15 papers described clinical studies, while 4 were preclinical/experimental. The characteristics of all included articles are shown in Table 1.

PET: radiolabeled tracers in the assessment of myocardial sympathetic innervation

The assessment of sympathetic innervation using PET may have incremental value in evaluating the arrhythmic substrate [12]. The superior spatial resolution of PET allows for a more detailed assessment of regional sympathetic innervation and innervation/perfusion mismatch areas. Also, dynamic imaging protocols enable absolute quantification of sympathetic nerve retention of tracers [13]. In addition, dependent on specific characteristics of the tracer used, several biological aspects of the cardiac neuronal function can be visualized [14].

^{11}C-hydroxyephedrine (HED)

To date, the most commonly used and studied tracers for PET imaging is the norepinephrine (NE) analogue ^{11}C-hydroxyephedrine (HED). Similarly to ^{123}I-MIBG, ^{11}C-HED shows high affinity for presynaptic NE uptake-1 allowing the visualization of *presynaptic* sympathetic nerve function [15, 16]. ^{11}C-HED uptake is commonly quantified via a retention index, which is defined as the

Table 1 Prospect of the studies included in the review, listed according to the study design and in chronological order. See the text for patient numbers, tracer and clinical relevance

Authors	Year	Journal	Patients	Tracer	Study design	Clinical relevance	Conclusion
Aoki H et al. [48]	2013	Ann Nucl Med	19	^{11}C-HED	Clinical/prospective	Relationship between innervation, function, and metabolism	Remodeled LV after myocardial infarction is associated with impaired sympathetic innervation and function even in the non-infarcted myocardial tissue. Oxidative metabolism in the non-infarcted myocardium seems to be operated by normal regulatory mechanisms rather than pre-synaptic sympathetic neuronal function
Harms HJ et al. [13]	2014	Eur J Nucl Med Mol Imaging	30	^{11}C-HED	Clinical/prospective	Quantification of myocardial kinetics	Compared to two-tissue compartment model, a single-tissue compartment model is preferred for routine clinical studies. RI and SUV showed a non-linear relationships with V_T
Fallavollita et al. [43]	2014	J Am Coll Cardiol	204	^{11}C-HED	Clinical/prospective	Prediction of life-threatening ventricular arrhythmias	In ischemic cardiomyopathy, sympathetic denervation predicts cause-specific mortality from SCA independently of LVEF and infarct volume
Hall AB et al. [50]	2014	Circulation	45	^{11}C-HED	Clinical/randomized	Response of cardiac sympathetic function to treatment	In patients with HF with reduced EF and OSA, short-term CPAP increased ^{11}C-HED retention, indicating improved myocardial sympathetic nerve function
Sinusas AJ et al. [33]	2014	J Nucl Med	12	^{18} F-LMI1195	Clinical/prospective	Myocardial kinetics and radiation dosimetry	^{18} F-LMI1195 is well tolerated; the radiation dose is comparable to that of other commonly used PET radiopharmaceuticals
Harms HJ et al. [19]	2015	J Nucl Med	17	^{11}C-HED	Clinical/prospective	Prediction of life-threatening ventricular arrhythmias	^{11}C-HED influx rate K1 can be used as an alternative to a separate MBF scan for assessing mismatch areas between MBF and myocardial innervation
Lautamaki R et al. [28]	2015	J Nucl Med	*x*	^{11}C-HED ^{11}C-EPI ^{11}C-PHEN	Preclinical/experimental	Comparison between innervation and perfusion in viable infarct border zone	In the viable infarct borderzone, neuronal vesicular catecholamine storage and protection from metabolic degradation are more severely altered than catecholamine uptake

Table 1 (continued)

