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Reproducible Quantification of Regional Sympathetic Denervation with [¹¹C]meta-Hydroxyephedrine PET Imaging

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Abstract

Background: Regional cardiac sympathetic denervation is predictive of sudden cardiac arrest in patients with ischemic cardiomyopathy. The reproducibility of denervation scores between automated software programs has not been evaluated. This study seeks to: 1) compare the inter-rater reliability of regional denervation measurements using two analysis programs: FlowQuant® and Corridor4DM®; 2) evaluate test-retest repeatability of regional denervation scores.

Methods: N=190 dynamic [¹¹C]meta-hydroxyephedrine (HED) PET scans were reviewed from the PAREPET trial in ischemic cardiomyopathy patients with reduced left ventricular ejection fraction (LVEF <35%). N=12 scans were excluded due to non-diagnostic quality. N=178 scans were analyzed using FlowQuant and Corridor4DM software, each by two observers. Test-retest scans from n=20 patients with stable heart failure were utilized for test-retest analysis. Denervation scores were defined as extent×severity of relative uptake defects in LV regions with <75% of maximal uptake. Results were evaluated using intraclass correlation coefficient (ICC) and Bland-Altman coefficient of repeatability (RPC).

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Results: Inter-observer, inter-software, and test-retest ICC values were excellent (ICC=94–99%) and measurement variability was small (RPC<11%). Mean differences between observers ranged 0.2% to 1.1% for Corridor4DM (p=0.28), FlowQuant (p<0.001), and between software programs (p<0.001). Kaplan-Meier analysis demonstrated HED scores from both programs were predictive of SCA.

Conclusion: Inter-rater reliability for both analysis programs was excellent and test-retest repeatability was consistent. The minimal difference in scores between FlowQuant and Corridor4DM supports their use in future trials.

Background

Imaging of the cardiac sympathetic nervous system is of growing interest, with applications to cardiac transplantation, heart failure, ischemic heart disease, and cardiomyopathies. [1, 2] While there have been many tracers developed for sympathetic imaging, C-11-metahydroxyephedrine ($[^{11}\text{C}]\text{mHED}$ or HED) is the most widely used PET tracer in humans. HED is a norepinephrine analog that is transported into the presynaptic nerve terminal through the norepinephrine reuptake transporter-1 (NET-1). [1, 3, 4] Its high specificity for NET-1 and minimal degradation by monoamine oxidase render it an excellent PET tracer to non-invasively assess sympathetic nerve density and function. [3]

Regional sympathetic denervation, measured using HED PET in the Prediction of Arrhythmic Events with Positron Emission Tomography (PAREPET) trial, has been shown to be predictive of sudden cardiac arrest (SCA) in patients with ischemic cardiomyopathy. [5, 6] Clinically, LVEF is the only parameter used routinely to identify patients at high risk for SCA. This recent research identifies the severity of SNS denervation as a novel risk factor. HED may have utility in the non-invasive selection of patients at highest risk of SCA and those most likely to benefit from ICD implantation, thus enabling more precise targeted patient selection. In the PAREPET trial, tracer uptake was assessed using a quantitative regional denervation score reflecting the combined extent and severity of defects, expressed as a percentage of the left ventricle (LV). [6] The use of this score was based on previous knowledge that the area of denervation is either equivalent or larger than the ischemic zone. [7–9] It is thought that these myocardial blood flow (MBF)-vs-denervation mismatch zones are uniquely susceptible to developing ventricular arrhythmias. [10, 11]

Many graphical and tracer kinetic methods have been employed to quantify HED uptake over time. Retention index (RI) and volume of distribution (V_T) are two commonly reported variables, and have been validated in both preclinical animal models and in human studies. [12–15] Our group recently demonstrated that regional HED uptake defect size is a reliable measure of sympathetic denervation, producing more consistent results than global LV mean retention index. [15] The HED denervation score was selected as the measure to investigate in this study, as it was found in the PAREPET trial to be the single best cardiac imaging predictor of sudden cardiac arrest. Despite the demonstrated prognostic value of the regional sympathetic denervation score in ICD patients [6] the reliability of this measure has not yet been characterized across different software implementations. There is known variation between software analysis programs, such as different ejection fraction and ventricular

