

Editorial in response to: Impaired Myocardial Innervation is Associated with Diastolic Dysfunction in Heart Failure with Preserved Ejection Fraction:  $^{11}\text{C}$ -hydroxyephedrine PET Study.

**Imaging of the Cardiac Sympathetic Nervous System Has Potential Value in the Evaluation of Patients with HFpEF**

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Heart failure (HF) is a major public health problem that affects more than 5.8 million people in the United States and 23 million people worldwide<sup>1</sup>. HF is a clinical syndrome, rather than a disease, and can occur in patients with reduced and preserved left ventricular ejection fraction (LVEF). Community-based studies indicate that approximately 50% of patients with the clinical diagnosis of HF have preserved EF (HFpEF), while the remaining patient population presents with HF with reduced EF (HFrEF)<sup>2,3</sup>. The values used to define “preserved” EF range in the literature from 40-55%, but current guidelines recommend EF > 50% with elevated natriuretic peptide (BNP or NTproBNP) levels and relevant structural heart disease, such as left atrial enlargement and/or LV diastolic dysfunction as criterion for HFpEF<sup>4,5</sup>. While clinical symptoms and mortality are similar amongst patients with HFpEF and HFrEF, there are pronounced differences between these HF phenotypes in patient demographics, responses to therapy and underlying pathophysiology of left ventricular remodeling<sup>6,7</sup>. Importantly, the prevalence of HFpEF relative to HFrEF is rising at a rate of 1% per year, and will thus dominate as the prevalent HF phenotype over the next decade<sup>8</sup>. Despite the rising prevalence, there are limited data to support effective therapies for HFpEF, and the role of diagnostic strategies and prognostic biomarkers remain ambiguous<sup>4,9</sup>.

Excessive cardiac sympathetic nervous system (SNS) activation is a hallmark of HF progression in patients with HFrEF<sup>10-12</sup>. A compensatory increase in adrenergic drive causes desensitization/downregulation of the norepinephrine (NE) transporter (NET or uptake-1 mechanism) on cardiac presynaptic nerve terminal due to excess NE in the synaptic cleft. The downregulation of uptake-1 exposes the heart and postsynaptic adrenergic receptors to greater concentrations of NE, which in turn causes desensitization/downregulation of  $\beta$ -adrenergic receptors, cardiac remodeling, and worsening of HF and prognosis<sup>10</sup>. Importantly, *in vivo* non-invasive assessment of sympathetic innervation with SPECT and PET imaging using

radiolabeled analogs of NE have provided valuable prognostic information in patients with HFrEF beyond currently available biomarkers, such as BNP and LVEF. The most commonly used SPECT tracer to assess cardiac sympathetic innervation is  $^{123}\text{I}$ -metaiodobenzylguanidine (mIBG), while the most commonly used PET tracer is,  $^{11}\text{C}$ -hydroxyephedrine (HED). Both of these tracers are NE radioanalogs, and their uptake primarily represents pre-synaptic nerve function (or density) in the heart.

LV diastolic dysfunction is a characteristic finding in patients with HFpEF, and increasing severity of diastolic dysfunction is related to HF progression and a worse prognosis in these patients<sup>13, 14</sup>. Several lines of evidence suggest that dysregulated SNS activity plays an important role in the pathophysiology of HFpEF, particularly in the development of diastolic dysfunction. Preclinical studies show that mimicking an elevation of SNS activity via isoproterenol administration leads to diastolic dysfunction, accompanied with increased myocardial stiffening, fibrosis and LV hypertrophy<sup>15</sup>. Grassi et al.<sup>16</sup> observed that patients with diastolic dysfunction and hypertension display higher SNS activity (e.g., muscle sympathetic nerve activity [MSNA]) and abnormal baroreflex modulation compared to hypertensive patients without diastolic dysfunction, and both these groups show higher MSNA compared to age-matched controls. In these studies, MSNA was significantly and inversely related to various transthoracic echocardiographic (TTE) indices of diastolic dysfunction (e.g., E/A wave ratio, deceleration time, and isovolumic relaxation time (IVRT)). Other human studies have observed similar findings with respect to the relationship between SNS activity and HFpEF<sup>15</sup>, although many of these studies are limited by the small sample sizes, and not all of these studies report on diastolic parameters. Interestingly, albeit in a limited number of studies, it has been shown that indices of sympathetic presynaptic nerve function derived from planar  $^{123}\text{I}$ -mIBG scintigraphy correlate

with the severity of diastolic dysfunction, exercise capacity, LV remodeling, response to therapy, HF severity, and are able to predict adverse cardiovascular events in patients with HFpEF<sup>17-19</sup>. More specifically the <sup>123</sup>I-mIBG heart-to-mediastinal ratio (H/M) and <sup>123</sup>I-mIBG washout rate have proved to be the most useful indices in these studies. Indeed, the small number of patients, the use of different definitions of HFpEF and/ diastolic dysfunction, and the application of only semi-quantitative analyses of <sup>123</sup>I-mIBG planar scintigraphy have limited the generalizability and strength of these findings.

