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Positron emission tomography (^{15}O-water, ^{11}C-acetate, ^{11}C-HED) risk markers and nonsustained ventricular tachycardia in hypertrophic cardiomyopathy

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ABSTRACT

Background: The objectives of the study were to describe positron emission tomography (PET) parameters, using the tracers ^{15}O-water at rest/stress, ^{11}C-acetate, and ^{11}C-HED, with regard to nonsustained ventricular tachycardia (NSVT) in hypertrophic cardiomyopathy (HCM). PET offers quantitative assessment of pathophysiology throughout the left ventricular segments, including the endocardium/epicardium. The potential use PET in risk stratification remains to be elucidated. NSVT provides a marker for sudden cardiac death.

Methods: Patients with a validated diagnosis of HCM who had an implantable cardioverter-defibrillator were interrogated at 12 months and independently of PET-examinations.

Results: In total, 25 patients (mean age 56.8 ± 12.9 years, 76% males) were included and 10 reported NSVT. Mean myocardial blood flow (MBF) at rest was 0.91 ml/g/min and decreased at stress, 1.59 ml/g/min. The mean gradient (endocardium/epicardium quotient) at rest was 1.14 ± 0.09, while inverse at stress (mean 0.92 ± 0.16). Notably, MBF gradient at stress was significantly lower in patients with NSVT ($p = 0.022$) and borderline at rest ($p = 0.059$) while global MBF at rest and stress were not. Mean myocardial oxygen consumption (MVO_2) was 0.088 ml/g/min (higher in NSVT, $p = 0.023$) and myocardial external efficiency 18.5%. Using ^{11}C-HED, the mean retention index was 0.11 min^{-1} and a higher volume of distribution ($p = 0.089$) or transmural gradient of clearance rate ($p = 0.061$) or lower clearance rate ($p = 0.052$) showed a tendency of association of NSVT.

Conclusions: The endocardium/epicardium MBF gradient at stress is significantly lower in HCM patients with NSVT. This provides a novel approach to further refine risk stratification of sudden cardiac death.

1. Introduction

Risk stratification for sudden cardiac death (SCD) due to ventricular arrhythmia in hypertrophic cardiomyopathy (HCM) remains a challenge. Current risk stratification according to the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) in primary prevention takes into account a family history of SCD, unexplained syncope, maximum left ventricular (LV) wall thickness, abnormal blood pressure response, and presence of nonsustained ventricular tachycardia (NSVT) [1]. Since 2014 an algorithm, endorsed by the European Society of Cardiology (ESC), integrates these risk factors with age, left atrial size, and LV-outflow obstruction to provide a 5-year risk [2,3]. Both guidelines have been validated but are limited by low positive and modestly high negative predictive values [1,4,5]. Furthermore, less is known about HCM subpopulations, e.g. those who undergo myectomy. In addition to the established risk factors, several other markers have been suggested: LV apical aneurysm, certain mutation(s), but also late-gadolinium enhancement on cardiac magnetic resonance

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imaging [1]. So far, only echocardiography-derived parameters are included in guidelines [1,2]. Nevertheless, positron emission tomography (PET) provides quantitative assessment of physiological properties in the heart, including regional distribution and may have the potential to refine risk stratification [6].

An implantable cardioverter-defibrillator (ICD) system effectively terminates life-threatening arrhythmias, but has considerable long-term risk of complications and high cost, making careful patient selection crucial [5]. ICDs offer continuous monitoring of arrhythmias including NSVT with a time stamp over extended time periods in contrast to an ambulatory ECG which is typically applied for 24–48 h. Risk factors are usually assessed only at baseline, i.e. at time of implant, and are usually not updated even if conditions change. From that perspective, ICD interrogation offers a more complete assessment of outcome and uniform follow-up period in conjunction with PET examinations.

The overall objective of this study was to explore the potential association between PET-derived parameters that reflect microvascular dysfunction, oxidative metabolism, and innervation with the presence of NSVT during 12 months of ICD follow-up.

2. Methods

2.1. Study design

This study was performed using validation of medical records from all relevant management of the patient, including remote monitoring of the ICD and cross-sectional PET assessment.

