Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Regional Cardiac Denervation Predicts Sustained Ventricular Arrhythmias in Nonischemic Cardiomyopathy Patients Without LGE on CMR Imaging

Christiane Jungen, MD, PhD*; H. Sophia Chen, MD, PhD*; Adrianus P. Wijnmaalen, MD, PhD; Petra Dibbets-Schneider, MSc; Augusto Meretta, MD; Sebastiaan R. Piers, MD, PhD; Yoshitaka Kimura, MD, PhD; Alexander F.A. Androulakis, MD; Rob J. van der Geest, MSc, PhD; Lioe-Fee de Geus-Oei, MD, PhD; Bart J.A. Mertens, MD, PhD; Arthur J.H.A. Scholte, MD, PhD; Hildo J. Lamb, MD, PhD; Monique R.M. Jongbloed, MD, PhD; Katja Zeppenfeld, MD, PhD

BACKGROUND: In patients with nonischemic cardiomyopathy and no late gadolinium enhancement (LGE) on cardiac magnetic resonance, risk prediction for the occurrence of sustained ventricular arrhythmias (VA) is challenging. Global and regional sympathetic denervation has been associated with VA in patients with ischemic cardiomyopathy. Its prognostic relevance in nonischemic cardiomyopathy is unknown.

METHODS: Consecutive patients from the Leiden Nonischemic Cardiomyopathy Study who underwent programmed electrical stimulation, LGE-cardiac magnetic resonance, and 123-iodine meta-iodobenzylguanidine imaging between 2011 and 2019 were included. The presence of LGE and global and regional sympathetic denervation on 123-iodine meta-iodobenzylguanidine were evaluated, and patients were followed for the occurrence of VA. Global denervation was assessed using the heart-to-mediastinum ratio. Regional denervation was evaluated by calculating the number of denervated segments (DS), the ratio of DS, the summed defect score, and the weighted denervation size.

RESULTS: Of 75 included patients (median age 63 years [25th–75th interquartile range (IQR) 54–68], 79% male, left ventricular ejection fraction 36% [IQR, 27–44], 37% inducible for VA), 35 had no LGE. During 4.5±1.6 years of mean follow-up, VA occurred in 8 of 35 (23%) patients without LGE and in 18 of 40 (45%) patients with LGE. Among patients without LGE, those with VA had greater regional sympathetic denervation (median number of DS 8 [IQR, 7–10] versus 2 [IQR, 1–5], P=0.004; median ratio of DS 0.5 [IQR, 0.5–0.7] versus 0.2 [IQR, 0.1–0.4], P=0.007; median defect score 36 [IQR, 30–41] versus 18 [IQR, 14–24], P=0.01; median weighted denervation size 47 [IQR, 38–54] versus 22 [IQR, 14–30]; P=0.01). In bivariate analysis, the number of DS (hazard ratio, 1.25 [95% CI, 1.06–1.46]; P=0.006) was associated with the occurrence of VA in patients without LGE. Denervation of ≥7 segments identified patients without LGE at risk for VA (area under the curve, 0.83; sensitivity, 88%; specificity, 89%). Among patients with LGE, the innervation state was not associated with VA during follow-up.

CONCLUSIONS: In patients with nonischemic cardiomyopathy without LGE the extent of regional denervation may contribute to risk stratification for VA.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: gadolinium ■ humans ■ iodine ■ prognosis ■ risk assessment

Correspondence to: Katja Zeppenfeld, MD, PhD, Willem Einthoven Center for Cardiac Arrhythmia research and Management, Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands. Email k.zeppenfeld@lumc.nl
*C. Jungen and H.S. Chen contributed equally as first authors.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCEP.124.013150.
For Sources of Funding and Disclosures, see page 614.

Circulation: Arrhythmia and Electrophysiology is available at www.ahajournals.org/journal/circep

WHAT IS KNOWN?

- Risk prediction for ventricular arrhythmias in patients with nonischemic cardiomyopathy is challenging, in particular in those without late gadolinium enhancement.
- Regional sympathetic denervation has been associated with the risk for ventricular arrhythmias in patients with ischemic cardiomyopathy.

WHAT THE STUDY ADDS

- Among nonischemic cardiomyopathy patients without late gadolinium enhancement, regional denervation quantified as number of denervated segments is associated with the occurrence of ventricular arrhythmias.
- More extensive denervation (specifically ≥7 denervated segments) may identify patients at risk for ventricular arrhythmias.

Nonstandard Abbreviations and Acronyms

^{123}I-MIBG	123-iodine meta-iodobenzylguanidine
ATP	antitachycardia pacing
CMR	cardiac magnetic resonance
DS	denervated segments
HMR	heart-to-mediastinum ratio
ICD	Implantable Cardioverter Defibrillator
IQR	interquartile range
LGE	late gadolinium enhancement
LGE-CMR	late gadolinium-enhanced cardiac magnetic resonance imaging
LVEF	left ventricular ejection fraction
NICM	nonischemic cardiomyopathy
PES	programmed electrical stimulation
SPECT	single-photon emission computed tomography
VA	ventricular arrhythmia
VT	ventricular tachycardia

Patients with nonischemic cardiomyopathy (NICM) are at risk for sustained ventricular arrhythmias (VA), with an annualized event rate of ≈4.5%.[1,2] The primary prevention indication for Implantable Cardioverter Defibrillator (ICD) in patients with NICM is based on a reduced left ventricular ejection fraction (LVEF), and more recently also on the presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging.[3–12] However, NICM patients are a heterogeneous group, and life-threatening VA does occur in the absence of a severely depressed LVEF and in the absence of LGE.[12,13]

Cardiac denervation, as assessed by 123-iodine meta-iodobenzylguanidine (^{123}I-MIBG) imaging, has also been related to VA in NICM.[14] Global sympathetic denervation, using the heart-to-mediastinum ratio (HMR), has been associated with VA and sudden cardiac death in mixed cohorts of patients with ischemic cardiomyopathy and NICM [15–18] and with sudden cardiac death or combined cardiac end points including cardiac death, rehospitalization for heart failure, and VA in patients with NICM.[19,20]

Regional denervation has also been analyzed in patients with NICM and associated with cardiac mortality,[21] or with the combined end point of mortality or hospitalization due to heart failure or any arrhythmia.[22] Methods for ^{123}I-MIBG imaging to determine regional denervation in patients with NICM are mostly voxel-based and include a total extent score, representing the area of reduced MIBG uptake, and a total severity score, representing the severity of the defect.[21,22] Additional methods are based on the 17-segment model and include a summed segmental dysinnervation score and number of dysinnervated segments.[21,23]

In a cohort of patients with heart failure, regional denervation provided additional prognostic value to abnormal global innervation for sudden cardiac death prediction.[17] Of interest, the regional extent of LGE was a significant and independent predictor of regional sympathetic denervation in a cohort of patients with nonischemic heart failure and relatively preserved function,[24] raising the question of whether regional denervation may indicate nonischemic replacement fibrosis as 1 substrate for life-threatening VA. However, regional denervation may also contribute to arrhythmogenicity in patients with NICM and diffuse fibrosis not identified by late gadolinium-enhanced cardiac magnetic resonance imaging (LGE-CMR).