volume results in gated MPI analysis.[16] The HED denervation scores in PAREPET (NCT01400334) were generated using FlowQuant which is a research software program not amenable for widespread clinical use. In order to support the broader applicability for PET imaging of sympathetic innervation, the goal of this study was to determine whether accurate denervation scoring could be implemented using a commercial software platform, producing consistent results for use in current and future trials and eventually in clinical practice. This analysis serves as a bridging study to support the analysis of subsequent clinical trials such as PAREPET II (NCT03493516) which is ongoing and will utilize Corridor4DM for the core laboratory image analysis of denervation scores to evaluate the primary outcome.

Specifically, the purpose of this study was to compare quantitative sympathetic denervation scores measured using two automated analysis software programs: FlowQuant and Corridor4DM. The aim was to characterize the test-retest repeatability and inter-rater variability for both methods, as well as the variability between programs in patients with ischemic cardiomyopathy enrolled previously in the PAREPET trial.

Methods

Patient Population

The present study is a retrospective analysis of the PAREPET trial dynamic HED PET imaging data (NCT01400334).[6, 17] PAREPET was a prospective observational trial of 204 patients with ischemic cardiomyopathy (LVEF $\geq$ 35%) aimed at determining whether sympathetic imaging with HED to quantify inhomogeneity in myocardial SNS innervation predicts SCA. Patients with previously resuscitated SCA, sustained ventricular tachycardia, implantable cardioverter-defibrillator discharge, unexplained syncope, recent myocardial infarction in the last 30 days, percutaneous coronary intervention in the last 3 months, coronary bypass surgery in the last year, and comorbidities leading to a reduced life expectancy of < 2 years were excluded. The University of Buffalo Institutional Review Board approved the original study protocol. Selection of patients for the current study is illustrated in Figure 1. Of the 204 patients enrolled originally, 190 had HED PET scans performed; 12 of these were excluded for technical reasons leaving 178 scans of suitable quality for the present analysis.

To analyze the test-retest repeatability of the denervation scoring method, a secondary analysis was performed using data from a previous study which enrolled a control group of patients with stable heart failure (NYHA class II) and reduced left ventricular ejection fraction (LVEF $< 40\%$).[18] That study evaluated the impact of continuous positive airway pressure (CPAP) on cardiac energetics in patients with heart failure and obstructive sleep apnea (OSA). The control patients had the same inclusion and exclusion criteria as in the main study but did not have OSA. All subjects provided written informed consent to participate in the study, as approved by the institutional Human Research Ethics Board.

PET Imaging

[¹¹C]mHED was produced through methylation of metaraminol free base in dimethylformamide with [¹¹C]methyl-iodide, which was subsequently heated and purified using semi-preparative HPLC.[19] All study participants underwent dynamic cardiac PET imaging to quantify sympathetic innervation using HED with the ECAT EXACT HR+ (CTI, Knoxville, TN) PET scanner (15.5 cm axial field of view; 5 mm isotropic spatial resolution). 740 MBq (20 mCi) of HED was administered as a bolus intravenous injection, and dynamic imaging was performed in 2D-mode for 60 minutes (6 × 30 sec, 2 × 60 sec, 2 × 150 sec, 2 × 300 sec, 2 × 600 sec, 1 × 1200 sec frames). Decay-corrected PET images of ¹¹C-activity concentration were reconstructed using filtered back-projection and 12 mm Gaussian post-filtering, resulting in a final reconstructed PET image resolution of 13 mm full-width-at-half-maximum.