2.2. Setting

In total, 25 patients with an ICD due to HCM were identified through the Swedish Pacemaker and ICD Registry with a postal address in Region Gävleborg, Dalarna, Västerbotten or Värmland [7]. The PET scans were performed between May 2017 and February 2018.

2.3. Participants

Adults with a definite diagnosis of HCM, reassessed by echocardiography, with ICDs were included after oral and written informed consent. Patients with concomitant epicardial coronary disease with lumen narrowing $\geq$50% at angiography, phenocopies (e.g. amyloidosis), decompensated heart failure, resynchronization therapy, pregnancy, lactation, claustrophobia, known intolerance/allergic reaction to adenosine, systolic hypotension, increased intracranial pressure, hypovolemia, and treatment with dipyramidole were excluded.

2.4. Definitions of arrhythmias

NSVT was defined as 3 consecutive beats of ventricular origin $\geq$160 bpm reported on ICD-stored electrogram in 12 months. Sustained ventricular arrhythmias were the composite endpoints of a ventricular arrhythmia exceeding 30 s with hemodynamic compromise, cardiac arrest, and appropriate ICD therapy with either antitachycardia pacing or discharge.

2.5. PET scanning

Patients were scanned using a GE Discovery MI (GE Healthcare, Waukesha, WI). Scans with ^{15}O-water at rest and stress, ^{11}C-acetate, and ^{11}C-HED were performed on the same day after fasting since midnight. Caffeine and tobacco use were prohibited for 24 h before examination.

^{15}O-water: The protocol began with a respiration-averaged low-dose computerized tomography (CT) for attenuation correction. After the CT, 400 MBq of ^{15}O-water was administered intravenously using an automated injector as a fast bolus (5 ml at 1 ml/s, followed by 35 ml saline at 2 ml/s) and a 6 min (min) dynamic list mode emission scan was simultaneously started. Scanning was performed during rest and again during adenosine induced stress. Data were reconstructed into 22 frames (1x10, 8x5, 4x10, 2x15, 3x20, 2x30, and 2x60 s) using a standard protocol.

^{11}C-acetate: The CT used for ^{15}O-water was also used for attenuation correction of ^{11}C-acetate. Activity (433 ± 84 MBq) was administered using an automated injector as a bolus (1 ml/s, followed by 35 ml saline at 1 ml/s) and a 27 min dynamic list mode emission scan was simultaneously started. Data were reconstructed into 31 frames (12x5, 6x10, 4x30, 4x60, 2x120, 3x300 s) using a standard protocol.

^{11}C-HED: A new, low-dose respiration-averaged CT was performed because the patients left the scanner before this scan. Activity (385 ± 70 MBq) was administered using an automated injector as a bolus (1 ml/s, followed by 35 ml saline at 1 ml/s) and a 35 min dynamic list mode emission scan was simultaneously started. Data were reconstructed into 31 frames (12x5, 6x10, 4x30, 2x60, 2x120, 5x300 s) using a standard protocol.

2.6. Data analyses

The scans were analyzed using tools developed in-house and incorporated in the aQuant software [8]. For all scans, arterial and right-ventricular concentrations were automatically obtained using cluster analysis [8,9]. The LV wall was divided using the 17-segment model [10]. Two expert reviewers blinded to outcome analyzed all PET studies.

^{15}O-water was quantified using the standard one tissue compartment model as described previously [11]. MBF at rest (corrected for rate pressure product) and stress were quantified on the global and 5 regional segments (anterior, septal, inferior, lateral, and apex). A heterogeneity index was calculated by dividing the maximum MBF by the lowest MBF [12]. A transmural perfusion gradient (TPG) was calculated as a ratio of endocardial/epicardial MBF by splitting the 17 segments each in equal halves based on the distance to the LV cavity. Defect size was defined as total volume of the LV with MBF $\times$ perfusable tissue index below 50% of maximum for rest and MBF <69% of maximum for stress.