In this current issue of the Journal of Nuclear Medicine, Aikawa and colleagues<sup>20</sup> performed PET imaging with <sup>11</sup>C-HED in 41 subjects with HFpEF (LVEF  $\geq$  40%) and 12 normal volunteers in an effort to establish the relationship between impaired cardiac SNS innervation and left ventricular diastolic dysfunction in HFpEF patients. As outlined above, although previous studies have already reported similar relationships with <sup>123</sup>I-mIBG planar scintigraphic indices in HFpEF patients<sup>18, 19</sup>, the novelty of this study relates to use of <sup>11</sup>C-HED PET imaging, which allows for improved global and regional quantification of SNS innervation due to better spatiotemporal resolution and more quantitative image analysis compared to conventional <sup>123</sup>I-mIBG planar imaging. In this study, <sup>11</sup>C-HED derived indices of cardiac sympathetic function were related to TTE indices of diastolic dysfunction as established in the 2009 American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE) Recommendations<sup>21</sup>. Global cardiac SNS innervation was expressed using the semi-quantitative, retention index (RI [ $\text{min}^{-1}$ ]), and a 17-segment model was used to calculate RI in different myocardial regions. The heterogeneity of cardiac SNS innervation was determined by the coefficient of variation among the RIs for each of the 17 segments. Aikawa et al. report that <sup>11</sup>C-HED uptake was globally reduced and more heterogeneous in HFpEF patients relative to age-

matched controls, and that patients with more severe diastolic dysfunction (grade 2-3) had a greater reduction in global  $^{11}\text{C}$ -HED uptake with more heterogeneous uptake compared to patients with less severe diastolic dysfunction (grade 0-1). Importantly, since myocardial ischemia and infarction have been shown to independently influence  $^{11}\text{C}$ -HED uptake, the investigators also compared global and heterogeneous uptake of  $^{11}\text{C}$ -HED in patients with a non-ischemic etiology of HF and found that only global RI, but not the variance of RI, was significantly different between grades of diastolic dysfunction amongst the HFpEF patients.

Although this study is novel and clinically relevant, there are several limitations that are worth mentioning. First, and most importantly, these authors define diastolic dysfunction based on the 2009 ASE and European Association of Cardiovascular Imaging (EACVI, formerly EAE) Recommendations, despite the recent publication of new guidelines by these same organizations<sup>22</sup>. As provided in a supplementary data of this manuscript, when the authors' used the most recent guidelines for diastolic function assessment, 70% of patients were reclassified, and global RI became similar among the HFpEF patients despite differences in the severity of diastolic dysfunction. It is possible that the reclassification of patients using the current guidelines lead a non-significant finding between different grades of diastolic dysfunction, since the recently recommended algorithm does not explicitly state on how to classify patients with atrial fibrillation. Consequently, the number of patients included in the analysis was reduced. However, it is worth noting that the new guidelines do provide alternatives for grading LV diastolic dysfunction in special populations, including atrial fibrillation. Notwithstanding the ambiguity in the new algorithm, the classification of diastolic dysfunction in the current manuscript is at odds with the 2009 ASE/ EACVI algorithm. Specifically, it appears that some patients were classified as having diastolic dysfunction despite having normal LA volumes

(Table 2). However, the 2009 ASE/ EACVI guidelines suggest that an enlarged LA volume index ( $\geq 34$  mL/m<sup>2</sup>) is an absolute criterion for diastolic dysfunction, especially for grades 2 and 3 dysfunction. Clearly, future studies exploring the relationship between <sup>11</sup>C-HED uptake and diastolic dysfunction in HFpEF will need to employ current criteria for grading diastolic dysfunction. On the other hand, the relation between dysfunctional SNS innervation to diastolic dysfunction may not be as important as the relationship between global <sup>11</sup>C-HED uptake to cardiovascular prognosis and mortality in these HFpEF patients. Along these lines, decreased global <sup>11</sup>C-HED RI is independently predictive of worse cardiovascular prognosis and all cause-mortality in patients with HFpEF<sup>23,24</sup>. More relevant to the topic at hand, other studies have reported that the <sup>123</sup>I-mIBG H/M ratio and washout rate can discriminate between HF severity and can predict worse prognosis and future cardiac events in HFpEF patients<sup>18,19</sup>.