The aim of this study was therefore to evaluate the prognostic significance of global and regional denervation for the occurrence of VA in NICM in patients both with and also specifically without LGE.

METHODS

Patient Population

Patients included in the prospective Leiden NICM study (REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01940081), conducted between October 2011 and September 2019, were analyzed. This study was designed to identify noninvasive and invasive parameters associated with sustained VA. It prospectively enrolled and followed consecutive patients with NICM (idiopathic dilated cardiomyopathy and nondilated LV cardiomyopathy) and documented sustained VA, suspected sustained VA (ie, palpitations and/or syncope likely caused by VA), or those considered to be at intermediate or high risk for sustained VA.[25] A high risk of sustained VA was defined as an LVEF ≤35%; an intermediate risk as an LVEF of 36% to 50% in the presence of late enhancement on LGE-CMR. Patients with other nonischemic cardiomyopathies (ie, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, noncompaction cardiomyopathy, cardiac

sarcoidosis, tachycardiomyopathy, Chagas cardiomyopathy, amyloidosis, and congenital heart disease) were excluded.[26]

Per protocol, all patients underwent a comprehensive evaluation at baseline, including ECG, Holter registration, transthoracic echocardiography, LGE-CMR (if not contraindicated), ^{123}I-MIBG imaging, blood sampling, programmed electrical stimulation (PES), endomyocardial biopsy and genetic analysis of ≥55 cardiomyopathy-related genes.

Patients in whom ^{123}I-MIBG single-photon emission computed tomography (SPECT) imaging and LGE-CMR were available for analysis were included in this study (Figure 1).

The study protocol was reviewed and approved by the Medical Research Ethics Committee of the Leiden University Medical Center. All patients provided written informed consent. To maintain patient confidentiality, data and study materials will not be made available to other researchers for the purpose of replicating the results.

Follow-Up

ICD implantation was performed according to the ESC guidelines valid at the time of evaluation. Patients were followed for VA occurrence and mortality. Follow-up was performed at 6- to 12-month intervals at the outpatient clinic, and devices were interrogated every 6-month intervals. ICD settings included a monitor zone (from 150–170 to 188–200 beats per minute), a fast ventricular tachycardia (VT) zone with antitachycardia pacing (ATP) and shocks (from 188–200 to 220–231 beats per minute), and a ventricular fibrillation zone with ATP before or during charging and shocks (>220–231 beats per minute). All VA, that lasted >30 seconds or terminated by ATP or ICD shock were collected. Each episode was analyzed for electrogram morphology and cycle length stability, and classified as sustained monomorphic VT or polymorphic VT/ventricular fibrillation, as described previously. Patients were followed for a minimum of 2 years after inclusion. Ablation of VA was performed if clinically indicated. Transthoracic echocardiography and LGE-CMR were repeated if clinically indicated.

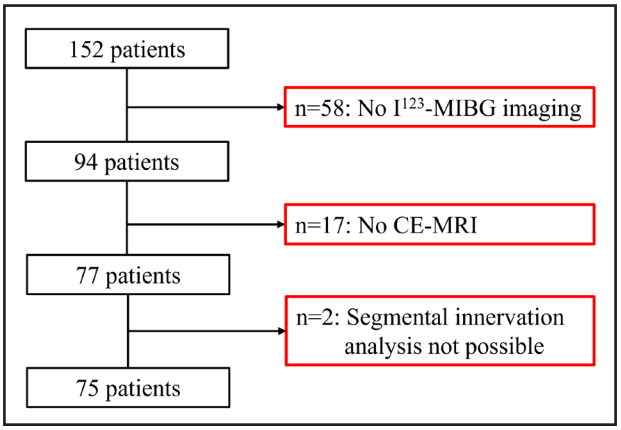

Figure 1. Flowchart of patient selection.
Of 152 patients from the Leiden nonischemic cardiomyopathy (NICM) study, only patients with regional sympathetic innervation imaging (123-iodine meta-iodobenzylguanidine [^{123}I-MIBG] imaging) and contrast-enhanced (CE)–cardiac magnetic resonance (CMR) were included in the final analysis.

Electrophysiology Study

Antiarrhythmic drugs were discontinued for at least 5 half-lives, if possible. PES consisted of 3 drive trains of 8 beats (cycle lengths: 600, 500, and 400 ms) with up to 3 ventricular extrastimuli (starting at coupling intervals of 350 ms, down by 10 ms to the ventricular effective refractory period or 200 ms), and burst pacing with a stimulus strength of twice the diastolic threshold from the RV apex and the RV outflow tract. If no sustained VA was induced after completing the protocol, the PES protocol was repeated with isoprenaline (2–10 µg/min). The positive end point of stimulation was the induction of sustained monomorphic VT, which was defined by similar beat-to-beat QRS morphology and duration >30 seconds or the requirement for termination because of hemodynamic compromise.

LGE-CMR Imaging

LGE-CMR imaging was performed using a 1.5 T Gyroscan ACS-NT/Intera magnetic resonance imaging scanner or a 3.0 T Ingenia magnetic resonance scanner (Philips Medical Systems, Best, the Netherlands) at our institution. Images were acquired ≈15 minutes after intravenous bolus injection of gadolinium diethylenetriamine penta-acetic acid (Magnevist, Schering/Berlin, Germany; 0.15 mmol/kg) during breath-holds of 15 seconds using ECG gating. The heart was imaged covering the entire LV, the inversion time was optimized for optimal nulling of normal myocardium signal. Short-axis cine CMR images were used to compute the LV end-systolic and end-diastolic volumes and calculate the LVEF.

LGE-CMRs that were performed at other centers before referral, were acquired on various systems, always including LGE images in the long-axis and short-axis views covering the entire LV. LGE-CMR images were analyzed using MASS (research version V2021-EXP; Leiden University Medical Center, Leiden, the Netherlands). The RV insertion point was determined at 1/3 from the base, and segmental borders were then automatically appointed for all 17 segments. Delayed enhancement was only considered to be present if it was visible in 2 orthogonal views. The LGE-CMR images were qualitatively evaluated separately by 2 observers (C.J. and H.S.C.). The observers were blinded for patient information and VA outcomes. Scar size was determined for 16 segments; segment 17 (apex) was not analyzed. The mean of the scar size amount was taken from both observers. Disagreement on the presence of scar was solved by expert consultancy (A.P.W.).

LGE scar was quantified using the following parameters: number of segments with LGE, summed scar score and weighted scar size (Figure 2A). The number of segments with LGE was the absolute number of affected segments. For the summed scar score each segment was given a score according to the LGE percentage (score 1=1% to 25% LGE, score 2=26% to 50% LGE, score 3=51% to 75% LGE, score 4=76% to 100% LGE) followed by summation of all scores. Finally, the weighted scar size was calculated by summing the segments with LGE (each weighted by the mid of the range of LGE per segment, e.g, 1%–25%=13%, 26%–50%=38%, 51%–75%=63%, 76%–100%=88%) and dividing by 16, as described previously.[12]

^{123}I-MIBG Scintigraphy

One week before ^{123}I-MIBG scintigraphy tricyclic antidepressant drugs, sympathetic agents and other drugs known to interfere with ^{123}I-MIBG uptake were discontinued.