^{11}C-acetate was modelled using a one tissue compartment model with corrections for blood volume fraction and spillover from blood [13]. Plasma input functions were calculated by applying the average plasma metabolite correction [14]. From the clearance rate (k_2), myocardial oxygen consumption (MVO_2) was converted using empirically derived conversion factors [14]. Myocardial external efficiency (MEE), the ratio of kinetic energy from cardiac work and chemical energy from MVO_2, were calculated using forward cardiac output and LV mass derived from PET images [13]. Transmural gradient (TG) was calculated for MVO_2 similarly as for MBF.

LV mass, ECG-gated end-diastolic volume (EDV), end-systolic volume (ESV), and stroke volume (SV) were calculated and adjusted for body surface area [14]. Ejection fraction (EF) was calculated as SV/EDV.

^{11}C-HED was modelled using a one tissue compartment model, using an average plasma metabolite correction [15]. The volume of distribution (V_T) was calculated by the ratio of uptake rate to clearance rate. Retention index (RI) was calculated by dividing the late uptake activity by the integral of the non-metabolite corrected arterial input function. Defect size was defined as total volume of the LV with RI < 75% of maximum. TG was calculated for RI, V_T, and clearance rate.

2.7. Statistical analyses

Data were described as numbers (n), percentages, ranges, percentiles, interquartile ranges (IQRs), means and standard deviations (±). To analyze the association between PET parameters and outcome, the non-parametric Mann-Whitney *U* test was used. A two-sided p-value < 0.05 was considered significant, whereas associations with p-values between 0.05 and 0.10 were considered a tendency. For statistical analyses SPSS version 22 (IBM, Armonk, NY) was used.

2.8. Ethics and registration

The study was approved by Ethical Review Board in Uppsala (document number 2017/021) and registered at Clinical Trial Registration NCT03278457.

3. Results

3.1. Patient characteristics

The mean age of the 25 patients (19 males) at the time of the PET scan was 56.8 ± 12.9 years. Patient characteristics are summarized in Table 1. The first diagnosis of HCM was 12 ± 10 years earlier and the time since ICD implant was 6.3 ± 4.8 years. The majority (n = 22) had the ICD (VR, n = 5; DR, n = 20) for primary prevention based on: unexplained syncope (n = 10), NSVT (n = 14), family history of SCD (n = 5), abnormal blood pressure response (n = 1), maximum wall thickness ≥30 mm (n = 3), and mean left atrial size 45 ± 6.0 mm.

Table 1
Patient characteristics of 25 patients with hypertrophic cardiomyopathy.

Age, mean (years)	56.8	±12.9
Male	19	76%
Body-mass index (kg/m^2)	28.6	±4.4
Body surface area (m^2)	2.05	±0.27
Primary prevention	22	88%
Diabetes mellitus	5	20%
Hypertension	5	20%
Genopositive	13	52%
Alcohol septal ablation	0	0%
Myectomy	8	32%
Atrial fibrillation	7	28%
Medication		
Beta-blocker	22	88%
Calcium channel blocker	4	16%
Sotalol	0	0%
Disopyramide	0	0%
Amiodarone	1	4%
ACE-I/ARB	9	36%
Aldosterone receptor blocker	3	12%
Acetylsalicylic acid	4	16%
Warfarin	2	8%
Novel oral anticoagulant	5	20%
Hemodynamics at PET		
Systolic blood pressure (mmHg)	128	±17
Diastolic blood pressure (mmHg)	75	±15
Heart rate (beats per minute)	63	±9
Ventricular pacing at PET		
Intrinsic rhythm	20	80%
Pacing	4	16%
Mixed (intrinsic and pacing)	1	4%
Echocardiography		
Left atrial diameter (mm)	48	±10
Left atrial size/body surface area (ml/m^2)	53	±41
Left ventricular diameter, diastole (mm)	49	±6
Left ventricular diameter, systole (mm)	34	±6
Left ventricular outflow tract gradient (mmHg)	8	±5
Left ventricular outflow obstruction*(≥30 mmHg)	2	13%
Left ventricular ejection fraction (%)	57	±9
Maximal wall thickness (mm)	20	±4
Tricuspid annular plane systolic excursion (mm)	22	±4
Systolic pulmonary artery pressure (mmHg)	32	±10

ACE-I/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; PET, positron emission tomography.
* ≥30 mmHg at rest or Valsalva maneuver.