Authors	Year	Journal	Patients	Tracer	Study design	Clinical relevance	Conclusion
Higuchi T et al. [31]	2015	JACC Cardiovasc Imaging	*x*	^{18}F-LMI1195	Preclinical/experimental	Myocardial kinetics	^{18}F-LMI1195 presents similarities with ^{123}I-MIBG based on its benzylguanidine structure; the tracer is stored and released similarly to norepinephrine in the nerve terminals
Werner RA et al. [32]	2015	J Nucl Med	*x*	^{18}F-LMI1195 ^{11}C-HED	Preclinical/experimental	Myocardial kinetics	^{11}C-HEDwash-out from the heart is enhanced by the desipramine chase. In contrast, ^{18}F-LMI1195 and ^{123}I-MIBG are not influenced, demonstrating stable retention in the nerve terminals
Rijnierse MT et al. [49]	2015	Eur Heart J Cardiovasc Imaging	70	^{11}C-HED	Clinical/prospective	Comparison between innervation and perfusion in non-infarcted remote myocardium	In patients with ICMP and DCMP the microvascular dysfunction might be an important factor related to sympathetic nerve integrity
Capitanio S et al. [56]	2015	Nucl Med Biol	10	^{11}C-HED	Clinical/prospective	Response of cardiac sympathetic function to treatment	In patients with IHF disease after CRT, improvement in homogeneity of myocardial neuronal function reflected a selective improvement of tracer uptake in regions with more severe neuronal damage
Bravo PE et al. [57]	2015	Circ Cardiovasc Imaging	10	^{11}C-HED ^{11}C-EPI ^{11}C-PHEN	Clinical/prospective	Post-transplant reinnervation	In the reinnervating transplanted heart, regeneration of subcellular components of sympathetic nerve terminal function does not occur simultaneously
Harms HJ et al. [20]	2016	J Nucl Med	20	^{11}C-HED	Clinical/prospective	Quantification of myocardial kinetics	Absolute quantification of ^{11}C-HED kinetics can be performed noninvasively, enabling a more comprehensive analysis of sympathetic innervation without arterial cannulation
Werner RA et al. [22]	2016	Eur J Nucl Med Mol Imaging	*x*	^{11}C-HED	Preclinical/experimental	Comparison between innervation and perfusion after ischemia–reperfusion injury	Sympathetic neurons are more susceptible to ischemic injury than myocytes. Reinnervation was shown by differences in the pattern of ^{11}C-HED distribution in the subacute and the chronic phases.
Fujita W et al. [45]	2016	Ann Nucl Med	60	^{11}C-HED	Clinical/prospective	Prediction of life-threatening ventricular arrhythmias	The low global ^{11}C-HED retention is a marker of poor overall survival in patients with LV dysfunction

Table 1 (continued)

Authors	Year	Journal	Patients	Tracer	Study design	Clinical relevance	Conclusion
de Haan S et al. [47]	2016	J Nucl Cardiol	26	^{11}C-HED	Clinical/pilot	Prediction of life-threatening ventricular arrhythmias	Denerved residual viable myocardium in ICMP is related to the heterogenic scar zone as assessed with LGE CMR
Duvernoy CS et al. [55]	2016	J Nucl Cardiol	55	^{11}C-HED	Clinical/prospective	Relationship between innervation, function, and metabolism	Myocardial function, metabolism, blood flow, and sympathetic activation were preserved in young, otherwise healthy, T1DM patients. T1DM women presented greater myocardial oxidative metabolism requirements than men
Aikawa T et al. [53]	2017	J Nucl Med	41	^{11}C-HED	Clinical/prospective	Relationship between innervation and function	Myocardial sympathetic innervation is impaired in HFpEF patients and is associated with the presence of advanced diastolic dysfunction in HFpEF
Aikawa T et al. [54]	2017	Eur J Nucl Med Mol Imaging	41	^{11}C-HED	Clinical/prospective	Relationship between innervation, function, and fibrosis	Regional sympathetic denervation is associated with contractile dysfunction and fibrotic burden in HFpEF patients