Regional Denervation Scores

The regional sympathetic denervation score used in the PAREPET trial is a continuous variable expressed as the extent × severity of relative uptake defects as a percent of the left ventricle. The same analysis method was implemented in Corridor4DM as reported using FlowQuant originally to quantify the percent LV denervation as follows. Steady-state tracer activity was measured in the LV following clearance of the blood activity, by averaging the dynamic HED images starting at 20 minutes post-injection. The images were rotated automatically into the short axis reference frame, and the transmural average activity was sampled automatically in polar-map sectors (496 sectors for FlowQuant and 460 for Corridor4DM) extending from the LV apex to the base of the membranous septum, as shown in Figure 2A,B. The polar-map values were normalized to peak HED uptake, and sectors 75% of the maximum value were defined as normal and set equal to 100% (see Figure 3). The innervation defect (denervation) score was then calculated as 100% minus the average polar-map value, expressed as %LV and illustrated in Figure 2E,F. A threshold of 75% was chosen based upon the methodology of the original PAREPET trial. This threshold is also consistent with PET myocardial perfusion imaging methodologies as reported previously. [20, 21]

To evaluate the interobserver repeatability of regional denervation score measurements within and between programs, scans from the PAREPET trial (n=178) were analyzed using FlowQuant® version 2.5 (University of Ottawa, Heart Institute, Ottawa, ON) and a customized version of Corridor4DM (v2018.0.0.98) (INVIA Medical Imaging Solutions, Ann Arbor, MI), each by two observers (JW, NK or DB). The observers were blinded to patients' clinical data and other operator results.

For test-retest repeatability, test and retest scans from the OSA trial (n=20) were analyzed independently by two observers (NK and KW) using the FlowQuant program. The results were compared for test vs retest scans using the same and different observer.

Statistical Analysis

Inter-observer reproducibility and inter-software variability was assessed by comparing observer 1 and 2 for FlowQuant, observer 2 and 3 for Corridor4DM, and observer 2a

and 2b values for FlowQuant vs Corridor4DM. Test-retest variability was assessed by comparing test and retest scores from the same observer or from different observers. The results were evaluated using absolute-agreement intraclass correlation coefficients (ICC) with two-way mixed effects models.[22] The cutoffs for ICC assessment were as follows: ICC >90% was excellent; ICC 75% to 90% was good; ICC 50 to 75% was moderate; and ICC <50% was poor.[22] Furthermore, Bland-Altman plots were used to assess the limits of agreement of repeated measures using the mean $\pm$ coefficient-of-repeatability (RPC= $1.96 \times \text{SD}$).[19] The confidence intervals on the limits of agreement were calculated as $3/n \times \text{SD} \times (t_{95\%, N-1})$. [23] The variance between the inter-observer and inter-software paired differences were evaluated using Pitman-Morgan tests.[24] A two-tailed $p < 0.05$ was considered statistically significant for all tests. To assess whether the prognostic analysis methods from the PAREPET trial still demonstrated findings consistent with the original trial, Kaplan Meier analysis was performed using the original PAREPET trial scores, as well as the reprocessed FlowQuant and Corridor4DM scores. All analyses and graphical representations were performed using Excel 2016 (Microsoft) or SPSS 23.0 (IBM).

Results

Patient Demographics

The patient baseline demographics are listed in Table 1. The average age of the population was 68 ± 12 years and predominantly male (89%) with a BMI of 28 ± 5 . The majority of study participants were on medications including beta-blockers (96%) and/or angiotensin inhibition therapy (89%). Most participants were experiencing NYHA Class II symptoms (51%) and their average LV ejection fraction was $28 \pm 9\%$.

Regional Denervation Scores

Representative HED images and polar maps from FlowQuant and Corridor4DM from a patient with ischemic cardiomyopathy appear in Figure 2. Both software programs demonstrated similar regional patterns of tracer uptake and quantitative denervation scores.

Inter-Software and Inter-Observer Reliability

The average regional denervation score was $30.0 \pm 11.4\%$ for FlowQuant and $29.5 \pm 11.2\%$ for Corridor4DM. ICC was excellent (98–99%) for all three comparisons of the denervation scores, as shown in Table 2. Correlation and Bland Altman plots for all three comparisons are shown in Figure 4. Regional denervation scores measured between observers were not significantly different for Corridor4DM (mean bias = $0.2 \pm 4.6\%$, $p = 0.283$). There was a small bias between observers for the FlowQuant scores (mean bias = $1.1 \pm 5.9\%$, $p < 0.001$) and between the Corridor4DM vs FlowQuant values (mean bias = $-0.5 \pm 6.3\%$; $p = 0.043$). Variability of the inter-operator differences was significantly smaller using Corridor4DM vs FlowQuant ($\text{SD} = 2.3\%$ vs 3.0% ; $p = 0.002$). There were only 3 patients with differences > 10% in the denervation scores, all of whom had large apical defects in HED uptake, making it more difficult to estimate the true apex-to-base dimension of the LV.