3.2. Outcome

In total, 10 patients (40%) experienced NSVT at 12 months. The composite endpoint of appropriate ICD therapy and secondary ICD indication was reported in 8 (32%) patients.

3.3. PET exams

In one patient ^{15}O-water at stress was not possible due to emotional distress; in the remaining patients, all four exams were successfully performed. Modelling parameters from one HED scan was excluded due to patient motion, but the RI was determined to be applicable when RI interval was calculated without motion.

MBF mean at rest, adjusted for rate pressure product, was 0.91 ml/g/min (IQR: 0.77–1.00) and severely decreased at stress (mean 1.59 ml/g/min, IQR 0.94–2.29). The mean gradient (endocardium/epicardium quotient) at rest was 1.14 ± 0.09, but inversed at stress (mean 0.92 ± 0.16). Notably, the MBF gradient at stress was significantly lower in patients with NSVT (Mann-Whitney *U* test, p = 0.022) and borderline at rest (p = 0.059) while global MBF rest (p = 0.405) and stress (p = 0.114) were not.

MVO_2 mean was 0.088 ml/g/min (IQR 0.070–0.100) and MEE was 18.5% (IQR 13.3–20.9). RI mean was 0.11 min^{-1} (IQR 0.090–0.0126). MVO_2 was significantly higher among patients with NSVT (p = 0.023). A lower V_T and a higher clearance rate respectively were both borderline significant with regard to NSVT.

PET results from ^{15}O-water ^{11}C-acetate ^{11}C-HED are summarized in Table 2 and its association with NSVT in Table 3. Regional differences are depicted in Table 4. The prevalence of myectomy with regard to NSVT was similar (p = 0.607).

We also analyzed the same PET parameters with regard to sustained ventricular tachycardia; all p-values were non-significant.

4. Discussion

4.1. ^{15}O-water

Dynamic coronary microvascular function adjusts vascular tone to meet metabolic requirements, including oxygen demand, whereas complex pathophysiological mechanisms lead to cellular dysfunction, thrombosis, and fibrosis [16]. In HCM, signs of microvascular disease have been detected in SCD victims and in the vast majority of necropsies [17,18]. Morphological abnormalities of intramural coronary arterioles constitute a basis for impaired functional capacity, i.e. MBF at stress [19,20,21]. At rest, MBF was 0.91 ml/g/min and during stress 1.59 ml/g/min which is clearly below the ischemic cut-off of 2.3 ml/g/min [22]. Using the cut-off 2.3 at stress allows high diagnostic accuracy, superior to computed tomography angiography and single-photon emission tomography in ischemic heart disease (SPECT) [23,24]. Coronary microvascular dysfunction in HCM has been linked to remodeling of arterioles, fibrosis, increased mass, capillary rarefaction, myocyte disarray, spasm, luminal narrowing, and extrinsic compressive forces [25,26,27]. These extrinsic forces due to increased LV cavity pressure, wall stress/thickness, and possibly outflow obstruction explain the impaired perfusion in the subendocardial layers [25,28].

Interestingly, Knaapen et al. demonstrated, using ^{15}O-water that MBF at stress was blunted in HCM vs. controls (2.26 ± 0.97

Table 2
PET results from ^{15}O-water, ^{11}C-acetate, and ^{11}C-HED.

