Quantifying radiotracer activity on cardiac sympathetic imaging: Does it really matter?

Ehimen C. Aneni, MD, MPH,^a and Albert J. Sinusas, MD^{a,b,c}

^a Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT

^b Department of Radiology and Biomedical Imaging, Yale University School of Medicine, New Haven, CT

^c Department of Biomedical Engineering, Yale University, New Haven, CT

Received Jun 6, 2021; accepted Jun 7, 2021
doi:10.1007/s12350-021-02738-z

See related article, pp. 413–425

With the development of norepinephrine analog radiotracers such as [¹²³I]- Meta-Iodo-Benzyl-Guanidine (MIBG) and later on [¹¹C] meta-hydroxyephedrine (HED), there has been growth in the experimental and clinical use of cardiac sympathetic imaging. This use is expected to expand further with the recent development of ¹⁸F-labeled radiotracers such as ¹⁸F-Flubrobenguane (FBBG), 4-[¹⁸F]fluoro-metahydroxyphenethylguanidine ([¹⁸F]4F-MHPG) and 3-[¹⁸F]fluoro-para-hydroxyphenethylguanidine ([¹⁸F]3F-PHPG).^{1,2} The utility of cardiac sympathetic imaging is most widely studied in patients who have heart failure with reduced ejection fraction (HFrEF). In this population, the extent of myocardial denervation measured by cardiac sympathetic imaging is strongly associated with adverse cardiovascular events such as cardiac and all-cause mortality, progression of heart failure, and malignant arrhythmias.³ These initial findings spurred further investigation into the utility of cardiac sympathetic imaging in risk stratification of individuals with HFrEF.

In the Prediction of ARrhythmic Events with Positron Emission Tomography (PAREPET) study, a longitudinal study of 204 individuals with ischemic cardiomyopathy (left ventricular ejection fraction

≤ 35%) who received cardiac positron emission tomography (PET) sympathetic imaging with HED, the extent of myocardial denervation was predictive of sudden cardiac arrest (SCA) over a follow-up period of approximately 4 years.⁴ In the PAREPET study, as is standard with other clinical cardiac imaging studies and clinical practice, semi-quantitative measures of myocardial sympathetic denervation such as tracer uptake and retention index were used to estimate the extent of myocardial denervation. In the present sub-study of PAREPET,⁵ the authors raise some important study questions about the methodology used in the tracer analysis. First, they note that HED has been dubbed a “flow-limited tracer”⁶ since myocardial perfusion is required to transport the radiotracer to the cardiac neuronal cells. Consequently, HED has been postulated to have greater dependence on flow than neuronal uptake and there has been suggestion that HED activity is a surrogate for myocardial blood flow. Thus, it is unclear if the risk stratification ability of HED is independent of myocardial blood flow or if myocardial blood flow also predicts SCA. Second, semi-quantitative methods of assessing cardiac sympathetic denervation such as tracer uptake and the retention index are prone to inaccuracies from partial volume effects, motion artifacts, and intravascular activity of the tracer. Thus, it is unknown if parametric tracer analysis would show more extensive myocardial denervation and improve SCA risk stratification with HED.

In this important follow-up study,⁵ the authors re-analyzed data from 174 participants of the PAREPET study who had both ¹³N-ammonia (NH₃) resting myocardial perfusion and HED cardiac sympathetic PET scans, after excluding those studies that were of poor quality. The parametric measure analyzed was volume of distribution which represents the ratio of the tracer

Reprint requests: Albert J. Sinusas, MD, Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, PO Box 208017 Dana 3, New Haven, CT 06520-8017; albert.sinusas@yale.edu

J Nucl Cardiol 2022;29:426–9.
1071-3581/\$34.00

Copyright © 2021 American Society of Nuclear Cardiology.

concentration in the myocardium to that in the arterial plasma at equilibrium. This was corrected for blood metabolites and partial volume effects. In addition, resting myocardial blood flow using NH_3 was estimated. All parametric calculations were done using a one-tissue compartment model. For both uptake and parametric measures, perfusion defect and denervation percentages were estimated, and a perfusion-denervation mismatch score was derived.