A CMR

Parameter	Explanation	Example	Range
1) No. of segments with LGE		= 4	0 – 16
2) Summed scar score	0 = no hyperenhancement 1 = 1% to 25% hyperenhanced 2 = 26% to 50% 3 = 51% to 75% 4 = 76% to 100% (per segment) → Score per segment → Sum of all	= 7	0 – 64
3) Weighted scar size (as % of whole LV)	Segmental score weighted by the midpoint 1 = 13% 2 = 38% 3 = 63% 4 = 88% → Summed → Divided by analyzable segments	= 127 % / 16 segments = 7,9 %	0 – 88%

B MIBG

Parameter	Explanation	Example	Range
1) No. of denervated segments		= 8	0 – 16
2) Ratio of denervated segments	No of. denervated segments → Divided by analyzable segments	= 8 / 16 = 0.5	0 – 1
3) Summed defect score	0 = normal tracer uptake 1 = mildly reduced 2 = moderately reduced 3 = severely reduced 4 = no tracer uptake → Score per segment → Sum of all	= 32	0 – 64
4) Weighted denervation size (as % of whole LV)	Values from the summed defect score weighted by the midpoint: 1 = 13% 2 = 38% 3 = 63% 4 = 88% → Summed → Divided by analyzable segments	= 704 % / 16 segments = 44 %	0 – 88%

Figure 2. Overview of analysis and parameters for cardiac magnetic resonance (CMR) and 123-iodine meta-iodobenzylguanidine (^{123}I-MIBG) imaging.
A, CMR parameters for regional innervation analysis are explained. **B**, Regional MIBG parameters and their calculation are depicted.

Patients were pretreated with 120 mg of sodium iodide to block uptake of free 123-iodine by the thyroid gland. Sodium iodide was given orally 1 hour before intravenous administration of 185 MBq ^{123}I-MIBG (Adreview; General Electric Healthcare, NJ). Planar and SPECT imaging of the chest were acquired in supine position. A 10-minute planar image was acquired from an anterior thoracic view (256×256 matrix) 15 minutes after tracer injection. Thereafter, SPECT imaging (4° per step, 35 seconds per projection, 128×128 matrix with a zoom of 1.45) was performed using either a low-energy, parallel-hole, high-resolution collimator and a dual-head camera system (GCA-7200; Toshiba Corp., Tokyo, Japan) or the low-to-medium-energy general-purpose collimator or a dual-head camera system (Siemens Symbia T6; Siemens Healthcare, Erlangen, Germany). All images were acquired with a 15% energy window centered at the 160 keV photopeak of ^{123}Iodine. Planar and SPECT imaging were repeated after 4 hours of tracer administration.

To assess global sympathetic innervation, the HMR was calculated from the late (4 hours) planar images by dividing the mean counts per pixel within the myocardium by the mean counts per pixel within the mediastinum without the use of background correction. Regional sympathetic innervation was assessed by a blinded experienced observer (P.D.) scoring the segmental tracer uptake from the SPECT images using the 17-segment model.[27] Segment 17 (apex) was not analyzed.

Each myocardial segment was scored according to the following tracer uptake scale: 0=normal tracer uptake; 1=mildly reduced tracer uptake; 2=moderately reduced tracer uptake; 3=severely reduced tracer uptake; and 4=no tracer uptake. In

case of overlay from lung or liver, the affected segment was excluded. Segments were subsequently classified as normal (score 0), intermediate (score 1 or 2) or denervated (score 3 or 4).[21,28]

The number of denervated segments (DS) (Figure 2B-1) was determined and a ratio of DS (Figure 2B-2) was calculated by dividing the number of DS by all analyzable segments. The summed defect score (Figure 2B-3) was calculated by summation of regional tracer uptake scores for the late SPECT images for each patient.[28] The weighted denervation size (Figure 2B-4) as percentage of LV myocardium was calculated similar to the LGE-CMR analysis[12]: the summed segments with denervation (score 3 and 4; each weighed by the mid of the range of denervation per segment, for example, score 1=13%, score 2=38%, score 3=63%, score 4=88%) were divided by all analyzable segments.

Statistical Analysis

Continuous variables are reported as mean±SD or median (25th–75th interquartile range [IQR]). Categorical data are presented as number (percentage). Data were analyzed by means of the Student *t* test or Mann-Whitney *U* test for continuous variables and the Fisher exact test for categorical variables when appropriate. Survival curves were estimated using the Kaplan-Meier method and compared by the log-rank test. Receiver-operating characteristic curve-analysis was performed to determine the optimal cutoff values, defined as the value maximizing the sum of sensitivity and specificity. Bivariate Cox proportional hazard analysis was performed to test the association between the outcome event (sustained VA in the follow-up) and baseline parameters. Due to the low number of events no multivariable analysis was performed. Schoenfeld residuals were used to assess the validity of the Cox regression nonproportionality assumption. All tests were 2-sided, and a value of $P<0.05$ was considered as statistically significant. Statistical analysis was performed using SPSS, version 25 (IBM SPSS, Armonk, NY), R for Windows (version 4.5.0), or GraphPad Prism, version 6.07 (Graphpad, Inc, La Jolla, CA).

RESULTS

Baseline Evaluation

From the 152 patients participating in the Leiden NICM study, 58 patients did not undergo ^{123}I-MIBG imaging, 17 had no LGE-CMR imaging, and in 2 patients regional analysis of ^{123}I-MIBG imaging was not possible due to poor quality (Figure 1). The remaining 75 patients with NICM (79% male, 63 years [IQR, 54–68], LVEF 36% [IQR, 27–44]) were included in the present study. Baseline characteristics, results of PES, and imaging studies are presented in Tables 1 and 2.

Spontaneous sustained VA had been reported or premature ventricular complex/VT ablation had been performed in 24% and 9% of patients, respectively. Most patients were in New York Heart Association (NYHA) functional class I (37%) or II (43%) at baseline. Nonsustained VTs were present on the Holter analyses in 52%. After inclusion, substrate mapping and ablation for VT were performed in 20% (Figure S1).

Late Gadolinium-Enhanced Cardiac Magnetic Resonance Imaging

All 75 patients underwent LGE-CMR, and all 1200 segments could be analyzed. In 35 patients (47%), no LGE was present.

Patients with LGE (n=40, 53%) had a median number of 3 (2–7) segments containing LGE and a 4.4% (2.4–9.6) weighted scar size (percentage of whole LV; Table 2). There was no difference in LVEF, NYHA class, NT-proBNP (N-terminal prohormone of brain natriuretic peptide) levels, devices, or medication at baseline in patients with or without LGE (Tables 1 and 2). However, fewer patients without LGE had sustained VA in their history (9% versus 38%; $P=0.003$), were inducible for VA at PES (20% versus 53%; $P=0.004$), or underwent VT ablation (9% versus 30%; $P=0.02$) during initial admission (Tables 1 and 2).