Test-Retest Repeatability

Test-retest comparisons (n=20) showed excellent agreement between reviewers and between test vs retest scores (ICC=94–99%; see Table 3). Correlation and Bland Altman plots are shown in Figure 5. Test-retest variability was small using the same observer (mean bias = $-0.9 \pm 10.3\%$; $p=0.31$) and different observers (mean bias = $-0.6 \pm 11.0\%$; $p=0.34$). The variability between test and retest scores was greater than the inter-rater variability ($p<0.001$).

Prognostic Analysis

To assess whether the conclusions from the original PAREPET trial remain consistent across the different software implementations, Kaplan Meier analysis was performed with three sets of data (n=178): i. the original PAREPET trial scores, ii. FlowQuant re-analysis scores, and iii. 4DM re-analysis scores (Figure 6). All three sets of data show similar trends when stratifying risk of SCA by tertiles of denervation score (Figure 6a). Using the cut-off established in the original PAREPET trial, stratification of patients based on scores $> 37.6\%$ of LV was predictive of SCA using defect scores from the PAREPET trial, FlowQuant, and 4DM (Figure 6b). The defect scores were incorporated into the SCA Risk Factor Model similar to the original trial consisting of the following risk factors: i. HED defect score $> 37.6\%$ of LV; ii. larger LV end-diastolic volume index $> 99 \text{ ml/m}^2$, iii. elevated creatinine $> 1.49 \text{ mg/dl}$, and iv. no angiotensin inhibition therapy. The presence of 0, 1, or 2+ risk factors significantly predicted risk of SCA using all three sets of data (Figure 6c).

Discussion

This is the first study to compare regional HED sympathetic denervation measurements between two automated analysis programs. The FlowQuant program was used in the primary analysis of the PAREPET study, but is not a commercial product and may not permit widespread dissemination of the denervation scoring method. A key finding of this study was the commercial implementation in the Corridor4DM software showed consistent measurements of regional sympathetic denervation compared to the original FlowQuant program. These results suggest that automated analysis methods for quantification of regional sympathetic denervation can be implemented in a variety of contexts and applied using different software programs in clinical practice. It remains to be determined whether sympathetic imaging with HED PET can effectively guide treatment decisions regarding ICD implantation, and whether this translates to improved patient outcomes. Clinical research trials aimed at answering these questions are in progress, e.g. PAREPET II seeks to determine whether the risk factors identified in the original PAREPET trial can inform a clinically applicable approach to assessing candidacy for ICD implantation. In this context, the present study findings support the broad applicability and reproducibility of the regional denervation scoring approach for future multi-center clinical trials and eventually in clinical practice. This is particularly relevant given the ongoing development and evaluation of [^{18}F]flubrobenguane (LMI-1195), another sympathetic imaging tracer which will be utilized by the PAREPET II trial currently in progress. PAREPET II will utilize Corridor4DM for the core laboratory analysis, and the present study serves as a bridge towards implementation in this trial and in broader clinical contexts.

Observer Reproducibility for Corridor4DM and FlowQuant

The inter-rater agreement for both Corridor4DM and FlowQuant (ICC>98%) programs was very high, and the coefficients-of-repeatability were quite small (RPC = 4.6 and 6.0%), suggesting a high reproducibility between observers. While the difference in denervation scores measured using Flowquant vs Corridor4DM were statistically significant, the mean difference was only 0.5% which is not likely to be clinically important over the total range of measured scores from 0 to 60% in this patient population. There was also a small (~1%) but statistically significant difference between reviewers for the FlowQuant software. Kaplan-Meier analysis using the methods from the original PAREPET trial demonstrated conclusions similar to the original trial when using FlowQuant or Corridor4DM HED scores, suggesting that these analysis programs can be used reliably and interchangeably.