The authors show more extensive sympathetic denervation using the parametric analysis compared to the tracer uptake analysis. However, parametric analysis did not perform better than the tracer uptake measures in predicting SCA. The study also showed that the extent of denervation remained the best predictor of SCA while resting myocardial blood flow did not predict SCA. At every tertile of myocardial perfusion uptake defect, there was significantly larger areas of sympathetic denervation compared to perfusion defects, but this difference was greatest in the lowest tertile of myocardial uptake perfusion defect. Expectedly, innervation–perfusion mismatch was a strong predictor of SCA. However, it did not significantly outperform HED uptake in SCA prediction.⁵ These findings are important for several reasons. First, they show that even though the extent of denervation may have been underestimated by the uptake measures, the more robust parametric analysis did not improve SCA risk prediction. Parametric analysis is tedious, requiring technical expertise and longer PET scanning times which may not be feasible in many centers. In addition, it requires images to be of high quality which is not always possible as shown in this study where 14 scans were excluded due to poor quality.⁵ The finding of greater denervation compared to perfusion defects, particularly in the lowest tertile of abnormal myocardial perfusion supports the theory that cardiac neurons have greater sensitivity to ischemia relative to the cardiomyocytes. Notably, parametric analysis also showed greater innervation–perfusion mismatch scores than the uptake values. Yet, the extent of innervation–perfusion mismatch did not significantly improve SCA risk stratification over HED uptake. Taken together, the results show that a relatively simple uptake measure of myocardial denervation performed similarly to more complex parametric assessment in the risk stratification of SCA in this patient population.

While evaluation of flow/denervation mismatch may not improve prediction of SCA in this patient population, the evaluation of the mismatch zone might have important clinical implications for guiding ablations in the treatment of ventricular tachycardia (VT), which generally focuses on ablation of the infarct border zone that can be defined by this mismatch.⁷ Based on

these data, it appears that parametric mismatch might offer some advantage, although this seems to be underplayed. Ablation of local abnormal ventricular activations from areas of residual viability within the scar is believed to increase procedural success, but catheter mapping to identify of these sites during the ablation procedure is tedious and time consuming.⁸ The use of non-invasive external beam radiation ablation of VT is a highly promising approach that is wholly dependent on accurate non-invasive imaging of the ventricular substrate.⁹ Thus, the ability to accurately and efficiently identify the scar border zone and viable myocardium is critical for the success of VT ablation, and therefore, image integration to guide VT ablation may be useful.^{10,11}

Preclinical studies demonstrated that pigs with inducible VT following MI had larger area of innervation/perfusion mismatch in the infarct border zone compared to pigs that were not inducible.¹² Interestingly, there were no differences in denervation area measured with PET HED between inducible and non-inducible pigs.¹² Electrophysiological studies by the same group also showed that the innervation/perfusion mismatch ratio was strongly associated with reduced myocardial voltage and the site of earliest VT activation in pigs following an MI.¹³ In patients with VT, intracavity electrical abnormalities frequently originate at the site of viable but denervated regions and represent ultimate ablation targets.¹⁴ In a clinical study, quantitative uptake of a sympathetic-targeted radiotracer in the infarct border zone predicted VT inducibility on EP testing with promising accuracy.¹⁵

The authors note several limitations of their study including the small sample size and the limited number of clinical outcomes (27 compared to 34 in the original study) which may have been responsible for the absence of a significant improvement in the AUC scores.⁵ Beyond these limitations, the broader utility of HED cardiac PET imaging remains in question considering the short half-life of the radiotracer (~ 20 minutes) which makes the presence of an onsite cyclotron necessary. In the follow-up to the PAREPET study, the PAREPET II study addresses this major limitation by using a different radiotracer (N-[3-bromo-4-(3- ^{18}F -fluoro-propoxy)-benzyl]-guanidine (^{18}F -Flubrobenguane, FBBG, formerly F-LMI1195)).¹⁶ This radiotracer is a benzylguanidine analog (similar to MIBG) that is labeled with ^{18}F having a longer half-life (~ 110 minutes) compared to ^{11}C . Use of neuronal imaging agents with longer half-lives such as FBBG may circumvent the need for an onsite cyclotron which in turn may make cardiac PET neuronal imaging less expensive and more widely utilized.