Although useful for a general assessment of the cardiac pre-synaptic uptake-1 mechanism, <sup>11</sup>C-HED cannot distinguish between denervated myocardium and myocardium with intact neurons but with dysfunctional uptake-1 (dysinnervated myocardium). <sup>11</sup>C-HED uptake may be reduced through various mechanisms including: SNS presynaptic denervation, impairments in the energy required for proper NET function (i.e., ischemia), a down-regulation of NET receptors, and competitive inhibition of <sup>11</sup>C-HED for NET receptor sites by excess synaptic NE<sup>25,26</sup>. The mechanism leading to reduced <sup>11</sup>C-HED uptake may vary along the continuum of HFpEF progression, and may well also vary depending on the etiology of HFpEF (e.g., amyloidosis vs. hypertension). Although SNS presynaptic activity can be assessed semi-quantitatively with <sup>11</sup>C-HED (i.e., <sup>11</sup>C-HED washout), the consecutive use of multiple PET adrenergic tracers with different uptake and storage kinetics may also help to elucidate mechanisms of SNS innervation impairments in HFpEF patients with differing severities and

underlying pathophysiological disease processes. Along these lines, the consecutive use  $^{11}\text{C}$ -HED,  $^{11}\text{C}$ -epinephrine, and  $^{11}\text{C}$ -phenylephrine has provided valuable mechanistic information of sympathetic innervation impairments in post-infarct models and in the pattern of sympathetic neuronal regeneration in cardiac transplantation patients<sup>27, 28</sup>.

The benefit of performing PET imaging compared to SPECT imaging is related to the higher spatiotemporal resolution of PET imaging, and more established methods for kinetic modeling and absolute quantification of radiotracer uptake. Therefore, an important limitation to this study is the use of the semi-quantitative RI. Along these lines, it has been debated that the  $^{11}\text{C}$ -HED RI may not be sensitive enough to detect mild-to-moderate nerve loss<sup>29</sup>. Recently, a fully quantitative kinetic model has been established for  $^{11}\text{C}$ -HED<sup>30</sup>, and confirmed that the quantitative volume of distribution of ( $V_T$ ) is non-linearly related to SUV and RI, especially in the setting of lower radiotracer uptake. Interestingly, this same group has developed methods for absolute quantification of  $^{11}\text{C}$ -HED uptake that require dynamic imaging along with venous blood sampling, and application of a correction for metabolites sampled from venous blood<sup>31</sup>. Deriving  $V_T$  values non-invasively from  $^{11}\text{C}$ -HED PET studies will be beneficial for fully elucidating the relationship between cardiac denervation and different grades of left ventricular diastolic dysfunction in HFpEF patients, particularly if the differences in tracer uptake are subtle. On the other hand, quantitative  $^{123}\text{I}$ -mIBG SPECT imaging may provide an alternative to  $^{11}\text{C}$ -HED PET imaging in HFpEF patients, especially at sites without access to a cyclotron. Our group has recently reported a method for absolute quantitative evaluation of dynamic  $^{123}\text{I}$ -mIBG SPECT images using a high-resolution and high-sensitivity dedicated cardiac cadmium zinc telluride (CZT) imaging system (Discovery NM/CT 570c, GE Healthcare)<sup>32</sup>. This method utilizes a reversible two-tissue compartment model and population-based corrections for blood-

to-plasma ratio and metabolites<sup>32</sup>. Therefore, the quantitative evaluation of the SNS may also be feasible with <sup>123</sup>I-mIBG using appropriate kinetic models and newer high-resolution and high sensitivity dedicated cardiac CZT imaging systems.

In summary, this study was the first to show a relationship between impaired cardiac SNS innervation non-invasively assessed with <sup>11</sup>C-HED PET imaging and the severity of diastolic dysfunction using TTE in HFpEF patients. Despite the methodological limitations, this study provides the foundation for further exploration of the role of the SNS in HFpEF. PET imaging of SNS function with <sup>11</sup>C-HED may provide additional prognostic information over available biomarkers and imaging of cardiac diastolic function with echocardiography. Future studies should utilize methodologies that can provide an absolute quantification of SNS function, and should utilize current guidelines with respect to grading diastolic dysfunction in HFpEF patients. Quantitative <sup>123</sup>I-mIBG SPECT imaging may provide an alternative to <sup>11</sup>C-HED PET imaging in HFpEF patients, given that <sup>123</sup>I-mIBG is a readily available FDA approved pharmaceutical and quantitative analysis of dynamic <sup>123</sup>I-mIBG SPECT imaging is now possible<sup>32</sup>. The application of quantitative <sup>123</sup>I-mIBG SPECT imaging to assess SNS innervation in HF patients may provide an opportunity for centers that do not have access to a costly, onsite cyclotron for production of <sup>11</sup>C-HED to explore the clinically relevant role of cardiac SNS dysinnervation in the prognosis of HFpEF patients.



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