^{123}I-MIBG Imaging

On ^{123}I-MIBG imaging a median of 94% (81–100) of segments were analyzable. The median global sympathetic denervation (HMR) was 1.7 (1.5–2.0). The median number of DS was 4 (1–6), and the median summed defect score was 22 (14–30; Table 2). There was no difference in global or regional sympathetic denervation parameters between patients without or with LGE (Table 2).

VA During Follow-Up

During a mean follow-up period of 4.5±1.6 years, 26 (35%) patients experienced a sustained VA. Eighteen patients had a monomorphic VT, 5 patients had polymorphic VT/ventricular fibrillation and 3 patients had both. Thirteen patients died; 6 of those patients experienced a cardiac death (2 arrhythmic deaths, 4 due to heart failure).

Of the 40 patients with LGE, 18 (45%) had sustained VA (14/18 only sustained monomorphic VT, 2 of 18 only polymorphic VT/ventricular fibrillation, 2 of 18 both; 6 of 18 had sustained VA after a VT ablation at baseline), and of the 35 patients without LGE, 8 (23%) had sustained VA (4/8 only sustained monomorphic VT, 3/8 only polymorphic VT/ventricular fibrillation, 1/8 both; 1/8 had sustained VA after a VT ablation at baseline) during follow-up (Table 3 and Table S1).

Among patients with sustained VA during follow-up, patients with LGE tended to have more often a history of sustained VT (50% versus 13%; $P=0.099$) and sustained VA inducible at PES (61% versus 25%, $P=0.2$; Table S2) compared with those without LGE. The

Table 1. Baseline Characteristics for All Patients and According to Presence of LGE

	All (n=75)	No LGE (n=35)	LGE (n=40)	*P* value
General				
Male	59 (79)	25 (71)	34 (85)	0.15
Age, y	63 (54–68)	63 (57–68)	63 (53–69)	0.72
BMI, kg/m²	27 (25–28)	27 (25–28)	27 (24–29)	0.69
Comorbidities				
Arterial hypertension	26 (35)	14 (40)	12 (30)	0.36
Diabetes type II	12 (16)	8 (23)	4 (10)	0.13
History of				
Atrial fibrillation/flutter	20 (27)	8 (23)	12 (30)	0.49
Sustained VA	18 (24)	3 (9)	15 (38)	**0.003**
VT ablation	7 (9)	1 (3)	6 (15)	0.11
OHCA	7 (9)	5 (14)	2 (5)	0.24
NYHA	2 (1–2)	2 (1–2)	2 (1–3)	0.32
I	28 (37)	14 (40)	14 (35)	0.66
II	32 (43)	12 (34)	20 (50)	0.17
III	15 (20)	9 (26)	6 (15)	0.25
IV	0 (0)	0 (0)	0 (0)	/
Genetic testing				
Pathogenic or likely pathogenic variant	23 (31)	10 (29)	13 (33)	0.71
Holter analysis				
Presence of nsVTs	33 (52)*	14 (47)*	19 (56)*	0.46
ECG				
QRS duration, ms	116 (103–158)	133 (104–166)	111 (101–137)	0.11
QTc, ms	437±32	439±33	434±32	0.53
Performed ablation at baseline				
VT ablation	15 (20)	3 (9)	12 (30)	**0.02**
PVC ablation	6 (8)	4 (11)	2 (5)	0.41
Any VA ablation	21 (28)	7 (20)	14 (35)	0.15
Device at discharge				
Any device (ICD or CRT)	64 (85)	29 (83)	35 (88)	0.34
CRT	27 (36)	15 (43)	12 (30)	0.25
Laboratory parameters				
eGFR, mL/min per 1.73 m²	84 (72–96)	83 (70–92)	85 (73–97)	0.40
NT-proBNP, ng/mL	621 (148–1500)	481 (172–1642)	629 (148–1204)	0.86
Medication at discharge				
Heart failure medication				
β-Blocker	63 (84)	29 (83)	34 (85)	0.80
ACE inhibitors/ARBs	63 (84)	32 (91)	31 (78)	0.10
Aldosterone antagonist	29 (39)	16 (46)	13 (33)	0.24
Loop diuretics	36 (48)	20 (57)	16 (40)	0.14
Antiarrhythmic drugs				
Class I antiarrhythmics	2 (3)	1 (3)	1 (3)	1.0
Sotalol	8 (11)	4 (11)	4 (10)	1.0
Amiodarone	6 (8)	1 (3)	5 (13)	0.21
Calcium-channel blocker	3 (4)	1 (3)	2 (5)	1.0
Digoxin	6 (8)	3 (9)	3 (8)	1.0

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; OHCA, out-of-hospital cardiac arrest; PVC, premature ventricular complex; VA, ventricular arrhythmia; and VT, ventricular tachycardia.

*Holter data were available in 64 patients (30 in the No LGE group, 34 in the LGE group). The numbers are presented as n (percentage), mean±SD or median (25th–75th percentile). *P* value for the discrimination between patients with or without LGE: a *P* value <0.05 is shown in bold.

Table 2. Results of Programmed Electrical Stimulation (PES) and Imaging Studies

	All (n=75)	No LGE (n=35)	LGE (n=40)	*P* value
PES				
Any sustained VA inducible	28 (37)	7 (20)	21 (53)	**0.004**
SMVT	21 (28)	4 (11)	17 (43)	**0.003**
PVT/VF	7 (9)	3 (9)	4 (10)	1.0
CMR cine				
LVEF, %	36 (27–44)	32 (24–41)	39 (28–47)	0.39
LVEF ≥35%	39 (52)	17 (49)	22 (55)	0.58
LVEDV index, mL/m^2	126±39	124±37	127±41	0.79
LVESV index, mL/m^2	87±40	87±40	86±41	0.98
LV mass, g	125±34	119±32	130±35	0.15
CE-CMR imaging				
No. of segments with LGE	1 (0–4)	…	3 (2–7)	…
Summed scar score	1.0 (0.0–5.0)	…	4.5 (3–9)	…
Weighted scar size (% of whole LV)	0.8 (0.0–4.8)	…	4.4 (2.4–9.6)	…
^{123}I-MIBG imaging				
Global innervation				
HMR	1.7 (1.5–2.0)	1.7 (1.4–2.0)	1.7 (1.5–2.0)	0.98
Wash-out rate, %	29 (18–42)	30 (20–42)	28 (17–43)	0.63
Regional innervation				
No. of denervated segments	4 (1–6)	4 (1–8)	4 (2–6)	0.92
Ratio denervated segments	0.3 (0.1–0.5)	0.3 (0.1–0.5)	0.3 (0.1–0.4)	0.96
Summed defect score	22 (14–30)	20 (14–31)	23 (14–29)	0.95
Weighted denervation size (% of whole LV)	28 (17–37)	25 (17–39)	28 (16–37)	0.94

The numbers are presented as n (percentage), mean±SD or median (IQR). ^{123}I-MIBG indicates 123-iodine meta-iodobenzylguanidine; CE-CMR, contrast-enhanced cardiac magnetic resonance imaging; HMR, heart-to-mediastinum ratio; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; nSVT, nonsustained ventricular tachycardia; PES, programmed electrical stimulation; PVC, premature ventricular complex; PVT/VF, polymorphic ventricular tachycardia or ventricular fibrillation; SMVT, sustained monomorphic ventricular tachycardia; VA, ventricular arrhythmia; and VT, ventricular tachycardia.