A one-tissue compartment model was used for all the parametric analysis in this sub-study. In a study comparing parametric analysis to standard uptake values and retention index of HED conducted in 30 individuals, Harms and colleagues showed that a two-tissue compartment model was preferred in most of the myocardial segments although the one-tissue compartment model performed very well at clinically relevant noise levels.¹⁷ As such, one wonders if a two-tissue compartment model would have been feasible in the PAREPET population and if it would have outperformed the uptake measures in predicting SCA.

The authors do a great job of discussing the utility of cardiac sympathetic imaging in other clinical scenarios. For instance, regional abnormalities in MIBG cardiac sympathetic imaging were frequently seen in persons with arrhythmogenic right ventricular cardiomyopathy (ARVC) and predicts recurrence of ventricular tachyarrhythmias in that population.¹⁸ More recently, Stirrup and colleagues published promising data suggesting that cardiac sympathetic imaging with MIBG correctly identified ganglionated plexi in most individuals who had invasive identification of these plexi during an ablation procedure.¹⁹ Perhaps of larger population health significance will be the utility of cardiac sympathetic imaging in risk-stratifying persons with sleep-disordered breathing (SDB). SDB is highly prevalent, affecting up to 30 million US adults and is associated with more than 160 billion USD in healthcare expenditure.²⁰ SDB, particularly obstructive sleep apnea (OSA) which is the more common variety, is associated with a hyperadrenergic state, increased oxidative stress, and inflammation all of which are substrate for microvascular dysfunction, heart failure, and cardiac arrhythmias. Current guidelines suggest that those with SDB who benefit from CPAP management are persons with known cardiovascular disease, severe SDB, and those with symptoms. However, a large number of patients fall into a gray zone in which their SDB is considered moderate, do not have known cardiovascular disease and are asymptomatic. In this population, cardiac sympathetic imaging may be useful in risk stratifying these patients by identifying those who are at higher risk of cardiovascular events. Cardiac arrhythmias are common in persons with SDB. As such, cardiac sympathetic imaging may be useful in the pre-operative planning of those undergoing arrhythmia ablation and it might be a useful tool to predict arrhythmia recurrence in this population.

In conclusion, parametric analysis of HED cardiac PET imaging does not appear to significantly improve SCA risk stratification in this relatively small sample of individuals with HFrEF. These results bring some reassurance that the conventional method of tracer

uptake analysis is adequate for SCA risk stratification. This is an important step in garnering wider acceptability of cardiac PET neuronal imaging in SCA risk stratification. Yet more work needs to be done in this area to determine if these results hold true with a larger more diverse population and with other neuronal imaging tracers such as FBBG. Furthermore, as the utility of cardiac sympathetic imaging expands beyond HFrEF, there will be need to determine the optimal method or combination of methods for risk stratification in these individuals.