	Mean	Range	25th percentile	Median	75th percentile
^{15}O-water					
MBF_{REST} (ml/g/min)[†]	0.91	0.47–1.70	0.77	0.90	1.00
MBF_{STRESS} (ml/g/min)	1.59	0.64–3.50	0.94	1.36	2.29
Heterogenity $index_{REST}$	1.34	1.05–1.91	1.91	1.26	1.41
Heterogenity $index_{STRESS}$	1.58	1.11–2.26	1.31	1.55	1.79
Coronary flow reserve	1.78	0.75–3.61	1.28	1.60	2.32
Defect $size_{REST}$ (%)	1.97	0.02–10.20	0.09	0.27	3.32
Defect $size_{STRESS}$ (%)	29.51	0.47–63.62	7.07	30.46	50.80
TPG_{REST}	1.14	1.01–1.33	1.07	1.13	1.22
TPG_{STRESS}	0.92	0.67–1.20	0.77	0.91	1.05
^{11}C-acetate					
MVO_2 (ml/g/min)	0.088	0.047–0.15	0.070	0.085	0.10
MEE (%)	18.5	9.2–46.7	13.3	16.3	20.9
LV-mass (g/m^2)	109	59–217	77	102	129
EDV (ml/m^2)	94	59–137	80	96	106
ESV (ml/m^2)	36	13–91	22	31	53
SV (ml/m^2)	58	37–89	47	56	66
EF (%)	63.3	33.4–83.6	49.7	64.4	75.1
TG_{MVO2}	0.99	0.86–1.10	0.94	0.99	1.05
^{11}C-HED					
RI (min^{-1})	0.11	0.034–0.181	0.090	0.117	0.0126
Defect $size_{RI}$ (%)	14.92	1.16–39.87	7.19	13.60	20.04
Heterogenity $index_{RI}$	1.73	1.26–3.74	1.38	1.58	1.75
TG_{RI}	1.06	0.94–1.14	1.03	1.06	1.09
VT	17.43	2.95–27.36	15.83	17.76	22.35
Clearance rate	0.019	0.0063–0.056	0.014	0.018	0.020
TG_{VT}	0.960	0.65–1.15	0.88	0.99	1.03
$TG_{clearance\ rate}$	1.21	0.91–1.74	1.06	1.12	1.29
^{11}C-HED – ^{15}O-water					
Defect $size_{RI}$ - Defect $size_{REST}$ (%)	12.95	−1.15–38.23	3.88	11.86	17.94
Defect $size_{RI}$ - Defect $size_{STRESS}$ (%)	14.53	−59.55–26.48	−41.60	−13.39	10.39

[†] Corrected for rate pressure product; heterogenity index = MBF_{MAX}/MBF_{MIN}; TPG = $MBF_{ENDOCARDIUM}/MBF_{EPICARDIUM}$; MVO_2, myocardial oxygen consumption; MEE, myocardial external efficiency; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; TG, transmural gradient; RI, retention index; Heterogenity $index_{RI} = RI_{MAX}/RI_{MIN}$; VT, volume of distribution.

vs 2.93 ± 0.64 ml/g/min, $p < 0.05$). At stress compared to rest, the TPG among HCM patients was decreased (0.88 ± 0.18 vs 1.20 ± 0.11, $p < 0.01$) in contrast to controls (1.25 ± 0.19 vs 1.38 ± 0.15, not significant) [25]. Previously, TPG < 1.0 reflecting endocardial hypoperfusion has been shown among HCM patients using either ^{15}O-water or ^{13}N-ammonia [29,30,31]. The low TPG in our cohort is in line with these findings. The low TPG in HCM was confirmed in a more recent and larger study using ^{13}N-ammonia, in which transient LV cavity dilatation (52%) was associated with lower TPG (0.85 ± 0.22 vs 1.09 ± 0.39, $p < 0.001$) [32]. This characteristic finding of decreased TPG at rest and especially at stress may provide a substrate for ventricular arrhythmias. With regard to NSVT, our study showed TPG had borderline significance at rest and significance at stress. No previous study hypothesized TPG as a predictor of arrhythmia. In a landmark trial and later follow-up study ^{13}N-ammonia was used to quantify MBF; the worst tertile had a significantly higher risk of the composite endpoint of unfavorable outcome (5/16 arrhythmic events in the first study and 0/12 in the follow-up) [33,34].

The heterogeneity index, defined as the ratio of the highest to the lowest regional MBF, might be a predictor of arrhythmia in HCM. In a recent study, using ^{13}N-ammonia, a heterogeneity index of ≥1.85 was an independent marker of the composite endpoint of sustained ventricular arrhythmia and NSVT (assessed either by Holter monitoring or ICD interrogation in the 13% of patients with ICDs) [35]. In order to compare our data, the heterogeneity index of our cohort was calculated but had no significant association to NSVT assessed in a uniform way by 12-month ICD interrogation.