P value for the discrimination between patients with or without LGE: a *P* value <0.05 is shown in bold.

number of VA episodes and response to ICD therapy were not different between those with and without LGE (number of VA episodes: 3.0 [IQR, 2.0–6.5] versus 2.0 [IQR, 1.0–3.0], *P*=0.24; successful ATP: 44% versus 50%, *P*=1.0; appropriate ICD shock: 44% versus 63%, *P*=0.67; Table S2). Information for patients without sustained VA during follow-up is presented in Table S3.

VA and Sympathetic Denervation

In patients without LGE, global sympathetic denervation parameters (HMR, wash-out rate) did not differ between patients with or without sustained VA during follow-up (1.6 [IQR, 1.4–2.0] versus 1.7 [IQR, 1.5–2.0], *P*=0.55; Table 3). However, the extent of regional sympathetic denervation was significantly greater in patients with sustained VA compared with those without sustained VA (Table 3), including the number of DS (8 [IQR, 7–10] versus 2 [IQR, 1–5]; *P*=0.004), ratio of DS (0.5 [IQR, 0.5–0.7] versus 0.2 [IQR, 0.1–0.4]; *P*=0.007), the summed defect score (36 [IQR, 30–41] versus 18 [IQR, 14–24]; *P*=0.01), and the weighted denervation size (47% [IQR, 38–54] versus 22% [IQR, 14–30]; *P*=0.01). Using receiver-operating characteristic analysis, a cutoff of ≥7 denervated ^{123}I-MIBG segments identifies those with sustained VA occurrence during follow-up (area under the curve, 0.83; sensitivity, 88%; specificity, 89%; Figure 3). Only 1 patient with <7 DS and 7 of 8 patients with ≥7 DS had sustained VA during follow-up (*P*=0.001; Figure 3 and Table S2). In bivariate analysis only the number of DS was associated with an increased risk of a sustained VA during follow-up in patients without LGE (hazard ratio [HR], 1.25 [95% CI, 1.06–1.46]; *P*=0.006; Table 4). No statistically significant tests for nonproportionality were observed from the Schoenfeld residuals test for the parameters in Table 4.

Among patients with LGE, global and regional sympathetic denervation was not different for those with or without sustained VA (Table 3). In patients with LGE the occurrence of sustained VA during the follow-up was associated with a history of diabetes (HR, 4.73

Table 3. Sustained Ventricular Arrhythmia (VA) During Follow-Up According to Presence of Late Gadolinium Enhancement

	No LGE (n=35)			LGE (n=40)		
	No SVA (n=27)	SVA (nA=8)	*P* value	No SVA (n=22)	SVA (n=18)	*P* value
Genetic testing						
Pathogenic or likely pathogenic variant	8 (30)	2 (25)	1.0	7 (32)	6 (33)	0.9
Holter analysis						
Presence of nsVTs	9 (39)*	5 (71)*	0.2	5 (28)*	14 (88)*	**<0.001**
EP study						
SVA inducible	5 (19)	2 (25)	0.65	10 (46)	11 (61)	0.32
SMVT	2 (7)	2 (25)	0.22	7 (32)	10 (56)	0.13
PVTVF	3 (11)	0 (0)	1.0	3 (14)	1 (6)	0.40
Ablation at admission						
VT ablation	2 (7)	1 (13)	0.55	6 (27)	6 (33)	0.68
CMR cine						
LVEF, %	32 (24–42)	39 (25–41)	0.80	37 (28–48)	39 (27–45)	0.80
LVEF ≥35%	12 (44)	5 (63)	0.44	11 (50)	11 (61)	0.48
LVEDV index, mL/m^2	125±41	122±23	0.79	120±39	136±42	0.23
LVESV index, mL/m^2	87±43	87±30	0.95	83±40	91±44	0.55
LV mass, g	119±34	119±25	0.98	131±32	129±39	0.80
CE-CMR imaging						
No. of segments with LGE	…	…		3.0 (2–5)	4.5 (3–8)	0.16
Summed scar score	…	…		4.0 (2–7)	5.5 (3–10)	0.27
Weighted scar size (% of whole LV)	…	…		4.4 (2.2–7.7)	5.6 (2.4–9.6)	0.33
^{123}I-MIBG imaging						
Global innervation						
HMR	1.7 (1.5–2.0)	1.6 (1.4–2.0)	0.55	1.7 (1.4–2.0)	1.8 (1.5–2.1)	0.55
Wash-out rate, %	27 (20–43)	33 (26–39)	0.63	32 (16–47)	23 (17–39)	0.43
Regional innervation						
No. of denervated segments	2 (1–5)	8 (7–10)	**0.004**	4 (2–6)	3 (1–5)	0.21
Ratio denervated segments	0.2 (0.1–0.4)	0.5 (0.5–0.7)	**0.007**	0.32 (0.13–0.5)	0.19 (0.08–0.36)	0.14
Summed defect score	18 (14–24)	36 (30–41)	**0.01**	24 (15–29)	18 (13–29)	0.31
Weighted denervation size (% of whole LV)	22 (14–30)	47 (38–54)	**0.01**	30 (16–37)	20 (15–36)	0.26

The numbers are presented as n (percentage), mean±SD or median (IQR). ^{123}I-MIBG indicates 123-iodine meta-iodobenzylguanidine; CE-CMR, contrast-enhanced cardiac magnetic resonance imaging; EP, electrophysiological study; HMR, heart-to-mediastinum ratio; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; nsVT, nonsustained ventricular tachycardia; PVC, premature ventricular complexes; PVTVF, polymorphic ventricular tachycardia or ventricular fibrillation; SMVT, sustained monomorphic ventricular tachycardia; SVA, sustained ventricular arrhythmia; and VT, ventricular tachycardia.

*Holter data were available in patients (no LGE, no SVA group: 23 patients, no LGE, SVA group: 7 patients, LGE, no SVA group: 18 patients, no LGE, no SVA group: 16 patients). *P* value for the discrimination between patients with or without SVA: a *P* value <0.05 is shown in bold.

[95% CI, 1.27–17.58]; *P*=0.02), a history of out-of-hospital cardiac arrest (HR, 6.20 [95% CI, 1.25–30.84]; *P*=0.03), nonsustained VTs on 24-hour Holter (HR, 6.60 [95% CI, 1.49–29.17]; *P*=0.01) and the number of affected segments with any LGE (HR, 1.15 [95% CI, 1.03–1.28]; *P*=0.02) in bivariate analysis (Table S4). Both global and regional innervation parameters were not associated with sustained VA in patients with LGE (Table S4).

All results concerning innervation and VA occurrence remained similar when excluding the patients who underwent VT ablation from the analysis (Tables S5 and S6).