The differences between analysis programs are likely due to variations in placement of the basal slice for polar map sampling and patient specific factors such as the presence of apical defects. The largest differences in scores were found in patients with large apical defects, due to the difficulty in defining ventricular contours when tracer uptake is virtually absent in a large segment of the LV apex. A foreshortened apex can amplify the apparent size of the defect depending on where the corresponding ventricular contours are defined. Furthermore, definition of the basal slice between Corridor4DM and FlowQuant likely contributes a small difference, as FlowQuant appears to be slightly more strict in removing all the membranous septum, shortening the apex-to-base distance, and subsequently magnifying the size of any defects on the polar map. In this study, we attempted to minimize these variations by choosing the 'septal wall' setting in Corridor4DM as the landmark to define the valve-plane position for sampling of the polar-map.

Both software programs required little-to-no user interaction overall, lending to the very similar results between observers. Furthermore, the analysis can be conducted by relatively novice observers as the software is highly automated and did not require a high degree of training or supervision. All three reviewers in this study were novice observers with no prior experience in cardiac image analysis. The Corridor4DM software showed a slightly smaller inter-observer variability compared to the FlowQuant software, possibly because the Corridor4DM automated analysis interface often required slightly less user interaction than FlowQuant to complete the image analysis.

Test-Retest Repeatability

Test and retest scans were analyzed in a cohort of n=20 patients with similar demographics to the PAREPET trial. Test-retest repeatability was good (RPC=10–11%) but variations were higher than those of observer and inter-software reproducibility (RPC<6%). However, the difference is overall small compared to other HED measures reported in the literature. For instance, Wu et al (2019) examined test-retest in the same cohort of patients and found that the coefficient of repeatability for HED retention index was 12%, and for distribution volume was 19%. [15] The test-retest scans were obtained 6–8 weeks apart, potentially leading to some physiological variability. However, the high degree of agreement between test-retest scans as well as the stability of heart failure symptoms of study patients between study visits suggests this variability was minimal.

Comparison to the Current Literature

The PAREPET trial utilized a regional denervation score measured with FlowQuant as the prognostic measure for sudden cardiac arrest, defining abnormal regional sympathetic uptake as <75% of the maximal LV uptake. This paper did not assess intra-observer variability as previous studies have demonstrated that the largest sources of variation during PET imaging are typically inter-observer and test-retest differences. This study focused on the regional denervation score as demonstrated previously to be the single best predictor of sudden cardiac arrest in patients with ischemic cardiomyopathy. Previously in the literature, the non-parametric coefficient of repeatability for sympathetic regional denervation measurement was reported to be 12% for FlowQuant.[15] The population for this study was n=23 patients with stable heart failure (NYHA class II) and LVEF < 40%. In the literature, other parameters have been assessed using HED PET such as the global LV mean retention index and volumes of distribution.[15, 25] These have been shown to be more susceptible to variation than the regional denervation scores, using either the retention index model or the distribution volume model.[15] These studies have concluded that the largest sources of variation were factors related to test-retest variability, rather than variability between observers.[15]

The nuclear medicine tracer [¹²³I]meta-iodobenzylguanidine (mIBG) has been used for planar imaging of sympathetic innervation, and is predictive of cardiac events and mortality in individuals with stable class II-III heart failure with LVEF ≥ 35%.[26, 27] SPECT imaging of ¹²³I-labeled mIBG with conventional cameras and collimators is susceptible to poor contrast from very high septal penetration. As such, mIBG uptake is generally assessed using the heart-to-mediastinum ratio assessed on planar images acquired in the anterior-posterior direction. Bateman et al reported the test-retest limits-of-agreement of the mIBG heart-to-mediastinum ratio in this patient population to be ±13% and concluded that it was a reliable parameter for the measurement of sympathetic function.[28] Okuda et al also developed an automated analysis method for calculating mIBG heart-to-mediastinum ratios and reported ±10% limits of agreement.[29]

Conventional planar imaging has much lower spatial and contrast resolution compared to PET imaging, enabling HED to be more suitable for 3D tomographic imaging and quantification of regional defect sizes compared to mIBG.[3] The present study using HED PET demonstrated smaller limits-of-agreement in the range of 4 to 6% between operators and between analysis programs. To our knowledge, there have not yet been any studies comparing software programs for the automated measurement of mIBG heart-to-mediastinum ratios.