4.2. ^{11}C-Acetate

The heart relies almost exclusively on aerobic energy metabolism and clearance of ^{11}C-acetate represents MVO_2 [36,37]. In HCM, MVO_2 seems to be similar to controls. In one study, HCM patients and controls had similar MVO_2: 0.13 ± 0.05 ml/g/min vs. 0.12 ± 0.04 ml/g/min, $p = 0.64$. In another, HCM had increased MVO_2 compared to controls but these hypermetabolic alterations regressed with advanced hypertrophy [38]. Early studies showed a slight decrease of MVO_2 in HCM [39,40]. In a recent study of cardiac amyloidosis and controls using the same methodology as our study, MVO_2 was similar (0.09 ± 0.02 ml/g/min vs. 0.10 ± 0.02 ml/g/min) [41]. Notably, MVO_2 (mean 0.088 ml/g/min) was significantly higher among patients with NSVT in our cohort.

The MEE of 18.5% in our cohort was lower than controls in another study, where MEE was 23.6 ± 4.2% [42]. MEE seems to be affected in early stage HCM because a significant reduction compared to controls was also shown in patients solely with the genotype [43]. In another HCM cohort, MEE was 21 ± 10%, amyloidosis 13 ± 5%, aortic stenosis 17.2 ± 4.3%, and mitral regurgitation 18.0 ± 5.2% [44,41,42]. MEE was not significantly lower among NSVT patients in our cohort. Early findings showed that myectomy implied a reduction in MVO_2 but a later study on patients who underwent alcohol septal ablation could not confirm that even

Table 3
PET results from ^{15}O-water, ^{11}C-acetate, and ^{11}C-HED with regard to presence of nonsustained ventricular tachycardia.

	NSVT (p-value)
^{15}O-water	
MBF_{REST} (ml/g/min) †	0.405
MBF_{STRESS} (ml/g/min)	0.114
Heterogenity $index_{REST}$	0.134
Heterogenity $index_{STRESS}$	1.000
Coronary flow reserve	0.320
Defect $size_{REST}$ (%)	0.824
Defect $size_{STRESS}$ (%)	0.725
TPG_{REST}	**0.059**[a]
TPG_{STRESS}	**0.022**[a]
^{11}C-acetate	
MVO_2 (ml/g/min)	**0.023**[b]
MEE (%)	0.405
LV-mass (g/m^2)	0.579
EF (%)	0.120
TG_{MVO2}	0.542
^{11}C-HED	
RI (min^{-1})	1.000
Defect $size_{RI\_75\%}$ (%)	0.202
Heterogenity $index_{RI}$	0.120
TG_{RI}	0.698
VT	**0.089**[a]
Clearance rate	**0.061**[b]
TG_{VT}	0.380
$TG_{clearance\ rate}$	**0.052**[a]
^{11}C-HED – ^{15}O-water	
Defect $size_{RI}$ - Defect $size_{REST}$ (%)	0.267
Defect $size_{RI}$ - Defect $size_{STRESS}$ (%)	0.380

† Corrected for rate pressure product; heterogenity index = MBF_{MAX}/MBF_{MIN}; TPG = $MBF_{ENDOCARDIUM}$/EF, ejection fraction; $MBF_{EPICARDIUM}$; MVO_2, myocardial oxygen consumption; MEE, myocardial external efficiency; LV, left ventricle; NSVT, nonsustained ventricular tachycardia; TG, transmural gradient; RI, retention index; Heterogenity $index_{RI} = RI_{MAX}/RI_{MIN}$; VT, volume of distribution. Comparisons performed using Mann-Whitney *U* test.
[a] Lower rank in NSVT; [b] higher rank in NSVT.

Table 4
PET results from ^{15}O-water, ^{11}C-acetate, and ^{11}C-HED at regional level with regard to presence of nonsustained ventricular tachycardia (p-values).