RI retention index, *SUV* standardized uptake value, V_T volume of distribution, *SCA* sudden cardiac arrest, *LVEF* left ventricular ejection fraction, *HF* heart failure, *EF* ejection fraction, *OSA* obstructive sleep apnea, *CPAP* continuous positive airway pressure, *K1* rate of influx from blood to myocardium, *MBF* myocardial blood flow, *ICMP* ischemic cardiomyopathy, *DCMP* dilated cardiomyopathy, *IHF* idiopathic heart failure, *CRT* Cardiac resynchronization therapy, *LV* left ventricular, *LGE* late gadolinium-enhanced, *CMR* cardiac magnetic resonance imaging, *T1DM* Type 1 diabetes, *HFpEF* heart failure with preserved ejection fraction

ratio of the activity in the myocardium in the final image of a 40- or 60-min dynamic sequence to the integral of the image-derived arterial blood-time activity curve [17]. Recent studies found a close correlation between ^{11}C-HED retention index and late ^{123}I-MIBG heart-to-mediastinum rate [15, 18]. In addition, by calculating the influx rate (K1) from blood to myocardium of ^{11}C-HED scan, Harms et al. [19] recently demonstrated, in a study including 17 patients with known ischemic cardiomyopathy, the feasibility of assessing perfusion and innervation defects to evaluate mismatch areas using a single dynamic ^{11}C-HED PET scan. Moreover, in patients with ischemic or dilated cardiomyopathy, absolute quantification of ^{11}C-HED kinetics can be performed noninvasively, enabling a more comprehensive analysis of sympathetic innervation without arterial cannulation [20].

Animal studies suggest that non neuronal uptake can vary between ^{123}I-MIBG and ^{11}C-HED [21]. Specifically, ^{11}C-HED appears to have significantly less extraneuronal uptake and higher resistance to degradation by metabolic enzymes. These features make the detection of regional variations in myocardial sympathetic innervation more robust using ^{11}C-HED. The potential impact of this tracer in translational cardiovascular imaging has been elegantly shown in a recent paper, wherein higher susceptibility of sympathetic neurons compared to myocytes was confirmed in a rat model of myocardial transient ischemia (Fig. 1). Specifically, the authors reported a denervated zone larger than the perfusion defect, thus identifying a peri-infarct susceptibility area at increased risk to trigger VA. Interestingly, partial reinnervation was observed in the chronic phase as shown by recovery of subepicardial ^{11}C-HED uptake, thus highlighting a crucial role of the therapy [22].

Other tracers

^{11}C-epinephrine (EPI), A tracer that also evaluates cardiac sympathetic innervation [23], was mainly been employed in pre-clinical research [24, 25], but may be considered superior to HED, since it traces the entire pathway of catecholamine uptake, metabolism, and vesicular storage. *Münch* et al. directly compared EPI to HED in a study performed in healthy volunteers and patients after heart transplantation [26]. Interestingly, retention of EPI was higher than that of HED in normal hearts, but retention of EPI was lower than that of HED in transplanted (denervated) hearts, presumably reflecting lower non-specific uptake. Thus, EPI might have inherently higher sensitivity to detect changes in sympathetic innervation of the heart. Sasano et al. [27] also showed that the extent of viable but denervated myocardium quantified with ^{11}C-EPI and $^{13}NH_3$ PET was associated with inducible ventricular tachicardias (VTs) in a porcine model. Importantly, the area of denervated but viable myocardium was related to the site of initiation of the induced VTs as well as decreased endocardial voltage obtained by voltage mapping.

In addition, the uptake of multiple presynaptic tracers was explored in viable but denervated myocardium in a similar porcine myocardial infarction model [28]. In the viable infarct border zone, neuronal vesicular catecholamine storage and protection from metabolic degradation are more severely altered than catecholamine uptake. This alteration may reflect an intermediate state between normal innervation and complete denervation in advanced disease [28].