Limitations

There were N=12 (6.3% of 190) HED studies excluded from the present study due to severe image artifact (9), patient body motion (2) or low count-statistics (1) which rendered them non-diagnostic. The most common image artifact was incomplete measurement of the LV heart volume due to truncation of the inferior wall, resulting from incorrect patient positioning. This is a limitation of older PET scanners without x-ray CT available to guide patient positioning in this population with large dilated ventricles secondary to their

severe ischemic cardiomyopathy. Larger axial field-of-view PET scanners are currently available with CT for attenuation correction and accurate patient positioning, which should remove this limitation in clinical practice. These systems also have much higher count-rate sensitivity, therefore substantially shorter scan-times may be feasible which would also decrease the likelihood of non-diagnostic scans due to patient body motion.

The regional denervation score was selected as our primary outcome because of its biological and mechanistic relevance; PAREPET recently used this score and demonstrated the degree of denervation was associated with SCA, and PAREPET II (NCT03493516), which is currently enrolling patients, will also use this same measure of SNS denervation. Other quantitative metrics of sympathetic innervation, RI, standard uptake value and distribution volume, have been reported in the literature but remain experimental. The inter-software reliability of these measures is currently unknown, but remains an important avenue of future research. This study focused on implementation of the denervation score analysis technique in Corridor4DM and FlowQuant, which both define the basal slice of the LV perpendicular to the long-axis. Other analysis programs may utilize slanted or hybrid biplane approaches for the basal slice definition, and should be validated separately in future studies.

New Knowledge Gained

Prior to the PAREPET trial, the only imaging parameter used clinically to assess whether a patient may be at higher risk of sudden cardiac arrest was LVEF 35%. As the regional denervation score is predictive of SCA, it may also be useful in the future to help risk stratify patients. This study supports the use of a regional denervation score as a highly reliable measure with consistent results obtained across different software implementations. In a secondary analysis of the PAREPET study, the competing risks analysis revealed a 94% increase in SCD with a 10% increase in the regional denervation score.[5] With an inter-software RPC of 6%, this suggests that quantification of regional HED denervation is accurate enough to detect a clinically meaningful change of this magnitude.

Conclusion

Quantification of regional sympathetic denervation was highly consistent using two automated analysis software programs. This demonstrates that HED quantification with regional denervation scores is reproducible across various software implementations, supporting its potential use in future clinical trials or as part of clinical practice to predict the risk of sudden cardiac arrest in patients with ischemic cardiomyopathy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

CCS	Canadian Cardiovascular Society
DV	Volume of distribution
HED or [¹¹C]mHED	C-11-meta-hydroxyephedrine
ICD	Implantable cardioverter-defibrillator
NET-1	Norepinephrine reuptake transporter-1
NYHA	New York Heart Association
LVEF	Left ventricular ejection fraction
PAREPET	Prediction of Arrhythmic Events with Positron Emission Tomography
PET	Positron Emission Tomography
SCA	Sudden cardiac arrest
RPC	Coefficient-of-repeatability

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Fig. 1.
Patient Flow Diagram and Reasons for Exclusion

Fig. 2. Example horizontal long axis images (A,B) and polar-maps (C,D) of HED tracer uptake in the left ventricle (LV) measured using FlowQuant and Corridor4DM software programs. The normalized polar-maps (E,F) demonstrate similar distribution and SNS denervation scores. Red lines on the horizontal long axis images indicate the basal limit of the LV polar-map sampling.

Fig. 3. Calculation of the sympathetic denervation score. (A) Schematic of a circumferential profile of relative HED uptake passing through an inferior wall defect region is shown by the green line. The extent $\times$ severity of the HED defect (uptake $< 75\%$ of maximum) is shown as the orange hatched area. (B) Denervation score is calculated as the HED defect ($100\% - \text{uptake}$) extent $\times$ severity, also shown as the orange hatched area.

Fig. 4.