DISCUSSION

Main Findings

The present study is the first to analyze regional sympathetic denervation in relation to the occurrence of sustained VA in a prospective cohort of patients with NICM with a dilated or hypokinetic nondilated cardiomyopathy phenotype, excluding patients with an inflammatory cause such as cardiac sarcoidosis. In patients with NICM without LGE on CMR, the extent of regional sympathetic denervation was associated with sustained VA occurrence during follow-up. Denervation of ≥7 segments identified patients at high risk for VA during follow-up. In

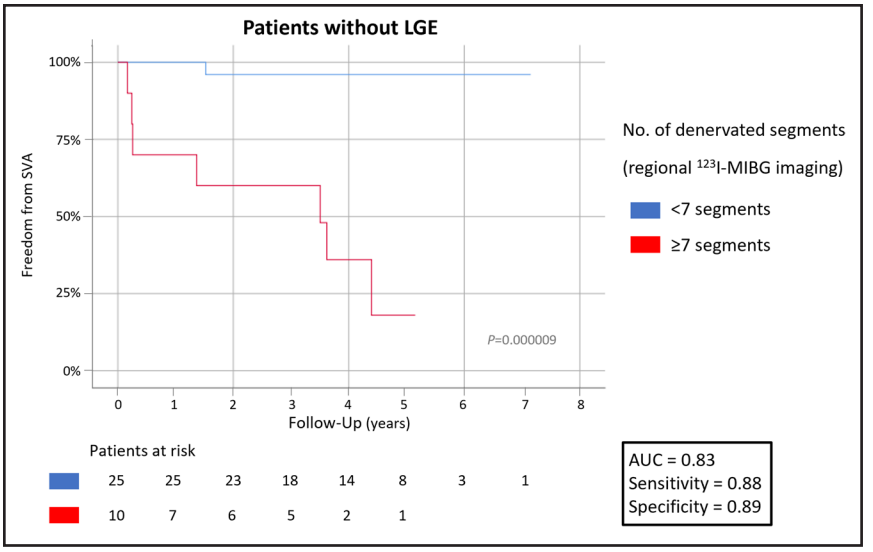

Figure 3. Association between the number of denervated segments in regional 123-iodine meta-iodobenzylguanidine (^{123}I-MIBG) imaging and sustained ventricular arrhythmias (VA) during follow-up in patients without late gadolinium enhancement (LGE).
A regional sympathetic denervation of ≥7 segments was associated with sustained VA during a mean follow-up period of 4.5±1.6 years. AUC indicates area under the curve.

contrast, in patients with LGE global and regional denervation was not associated with sustained VA.

Arrhythmic Risk Prediction and LGE in Patients With NICM

In addition to the LVEF, LGE on CMR imaging has been identified as an important predictor of ventricular arrhythmia events in patients with NICM.[29–31] Interestingly, the location and pattern of LGE may further refine the risk prediction for arrhythmic events.[11,32,33]

Other reported risk factors for life-threatening VA in patients with NICM include younger age, hypertension, LV dilatation, history of sustained VA and out-of-hospital cardiac arrest, and the presence of pathogenic or likely pathogenic variants in genes associated with VA.[2] However, patients with NICM form a heterogeneous group with different potential VA substrates, not all related to areas of replacement fibrosis, identifiable by LGE-CMR.[34]

The present study found that 45% of patients with LGE, but also 23% without LGE experienced a sustained VA during follow-up. These data support the association between LGE and sustained VA but also show that the absence of LGE does not exclude sustained VA during follow-up. In patients without LGE, there appeared to be no association between VA inducibility, nonsustained VTs on Holter monitoring, LVEF, and VA occurrence. This emphasizes the particularly challenging risk stratification in this subgroup of patients with NICM.

Arrhythmic Risk Prediction and Sympathetic Innervation in Patients With NICM

The present study has used different parameters to analyze the impact of regional sympathetic innervation of the left ventricle in patients with NICM. The number of DS and specifically, the presence of >7 DS (of 17 segments), which is easily to determine in clinical practice, could identify a patient at risk for sustained VA in patients without LGE. Other parameters, such as the ratio of DS, summed defect score, and weighted denervation size, also provided comparable but not superior results (based on receiver-operating characteristic and bivariate

Table 4. Parameters Associated With Sustained VA in Patients Without Late Gadolinium Enhancement

	Any sustained ventricular arrhythmia	
	HR (95% CI)	*P* value
Bivariate analysis		
Male	2.35 (0.28–19.51)	0.43
Age, per 1 y	1.07 (0.96–1.20)	0.22
History of sustained VT	3.53 (0.39–31.67)	0.26
History of OHCA	2.41 (0.49–12.00)	0.28
QRS, per 1 ms	0.99 (0.97–1.01)	0.30
QTc, per 1 ms	1.00 (0.98–1.02)	0.77
eGFR MDRD, per 1 mL/min	1.01 (1.00–1.01)	0.16
LVEF, per 1%	1.00 (0.95–1.05)	1.00
NT-proBNP, per 1 ng/mL	1.00 (1.00–1.00)	0.89
nSVT on Holter	3.27 (0.63–16.96)	0.16
Pathogenic mutation (class IV/V)	0.83 (0.17–4.13)	0.82
EP study at baseline: sustained VA inducible	1.93 (0.39–9.69)	0.42
^{123}I-MIBG imaging global: HMR >1.8	1.05 (0.25–4.47)	0.95
^{123}I-MIBG imaging regional: no. of denervated segments, per 1 segment	1.25 (1.06–1.46)	**0.006**
^{123}I-MIBG imaging regional: ≥7 denervated segments	25.4 (3.10–208.45)	**0.003**

^{123}I-MIBG indicates123-iodine meta-iodobenzylguanidine; eGFR, estimated glomerular filtration rate calculated using the modification of diet in renal disease (MDRD)-formula; EP, electrophysiological study; HMR, heart-to-mediastinum ratio; HR, hazard ratio; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; nSVT, nonsustained ventricular tachycardia; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OHCA, out-of-hospital cardiac arrest; VA, ventricular arrhythmia; VT, ventricular tachycardia. A *P* value <0.05 is shown in bold.

analyses [data not shown]) and require more detailed analysis. The underlying mechanisms leading to denervation in patients with NICM have not been described and are currently unknown. Previous studies on sympathetic innervation and arrhythmic risk prediction were mainly conducted in patients with ischemic cardiomyopathy or in a mixed group of patients with ischemic cardiomyopathy and NICM.[35] In studies investigating patients with NICM, global denervation has been associated with adverse outcomes (combined end points including cardiac deaths, rehospitalization for heart failure, implantation of a left ventricular assist device, and arrhythmias) or with sudden death when combining global denervation with late ventricular potentials.[19,20,36] However, in the present study, global sympathetic denervation did not predict sustained VA in NICM.