^{11}C-phenylephrine (PHEN) is a substrate for monoamine oxidase (MAO) and is thought to be useful in the assessment of vesicular leakage [29]. In a validation study of PHEN, which was compared to HED in healthy humans, the two

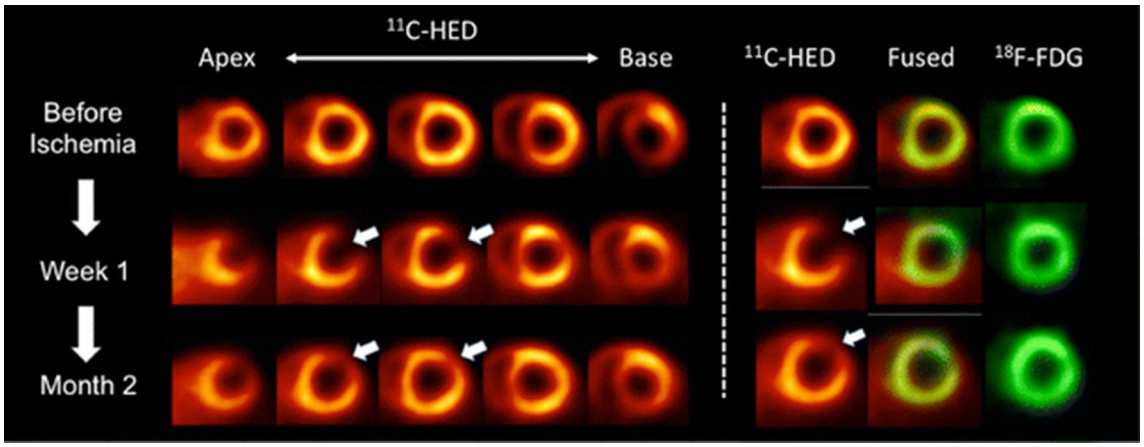

Fig. 1 In vivo serial PET scan using ^{11}C-HED and ^{18}F-FDG in a rat model of myocardial transient ischemia. ^{11}C-HED uptake defect (arrows) was observed only after ischemia. Myocardial viability performed with ^{18}F-FDG was preserved at the ^{11}C-HED defect zone. The ^{11}C-HED uptake at 1 week demonstrated reduction at month 2. Reprinted with permission of Springer from Werner et al. Eur J Nucl Med Mol Imaging. 2016;43:312-8 [22]

tracers gave initial uptake images of similar quality and uniformity, although PHEN showed much faster washout. This property of PHEN allows the calculation of storage half-life, which can provide additional useful information about the functional integrity of the cardiac sympathetic innervation [30].

To overcome the limitations related to the use of radionuclides with a short half-life, tracers labeled with Fluorine-18 have been studied. Due to the longer half-life of Fluorine-18 (110 min), they can be distributed to centers that do not have an on-site cyclotron. Moreover, clinical imaging with ^{18}F labeled tracers present more flexibility in the study design for the assessment of regional myocardial sympathetic activity.

The development of Fluorine-18–labeled radiopharmaceuticals is essential for a broader dissemination of sympathetic innervation imaging by PET in clinical practice. In this regard, ***^{18}F-LMI1195*** has been developed to overcome the limitations of conventional tracers and presents similarities with ^{123}I-MIBG based on its benzylguanidine structure [31]. Preliminary studies suggest that ^{18}F-LMI1195 is stored and released similarly to norepinephrine in the nerve terminals [31, 32]. The relationship between myocardial denervation and sudden cardiac death (SCD), along with the potential for an effective Fluorine-18-labeled tracer suggest the potential for ^{18}F-LMI1195 to help identifying high-risk patients for SCD and guide resynchronisation therapy [33]. In the first-in-human preliminary description of *^{18}F-LMI1195,* Sinusas et al. suggest that the tracer is well tolerated and yields a radiation dose comparable to that of other commonly used PET radiopharmaceuticals. The kinetics of myocardial and adjacent organ activity suggests that cardiac imaging should be possible with acceptable patient radiation dose [34].

Two additional radiopharmaceuticals, i.e., ***^{18}F–4F-MHPG*** and ***^{18}F–3F-PHPG***, were proven in animal models to yield accurate quantitative measures of regional nerve density along with a favorable heart-to-liver ratio. Initial biological studies demonstrated a slow uptake and longer retention time in sympathetic neurons, suggesting that these radiotracers may have the potential to show slight cardiac innervation impairment. A major advantage of these two tracers is the intrinsic potential for a robust absolute quantification of the myocardial uptake, as highlighted by a recent first-in-human study [35].