References

1. Raffel DM, Jung Y-W, Koeppe RA, Jang KS, Gu G, Scott PJH, et al. First-in-human studies of [¹⁸F]fluorohydroxyphenethylguanidines: PET radiotracers for quantifying regional cardiac sympathetic nerve density. *Circ Cardiovasc Imaging*. 2018;11:e007965
2. Sinusas AJ, Lazewatsky J, Brunetti J, Heller G, Srivastava A, Liu Y-H, et al. Biodistribution and RADIATION DOSIMETRY of LMI1195: First-in-human study of a novel 18F-labeled tracer for imaging myocardial innervation. *J Nucl Med* 2014;55:1445-51.
3. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure: Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. *J Am Coll Cardiol* 2010;55:2212-21.
4. Fallavollita JA, Heavey BM, Luisi AJ, Michalek SM, Baldwa S, Mashtare TL, et al. Regional myocardial sympathetic denervation predicts the risk of sudden cardiac arrest in ischemic cardiomyopathy. *J Am Coll Cardiol* 2014;63:141-9.
5. Wang J, Kaps N, Lavalley A, et al. Does quantification of [¹¹C]meta-hydroxyephedrine and [¹³N]ammonia kinetics improve risk stratification in ischemic cardiomyopathy. *J Nucl Cardiol* 1992;13:1-20.
6. Raffel DM, Koeppe RA, Jung Y-W, Gu G, Jang KS, Sherman PS, et al. Quantification of cardiac sympathetic nerve density with N-¹¹C-guanyl-meta-octopamine and tracer Kinetic analysis. *J Nucl Med Off Publ Soc Nucl Med*. 2013;54:1645-52.
7. Zhou S, Sapp JL, Horáček BM, Warren JW, MacInnis PJ, Davis J, et al. Automated intraprocedural localization of origin of ventricular activation using patient-specific computed tomographic imaging. *Heart Rhythm* 2020;17:567-75.
8. Sacher F, Lim HS, Derval N, Denis A, Berte B, Yamashita S, et al. Substrate mapping and ablation for ventricular tachycardia: The LAVA approach. *J Cardiovasc Electrophysiol* 2015;26:464-71.
9. Cuculich PS, Schill MR, Kashani R, Mutic S, Lang A, Cooper D, et al. Noninvasive cardiac radiation for ablation of ventricular tachycardia. *N Engl J Med* 2017;377:2325-36.
10. Dickfeld T, Kocher C. The role of integrated PET-CT scar maps for guiding ventricular tachycardia ablations. *Curr Cardiol Rep* 2008;10:149-57.
11. Dickfeld T, Lei P, Dilsizian V, Jeudy J, Dong J, Voudouris A, et al. Integration of three-dimensional scar maps for ventricular tachycardia ablation with positron emission tomography-computed tomography. *JACC Cardiovasc Imaging* 2008;1:73-82.
12. Lautamaki R, Sasano T, Higuchi T, Nekolla SG, Lardo AC, Holt DP, et al. Multiparametric molecular imaging provides mechanistic insights into sympathetic innervation impairment in the

- viable infarct border zone. *J Nucl Med Off Publ Soc Nucl Med* 2015;56:457-63.
13. Sasano T, Abraham MR, Chang K-C, Ashikaga H, Mills KJ, Holt DP, et al. Abnormal sympathetic innervation of viable myocardium and the substrate of ventricular tachycardia after myocardial infarction. *J Am Coll Cardiol* 2008;51:2266-75.
14. Gimelli A, Menichetti F, Soldati E, Liga R, Vannozzi A, Marzullo P, et al. Relationships between cardiac innervation/perfusion imbalance and ventricular arrhythmias: Impact on invasive electrophysiological parameters and ablation procedures. *Eur J Nucl Med Mol Imaging* 2016;43:2383-91.
15. Zhou Y, Zhou W, Folks RD, Manatunga DN, Jacobson AF, Bax JJ, et al. I-123 mIBG and Tc-99 m myocardial SPECT imaging to predict inducibility of ventricular arrhythmia on electrophysiology testing: A retrospective analysis. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol* 2014;21:913-20.
16. Canty J. Prediction of Arrhythmic Events With Positron Emission Tomography II [Internet]. *clinicaltrials.gov*; 2021. Report No.: NCT03493516. Available from: <https://clinicaltrials.gov/ct2/show/NCT03493516>. Accessed 20 May 2021.
17. Harms HJ, de Haan S, Knaapen P, Allaart CP, Rijnierse MT, Schuit RC, et al. Quantification of [11C]-meta-hydroxyephedrine uptake in human myocardium. *EJNMMI Res*. 2014;4:52.
18. Paul M, Wichter T, Kies P, Gerss J, Wollmann C, Rahbar K, et al. Cardiac sympathetic dysfunction in genotyped patients with arrhythmogenic right ventricular cardiomyopathy and risk of recurrent ventricular tachyarrhythmias. *J Nucl Med Off Publ Soc Nucl Med* 2011;52:1559-65.
19. Stirrup J, Gregg S, Baavour R, Roth N, Breault C, Agostini D, et al. Hybrid solid-state SPECT, CT left atrial innervation imaging for identification of left atrial ganglionated plexi: Technique and validation in patients with atrial fibrillation. *J Nucl Cardiol*. 2019. <https://doi.org/10.1007/s12350-018-01535-5>.
20. Frost & Sullivan. Hidden Health Crisis Costing America Billions [Internet]. American Academy of Sleep Medicine; 2016. Available from: <https://j2vjt3dnbra3ps7ll1clb4q2-wpengine.netdna-ssl.com/wp-content/uploads/2017/10/sleep-apnea-economic-crisis.pdf>. Accessed 30 Sep 2020.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.