This is in line with a prior study in which HMR was also not correlated with global denervation.[16] Studies that did report an association between global denervation and combined cardiac end points have mainly included patients with severe LV dysfunction.[20,37] The impact of global denervation on VA occurrence may differ in patients with mild or moderate LV dysfunction, which was a majority in our study. Two prior studies have described an association between the extent of regional denervation and cardiac death[21] or a combined end point of cardiac death or hospitalization and admission to hospital due to heart failure or arrhythmia.[22] Regional denervation as a predictor of sustained VA has not been reported before. The most important mechanism of VT in patients with LGE is scar-related reentry. Compact replacement fibrosis detectable by LGE-CMR may serve as 1 VT substrate. In ischemic cardiomyopathy denervation has been observed within the infarct core and adjacent viable myocardium.[38–41] Regional extent of LGE was a significant and independent predictor of regional sympathetic denervation in a cohort of patients with nonischemic heart failure and relatively preserved function,[24] suggesting that denervation may coincide with replacement fibrosis in subgroups of patients with NICM. In this context, it is interesting to speculate that in patients without LGE, the mechanism for VT may be fundamentally different. Nonhomogeneous innervation may result in regional differences in depolarization and repolarization gradients, contributing to arrhythmogenicity.[42–44] The numbers are small, but the trend toward faster VT, close to the ventricular refractory period responding to ATP, in patients without LGE compared with those with LGE, may support functional reentry as the underlying mechanism. It has recently been shown that heterogeneous cardiac sympathetic innervation gradients together with spatially inhomogeneous innervation promote arrhythmogenesis in murine dilated cardiomyopathy.[45] However, the underlying pathophysiologic mechanisms leading to the regional differences, their relevance for arrhythmogenesis in humans, and the potential underlying mechanism for VA with implications for treatment are not well understood yet.

Limitations

This hypothesis-generating study was performed in a tertiary referral center with a large interventional program for VA and a potential selection bias toward patients with LGE and prior VA. The study describes a relatively small cohort with a low number of events (sustained VA) during the follow-up period, particularly in the group without LGE. Further studies in larger patient cohorts are needed to determine the relevance of sympathetic innervation imaging on arrhythmic outcomes in patients with NICM. At baseline, catheter ablation for VA was performed in 30% of the patients with LGE, so the occurrence of VA, and possible relation with regional denervation may be underestimated in the LGE group. However, as VT ablation was performed more often in those with LGE, it is not likely that VT ablation changes our results in patients without LGE.

Conclusions

In patients with NICM without LGE, arrhythmic risk prediction is challenging. In this study, regional sympathetic denervation was found to be associated with sustained VA occurrence in patients without LGE, but not in patients with LGE. Larger, prospective studies are required to evaluate whether this parameter contributes to arrhythmic risk stratification.

ARTICLE INFORMATION

Received June 11, 2024; accepted June 24, 2025.

Affiliations

Department of Cardiology, Leiden University Medical Centre, the Netherlands (C.J., H.S.C., A.P.W., A.M., S.R.P., Y.K., A.F.A.A., A.J.H.A.S., M.R.M.J., K.Z.). Willem Einthoven Center of Arrhythmia Research and Management (WECAM), Leiden, the Netherlands (C.J., H.S.C., A.P.W., A.M., S.R.P., Y.K., A.F.A.A., A.J.H.A.S., M.R.M.J., K.Z.). West German Heart and Vascular Center, Department of Cardiology and Vascular Medicine, University Hospital Essen, Germany (C.J.). Department of Anatomy & Embryology, Leiden University Medical Centre, the Netherlands (H.S.C., M.R.M.J.). Department of Radiology, Leiden University Medical Center, the Netherlands (P.D.S., R.J.v.d.G., L.F.d.G.O., H.J.L.). Biomedical Photonic Imaging Group, University of Twente, Enschede, the Netherlands (L.F.d.G.O.). Department of Radiation Science & Technology, Delft University of Technology, the Netherlands (L.F.d.G.O.). Department of Biomedical Data Sciences, Leiden University Medical Center, the Netherlands (B.J.A.M.).

Sources of Funding

Dr Jungen is funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Projektnummer 447558597 and by the BMFTR (Federal Ministry of Research, Technology and Space) Advanced Clinician Scientist Programme UMEA² (01EO2104).

Disclosures

None.