PET with ***^{11}C-CGP12177*** has been employed to image the *postsynaptic* side of the adrenergic system [15, 32]. Reduction of myocardial β-adrenoreceptor density, as measured by ^{11}C-CGP12177, has been shown in patients with dilated cardiomyopathy and it has been related to the severity of HF [36]. Furthermore, myocardial β-adrenergic receptor density predicted improvement of cardiac function by carvedilol treatment, whereas cardiac contractile reserve as assessed by dobutamine stress echocardiography did not [37].

PET in clinical studies

The occurrence of inhomogeneity in myocardial sympathetic denervation can be related to myocardial infarction and may create a myocardial substrate particularly vulnerable to arrhythmic death [38, 39].

In addition, also reversible ischemia (from angina or silent ischemia) can cause an inhomogeneity in myocardial sympathetic innervation, occurring in both stunned and hibernating myocardium [40]. In pre-clinical models of hibernating myocardium, there is evidence of an increased risk of arrhythmic death from spontaneous ventricular tachycardia (VT)/ventricular fibrillation (VF), which is often unrelated to infarction and heart failure [38, 41, 42]. In this regard, PET imaging with ^{11}C-HED accurately demonstrates extensive sympathetic denervation [43, 44].

Fujita et al. [45] demonstrated in a retrospective analysis of observational study that low global ^{11}C-HED retention is a marker of poor overall survival in patients with LV dysfunction.

Recently, PET with ^{11}C-HED was employed to quantify the extent of regional sympathetic denervation and predict the risk of SCD in candidates for a primary prevention implantable cardioverter defibrillator (ICD) with ischemic cardiomyopathy [40, 43, 46]. In the prospective PAREPET observational cohort study, including 204 subjects with ischemic heart failure (LVEF $\leq$ 35%), ^{11}C-HED PET was used in combination with perfusion imaging with ^{13}N-ammonia and viability with insulin-stimulated ^{18}F-FDG. The primary end-point was a life-threatening arrhythmia, defined as arrhythmic death or ICD discharge for VT/VF > 240 bpm [40]. A higher rate of SCD was reported in patients with perfusion/innervation mismatch, consistent with the presence of viable but denervated myocardium. Of note, the PAREPET study also showed that the extent of the denervated myocardium is significantly correlated to the risk of SCD. Specifically, a denervated area greater than 37.6% of the LV predicts a higher risk. Interestingly, this holds true independently of LVEF and infarct size. Also a subsequent study confirmed the important prognostic role of the mismatch between myocardial innervation and perfusion, capitalizing on innervation and perfusion imaging with ^{11}C-HED and [^{15}O]H_2O PET [47].

Hirofumi et al. [48] investigated the relationship between sympathetic innervation (assessed by ^{11}C-HED PET), contractile function (measured by echocardiography), and the oxidative metabolism (using ^{11} C-acetate PET) of the non-infarcted myocardium in 19 patients with prior myocardial infarction. They showed that the remodeled LV presents with impaired sympathetic innervation and function even in the non-infarcted myocardial tissue ($r = 0.566$). Of note, the oxidative metabolism in the non-infarcted myocardium seems to be independent from pre-synaptic sympathetic neuronal

function and rather linked to normal regulatory mechanisms ($r=0.649$). This mismatch zone originates from residual viable myocardium that has sustained ischemic nerve injury and is related to the heterogenic scar zone as assessed with late gadolinium-enhanced (LGE) cardiac magnetic resonance imaging (CMR).