Scatter diagrams (n=178) with the regression lines of best fit for HED defect scores between observers for FlowQuant (A), between observers for Corridor4DM (C), and between programs for FlowQuant vs Corridor4DM (E). Corresponding Bland-Altman plots comparing HED uptake scores for FlowQuant (B), Corridor4DM (D), and FlowQuant vs Corridor4DM (F). Solid blue lines represent the mean difference, solid green lines represent the upper and lower 95% limits of agreement, and dotted green lines represent the confidence intervals for the limits of agreement

Fig. 5. Scatter diagrams (n=20 each with 2 observers) with the regression lines of best fit for HED defect scores using the same observer (A) and different observers (C). Corresponding Bland-Altman plots comparing test-retest HED uptake scores are shown in (B) and (D) respectively.

Fig. 6. Kaplan Meier curves illustrating incidence of SCA based on tertiles of HED denervation scores (A) and HED score $\geq$ 37.6% cut-off (B) using scores measured by the original PAREPET trial, FlowQuant reanalysis, and 4DM reanalysis. Figure part (C) demonstrates the Kaplan-Meier curves modelling SCA in patients with 0, 1, or $\geq$ 2 risk factors.

Table 1.**Clinical and Demographic Variables**

Variable	PAREPET (n=178)	TEST-RETEST (n=20)
Demographics		
Age (years)	67.5±11.6	67.4±9.5
Body mass index (BMI)	28.7±5.1	27.2±4.8
Male	159 (89%)	14 (70%) *
Left ventricular ejection fraction (%)	27.7±8.9	33.2±6.4
Diabetes Mellitus	83 (47%)	6 (30%)
History of Revascularization	139 (78%)	14 (70%)
Angina Class (CCS)		
Class I	66 (37%)	2 (10%) *
Class II	84 (47%)	1 (5%) *
Class III	27 (15%)	0 (0%)
Class IV	1 (1%)	0 (0%)
Heart Failure Class (NYHA)		
Class I	34 (19%)	0 (0%) *
Class II	92 (52%)	17 (85%) *
Class I-II	126 (71%)	17 (85%)
Class III	40 (22%)	3 (15%)
Class IV	12 (7%)	0 (0%)
Medications		
Beta blocker	171 (96%)	16 (80%) *
Antiarrhythmic therapy (Amiodarone)	19 (11%)	1 (5%)
Antiplatelet therapy (ASA or Clopidogrel)	155 (87%)	15 (75%)
Anticoagulant therapy (Warfarin)	73 (41%)	5 (25%)
Angiotensin therapy (ACE inhibitor or ARB)	159 (89%)	19 (95%)
Aldosterone antagonist	68 (38%)	NA
Cardiac glycosides (Digoxin)	68 (38%)	7 (35%)
Laboratory Variables		
Creatinine (mg/dL)	1.4±0.9	NA
B-type Natriuretic Peptide (ng/L)	423±453	NA
Hematocrit (%)	40.6±4.9	NA
Echocardiographic and Electrocardiographic Variables		
Resting Heart Rate (bpm)	65±12	64.5±17.0
LV End-Diastolic Volume Index (mL/m ²)	87±29	NA
LV End-Systolic Volume Index (mL/m ²)	64±26	NA
Mitral Regurgitation Severity (0 to 4)	1.6±1.1	NA
Left Atrial Volume Index (mL/m ²)	42±16	NA
QRS Duration (ms)	137±35	NA
LV Mass Index (g/m ²)	151±47	NA

*
P < 0.05 vs PAREPET cohort

NA = Not Available

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Table 2.

Inter-rater and inter-software reliability of denervation scores (n=178)

Software Program	ICC [95% CI]	Delta $\pm$ RPC	p-value
FlowQuant (R1 vs R2)	98% [97–99%]	$-1.1 \pm 5.9\%$	<0.001
Corridor4DM (R3 vs R2)	99% [98–99%]	$-0.2 \pm 4.7\%$	0.283
Corridor4DM vs FlowQuant (R2)	98% [97–98%]	$-0.5 \pm 6.3\%$	0.043

Table 3.

Test-retest repeatability (n=20)

Comparison	ICC [95% CI]	Delta $\pm$ RPC	p-value
Same observer	95% [91–97%]	$-0.9 \pm 10.3\%$	0.306
Different observers	94% [89–97%]	$-0.6 \pm 11.0\%$	0.335