	Anterior	Septal	Inferior	Lateral
^{15}O-water				
TPG_{REST}	0.134	0.244	**0.017**	**0.040**
TPG_{STRESS}	0.178	**0.019**[a]	**0.005**[a]	0.101
^{11}C-Acetate				
MVO_2 (ml/g/min)	**0.052**[b]	**0.086**[b]	**0.046**[b]	**0.027**[b]
TG_{MVO2}	0.222	0.956	**0.059**	0.542
^{11}C-HED				
TG_{RI}	0.292	0.824	0.782	0.698
VT	0.222	**0.027**[a]	0.267	**0.076**[a]
Clearance rate	**0.007**[b]	**0.023**[b]	0.183	**0.035**[b]

[a] Lower rank in NSVT.
[b] Higher rank in NSVT.

though MBF at stress was increased [45]. MEE may also be influenced by beta-blocker treatment and bradycardia pacing causing dyssynchrony.

4.3. ^{11}C-HED

There is a lack of standardized reference values of ^{11}C-HED parameters. In the PAREPET study, patients (n = 204) with ischemic cardiomyopathy and EF ≤ 35% were studied with regard to sustained VT [46]. RI in the segment with maximal uptake was 0.136 ± 0.037 min^{-1}, identical to our mean value. Moreover, the denervated myocardium, i.e. defect size, was significantly different between patients with sustained VT and those without (33 ± 10 vs 26 ± 11, p = 0.001). However, in our cohort, defect size was non-significantly different with regard to NSVT. Overall, the defect size was 27 ± 11% in PAREPET compared to 14.9% in our study. The larger size and wider range of defect sizes in a larger sample imply less risk of type 2 error.

RI as a semi-quantitative parameter is sensitive to motion, partial volume effects, intravascular activity, and spill-over from blood and has a non-linear relationship to VT [47]. These factors can be taken into account in the kinetic modelling which makes clearance rate and V_T more robust [47]. Interestingly, higher clearance rate and lower V_T showed a tendency towards significance with regard to NSVT. Again, the transmural gradient, reflecting a higher degree denervation of endocardial structures compared to the epicardium, turned out to be a sensitive marker of NSVT with a borderline significance.

Cardiac sympathetic denervation, assessed by SPECT, increases the risk of sustained ventricular tachycardia in patients with systolic heart failure [48]. In another SPECT-study, denervation was associated with an increased risk of appropriate ICD therapy; the mismatch between perfusion and denervation was significant in univariable but not multivariable analysis [49]. In PAREPET, the area of viable, denervated myocardium was higher in patients with sustained ventricular tachycardia [46]. We explored the mismatch between denervation and perfusion and found no statistical significance between defect size and perfusion at rest or stress.

5. Limitations

This is the first study of HCM patients with ICDs with a uniform assessment of the outcome NSVT using device interrogation. Even though NSVT is an established risk factor of SCD in HCM, it is not synonymous with life-threatening arrhythmias. The usage of three tracers during the same occasion allows for comparison without changes of the underlying disease over time. It should be noted that the cause of an arrhythmia is a complex interplay of several factors that are unknown or cannot be taken into account due to the small sample size. Moreover, the explorative design with several risk markers is prone to both type 1 and type 2 errors. Patients with ICDs have been selected based on judgment of established risk factors and it is unknown if our findings can be into generalized to HCM cohorts without devices. Thus, confirmatory studies are needed before these associations can be used for general risk stratification in HCM.

6. Conclusion

Patients with HCM and ICDs exhibit decreased myocardial blood flow, slightly decreased myocardial oxygen consumption and have substantial sympathetic denervation. The transmural gradient of MBF at stress is associated with NSVT. In addition, MBF at rest, VT, clearance rate, and transmural gradient of clearance rate constitute possible markers of NSVT. These risk markers provide a potential for refinement of risk stratification of SCD.

CRediT authorship contribution statement

Peter Magnusson: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Visualization, Supervision, Project administration, Funding acquisition. **Jonny Nordström:** Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing, Visualization, Project administration, Funding acquisition. **Hendrik J. Harms:** Methodol-

ogy, Software, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing. **Mark Lubberink:** Methodology, Software, Data curation, Writing - review & editing, Supervision. **Fredrik Gadler:** Methodology, Investigation, Writing - review & editing, Supervision. **Jens Sörensen:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - review & editing, Visualization, Supervision. **Stellan Mörner:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - review & editing, Visualization, Supervision.

Declaration of Competing Interest

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