Impaired innervation was also demonstrated in non-infarcted myocardium in ischemic and dilated cardiomyopathy (ICMP and DCMP). Factors affecting sympathetic nerve integrity in remote myocardium are still unknown. However, perfusion abnormalities such as microvascular dysfunction, even in the absence of detectable coronary artery disease (CAD), may underline a sympathetic dysfunction. In this regard, a recent study aimed to investigate the interrelations between myocardial perfusion, contractile function, and sympathetic innervation in non-infarcted myocardium in 70 patients with ICMP and DCMP and LVEF ≤ 35% [49]. ^{11}C-HED- and [^{15}O]H_2O PET were performed to quantify MBF at rest and under stress conditions as well as sympathetic innervation. The authors found that the hyperaemic MBF is independently associated with sympathetic innervation in non-infarcted and non-ischemic remote myocardium in patients with ICMP and DCMP. This confirms that microvascular dysfunction plays an important role to determine sympathetic nerve integrity. Nevertheless, it remains unclear whether the impaired hyperaemic MBF is the primary cause of this relation.

Obstructive sleep apnea (OSA) and heart failure (HF) with reduced ejection fraction (HFrEF) are two states of increased metabolic demand and sympathetic nervous system activation that often coexist. In a randomized trial with 45 patients with HFrEF and OSA undergoing ^{11} C-acetate and ^{11}C-HED PET, Hall et al. [50] demonstrated a significant increase in hydroxyephedrine retention in the group of patients allocated to CPAP, indicating reduced myocardial sympathetic dysregulation. Unfortunately, the authors failed to demonstrate significant favorable alterations in myocardial function or energetics overall in the treated group and further outcome-based investigation of the consequences of CPAP is warranted.

A few papers have evaluated the value of ^{11}C-HED PET to identify predictors of regional sympathetic denervation in patients with heart failure with preserved left ventricular ejection fraction (HFpEF). HFpEF is functionally characterized by diastolic dysfunction accompanying myocardial fibrosis [51, 52]. Aikawa et al. [53] demonstrated that myocardial sympathetic denervation, as assessed by ^{11}C-HED PET, was impaired in HFpEF patients and was associated with the presence of advanced diastolic dysfunction independently of LV ejection fraction.

More recently, the same authors [54] evaluated 34 patients with HFpEF (LVEF ≥ 40%) and 11 age-matched control volunteers without HF. All subjects underwent cardiac magnetic resonance imaging to measure LV size and function, and the extent of myocardial late gadolinium enhancement (LGE) and ^{11}C-HED PET to identify predictors of regional sympathetic denervation. These were quantified by means of ^{11}C-HED retention index (RI, %/min). They found that global ^{11}C-HED RI was significantly lower and more heterogeneous in HFpEF patients than in volunteers. Moreover, regional ^{11}C-HED RI was positively correlated with systolic wall thickening ($r=0.42$) and negatively with the extent of LGE ($r=-0.43$). Segments with a large extent of LGE in HFpEF patients had the lowest regional ^{11}C-HED RI among all segments. Multivariate analysis demonstrated that systolic wall thickening and the extent of LGE were significant predictors of regional ^{11}C-HED RI in HFpEF patients. In conclusion, the authors suggested that regional sympathetic denervation is associated with contractile dysfunction and fibrotic burden in HFpEF patients, thus providing an integrated measure of myocardial damage in HFpEF.

In a recent paper featuring young subjects with type 1 diabetes (IDDM) without evidence of cardiovascular disease, Duvernoy et al. [55] found no significant differences in LV function, innervation, or oxidative metabolism between IDDM and controls. Furthermore, T1DM women presented with greater myocardial oxidative metabolism requirements than men.

Finally, a few papers analyzed the role of ^{11}C-labeled catecholamines PET to identify imaging parameters that could predict the response to therapy.

In patient with end-stage HF, cardiac resynchronization therapy (CRT) may be the treatment option of choice. Capitanio et al. [56] evaluated the variation of cardiac adrenergic activity in patients with idiopathic heart failure (IHF, NYHA III-IV) after CRT using ^{11}C-HED PET/CT. They found that the improvement in homogeneity of myocardial neuronal function reflected a selective increase of tracer uptake in regions with more severe neuronal damage. These finding supported the presence of a myocardial regional variability in response of cardiac sympathetic system to CRT and a systemic response involving remote tissues with rich adrenergic innervation.

Post-transplant reinnervation is a unique model to study sympathetic neuronal regeneration in vivo but the differential role of subcellular mechanisms of catecholamine handling in nerve terminals is still unclear. Bravo et al. [57] speculated that there may be subtle differences in the regenerative capacity of subcellular mechanisms of nerve terminal function. Ten heart transplant recipients were included at > 1 year post transplantation. Three different ^{11}C-labeled catecholamine analogues were used to evaluate catecholamine transport (^{11}C-HED), vesicular storage (^{11}C-EPI), and metabolic degradation (^{11}C-1phenylephrine). Quantification of myocardial blood flow was performed with ^{13}N-NH_3 PET. The results of this paper suggest that the regeneration

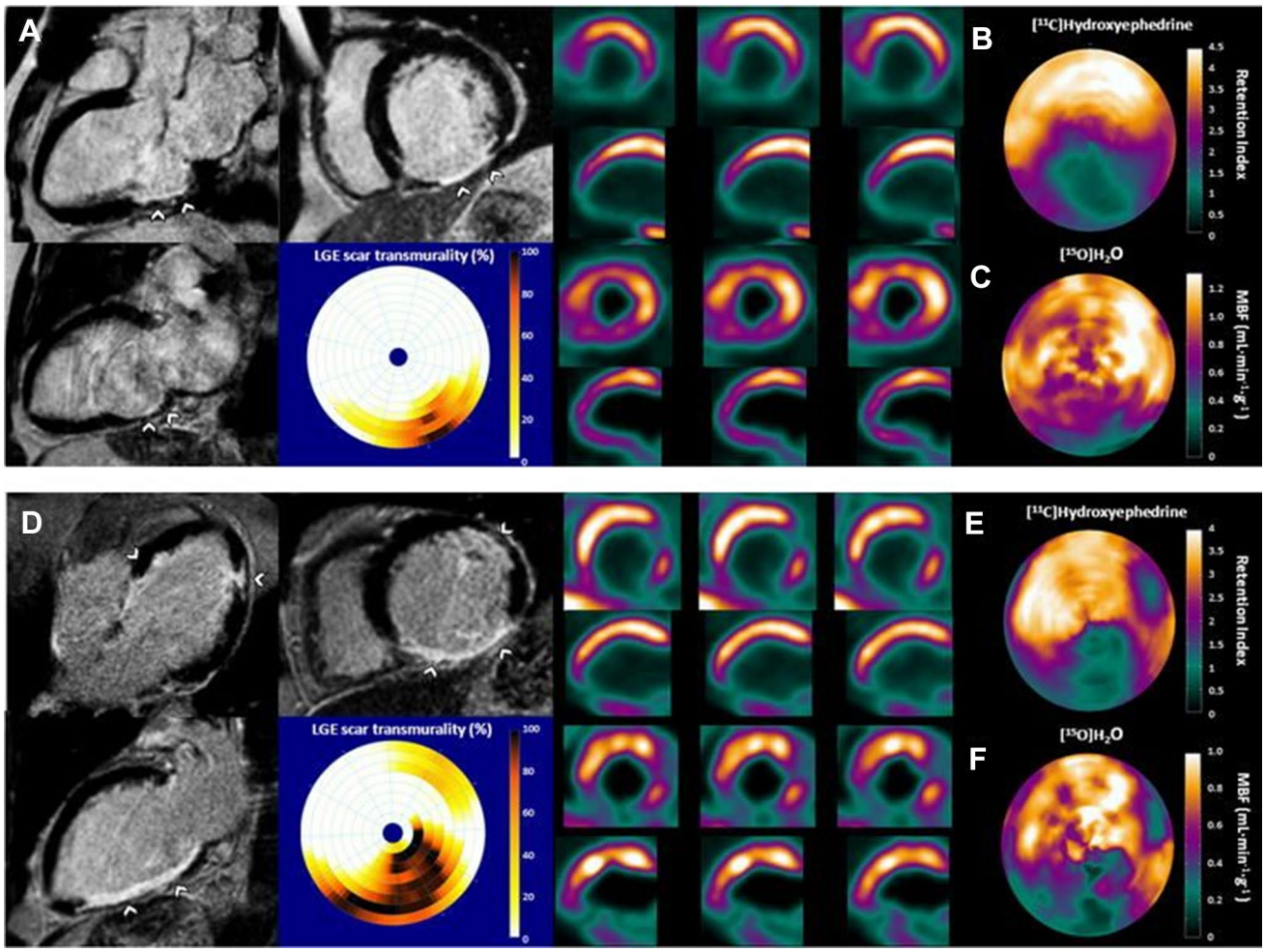

Fig. 2 Representative image showing the potential arrhythmic substrate in two patients with ischemic cardiomyopathy candidates for ICD implantation for primary prevention of sudden cardiac death who underwent ^{15}O-H2O PET, ^{11}C-HED PET, and LGE-CMR. Patient 1 **a**–**c** shows a basal inferior wall myocardial infarction with contrast enhancement in this region (**a**) and a corresponding perfusion defect (**c**) with an extensive innervation defect (**b**) that exceeded the infarct size, resulting in a significant innervation-perfusion mismatch. Patient 2 **d**–**f** shows a large inferior wall myocardial infarction with transmural contrast enhancement as well as subendocardial contrast enhancement at the anterolateral wall (**d**). ^{15}O-H2O PET and ^{11}C-HED PET indicate corresponding perfusion and innervation defects with only limited innervation-perfusion mismatch. *CMR* cardiovascular magnetic resonance, *LGE* late gadolinium enhancement, *PET* positron emission tomography. Reprinted under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/) from J Nucl Cardiol. 2016;23:218-34 [12]. No changes were made

of subcellular components of sympathetic nerve terminal function does not occur simultaneously. In the reinnervating transplanted heart, a region with normal catecholamine transport and vesicular storage is surrounded by a border-zone, where transport is already restored but vesicular storage remains inefficient, suggesting that vesicular storage is a more delicate mechanism. This observation may have implications for other pathologies involving cardiac autonomic innervation such as myocardial ischemia, infarction, heart failure, metabolic, and neurodegenerative diseases, where impaired innervation has been identified and where the presence and contribution of nerve regeneration is less well defined [43, 58–60]. Of note, vesicular storage may not only require more time for restoration but it may also be damaged at an earlier stage in disease, as suggested by preclinical work in myocardial infarction [27]. Whether this has implications for adverse outcome, or whether it may emerge as a target for regenerative therapies, should be a subject of future studies.

Conclusion

It is undoubtedly clear that the assessment of myocardial sympathetic activity in patients with heart failure will play a pivotal role in clinical practice. Its capability to predict the occurrence of life-threatening ventricular arrhythmias (VA) in the presence of still viable but denervated myocardium (Fig. 2) [12, 40] and the effectiveness of resynchronization therapy [56] makes this technique ideal in the era of personalized medicine.

An important advantage of PET imaging over other techniques is the potential for a full quantitative analysis of myocardial denervation. A quantitative analysis bears great importance to overcome limitations due to global down-regulation of myocardial catecholamine storage, which is frequently reported in patients with heart failure [61, 62].

Furthermore, PET allows also to evaluate the myocardial sympathetic innervation activity along with other molecular-targets, capitalizing on different half-lives of different radiopharmaceuticals used in multi-radioisotope investigations. This represents a unique approach to provide useful prognostic information in patients with heart failure. Very specific insights may be provided by combining information on myocardial sympathetic activity and other variables identifying, for example apoptosis, extracellular matrix activation, or angiogenesis [62].

In this regard, translational molecular imaging is expected to play an important role in boosting the research on the intimate pathophysiological mechanisms underlying LV denervation. This will also provide an invaluable tool to direct optimized targeted therapies.

Compliance with ethical standards

Conflict of interest All authors declare that they do not have any conflict of interest. This article does not contain results of studies with human subjects or animals performed by the authors.

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