Supplemental Material

Tables S1–S6
Figure S1

REFERENCES

1. Sammani A, Baas AF, Asselbergs FW, Te Riele ASJM. Diagnosis and risk prediction of dilated cardiomyopathy in the era of big data and genomics. *J Clin Med*. 2021;10:921. doi: 10.3390/jcm10050921
2. Sammani A, Kayvanpour E, Bosman LP, Sedaghat-Hamedani F, Proctor T, Gi WT, Broezel A, Jensen K, Katus HA, Te Riele ASJM, et al. Predicting sustained ventricular arrhythmias in dilated cardiomyopathy: a meta-analysis and systematic review. *ESC Heart Fail*. 2020;7:1430–1441. doi: 10.1002/ehf2.12689
3. Di Marco A, Anguera I, Schmitt M, Klem I, Neilan TG, White JA, Sramko M, Masci PG, Barison A, McKenna P, et al. Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. *JACC Heart Fail*. 2017;5:28–38. doi: 10.1016/j.jchf.2016.09.017
4. Akhtar M, Elliott PM. Risk stratification for sudden cardiac death in non-ischaemic dilated cardiomyopathy. *Curr Cardiol Rep*. 2019;21:155. doi: 10.1007/s11886-019-1236-3
5. Goldberger JJ, Subacius H, Patel T, Cunnane R, Kadish AH. Sudden cardiac death risk stratification in patients with nonischemic dilated cardiomyopathy. *J Am Coll Cardiol*. 2014;63:1879–1889. doi: 10.1016/j.jacc.2013.12.021
6. Halliday BP, Baksi AJ, Gulati A, Ali A, Newsome S, Izgi C, Arzanauskaite M, Lota A, Tayal U, Vassiliou VS, et al. Outcome in dilated cardiomyopathy related to the extent, location, and pattern of late gadolinium enhancement. *JACC Cardiovasc Imaging*. 2019;12:1645–1655. doi: 10.1016/j.jcmg.2018.07.015
7. Gulati A, Jabbour A, Ismail TF, Guha K, Khwaja J, Raza S, Morarji K, Brown TD, Ismail NA, Dweck MR, et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA*. 2013;309:896–908. doi: 10.1001/jama.2013.1363
8. Becker MAJ, Cornel JH, van de Ven PM, van Rossum AC, Allaart CP, Germans T. The prognostic value of late gadolinium-enhanced cardiac magnetic resonance imaging in nonischemic dilated cardiomyopathy: a review and meta-analysis. *JACC Cardiovasc Imaging*. 2018;11:1274–1284. doi: 10.1016/j.jcmg.2018.03.006
9. Halliday BP, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaite M, Vassiliou VS, Lota A, Izgi C, Tayal U, et al. Association between midwall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. *Circulation*. 2017;135:2106–2115. doi: 10.1161/CIRCULATIONAHA.116.026910
10. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, et al; ESC Scientific Document Group. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43:3997–4126. doi: 10.1093/eurheartj/ehac262
11. Di Marco A, Brown PF, Bradley J, Nucifora G, Claver E, de Frutos F, Dallaglio PD, Comin-Colet J, Anguera I, Miller CA, et al. Improved risk stratification for ventricular arrhythmias and sudden death in patients with non-ischemic dilated cardiomyopathy. *J Am Coll Cardiol*. 2021;77:2890–2905. doi: 10.1016/j.jacc.2021.04.030
12. Klem I, Klein M, Khan M, Yang EY, Nabi F, Ivanov A, Bhatti L, Hayes B, Graviss EA, Nguyen DT, et al. Relationship of LVEF and myocardial scar to long-term mortality risk and mode of death in patients with nonischemic cardiomyopathy. *Circulation*. 2021;143:1343–1358. doi: 10.1161/CIRCULATIONAHA.120.048477
13. Voskoboinik A, Wong MCG, Elliott JK, Costello BT, Prabhu S, Mariani JA, Kalman JM, Kistler PM, Taylor AJ, Morton JB. Absence of late gadolinium enhancement on cardiac magnetic resonance imaging in ventricular fibrillation and nonischemic cardiomyopathy. *Pacing Clin Electrophysiol*. 2018;41:1109–1115. doi: 10.1111/pace.13426
14. Chen HS, Jungen C, Kimura Y, Dibbets-Schneider P, Piers SR, Androulakis AFA, van der Geest RJ, de Geus-Oei LF, Scholte AJHA, Lamb HJ, et al. Ventricular arrhythmia substrate distribution and its relation to sympathetic innervation in nonischemic cardiomyopathy patients. *JACC Clin Electrophysiol*. 2022;8:1234–1245. doi: 10.1016/j.jacep.2022.07.006
15. Verschure DO, de Groot JR, Mirzaei S, Gheysens O, Nakajima K, van Eck-Smit BLF, Aernout Somsen G, Verberne HJ. Cardiac (123)I-mIBG scintigraphy is associated with freedom of appropriate ICD therapy in stable chronic heart failure patients. *Int J Cardiol*. 2017;248:403–408. doi: 10.1016/j.ijcard.2017.08.003
16. Kasama S, Toyama T, Sumino H, Nakazawa M, Matsumoto N, Sato Y, Kumakura H, Takayama Y, Ichikawa S, Suzuki T, et al. Prognostic value of serial cardiac 123I-MIBG imaging in patients with stabilized chronic heart failure and reduced left ventricular ejection fraction. *J Nucl Med*. 2008;49:907–914. doi: 10.2967/jnumed.107.047548
17. Yamamoto H, Yamada T, Tamaki S, Morita T, Furukawa Y, Iwasaki Y, Kawasaki M, Kikuchi A, Kondo T, Ozaki T, et al. Prediction of sudden cardiac death in patients with chronic heart failure by regional washout rate in cardiac MIBG SPECT imaging. *J Nucl Cardiol*. 2019;26:109–117. doi: 10.1007/s12350-017-0913-0
18. Tamaki S, Yamada T, Okuyama Y, Morita T, Sanada S, Tsukamoto Y, Masuda M, Okuda K, Iwasaki Y, Yasui T, et al. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction: results from a comparative study with signal-averaged electrocardiogram, heart rate variability, and QT dispersion. *J Am Coll Cardiol*. 2009;53:426–435. doi: 10.1016/j.jacc.2008.10.025
19. Kasama S, Toyama T, Kaneko Y, Iwasaki T, Sumino H, Kumakura H, Minami K, Ichikawa S, Matsumoto N, Sato Y, et al. Relationship between late ventricular potentials and myocardial 123I-metaiodobenzylguanidine scintigraphy in patients with dilated cardiomyopathy with mild to moderate heart failure: results of a prospective study of sudden death events. *Eur J Nucl Med Mol Imaging*. 2012;39:1056–1064. doi: 10.1007/s00259-012-2092-1
20. Chimura M, Yamada S, Taniguchi Y, Yasaka Y, Kawai H. Late gadolinium enhancement on cardiac magnetic resonance combined with 123I-metaiodobenzylguanidine scintigraphy strongly predicts long-term clinical outcome in patients with dilated cardiomyopathy. *PLoS One*. 2019;14:e0217865. doi: 10.1371/journal.pone.0217865
21. Clements IP, Kelkar AA, Garcia EV, Butler J, Chen J, Folks R, Jacobson AF. Prognostic significance of (123)I-mIBG SPECT myocardial imaging in heart failure: differences between patients with ischaemic and non-ischaemic heart failure. *Eur Heart J Cardiovasc Imaging*. 2016;17:384–390. doi: 10.1093/ehjci/jev295
22. Fujimoto S, Inoue A, Hisatake S, Yamashina S, Yamashina H, Nakano H, Yamazaki J. Usefulness of meta-[123I]iodobenzylguanidine myocardial scintigraphy for predicting cardiac events in patients with dilated cardiomyopathy who receive long-term beta blocker treatment. *Nucl Med Commun*. 2005;26:97–102. doi: 10.1097/00006231-200502000-00003
23. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–542. doi: 10.1161/hc0402.102975
24. Aikawa T, Naya M, Obara M, Oyama-Manabe N, Manabe O, Magota K, Ito YM, Katoh C, Tamaki N. Regional interaction between myocardial sympathetic denervation, contractile dysfunction, and fibrosis in heart failure with preserved ejection fraction: (11)C-hydroxyephedrine PET study. *Eur J Nucl Med Mol Imaging*. 2017;44:1897–1905. doi: 10.1007/s00259-017-3760-y
25. Piers SR, Androulakis AF, Yim KS, van Rein N, Venlet J, Kapel GF, Siebelink HM, Lamb HJ, Cannegieter SC, Man SC, et al. Nonsustained ventricular tachycardia is independently associated with sustained ventricular arrhythmias in nonischemic dilated cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2022;15:e009979. doi: 10.1161/CIRCEP.121.009979
26. Piers SR, Askar SF, Venlet J, Androulakis AF, Kapel GF, de Riva Silva M, Jongbloed JJ, van Tintelen JP, Schalij MJ, Pijnappels DA, et al. QRS prolongation after premature stimulation is associated with polymorphic ventricular tachycardia in nonischemic cardiomyopathy: results from the leiden nonischemic cardiomyopathy study. *Heart Rhythm*. 2016;13:860–869. doi: 10.1016/j.hrthm.2015.12.021
27. van Werkhoven JM, de Boer SM, Schuijf JD, Cademartiri F, Maffei E, Jukema JW, Boogers MJ, Kroft LJ, de Roos A, Bax JJ. Impact of clinical presentation and pretest likelihood on the relation between calcium score and computed tomographic coronary angiography. *Am J Cardiol*. 2010;106:1675–1679. doi: 10.1016/j.amjcard.2010.08.014
28. Boogers MJ, Borleffs CJ, Henneman MM, van Bommel RJ, van Ramshorst J, Boersma E, Dibbets-Schneider P, Stokkel MP, van der Wall EE, Schalij MJ, et al. Cardiac sympathetic denervation assessed with 123-iodine metaiodobenzylguanidine imaging predicts ventricular arrhythmias in implantable cardioverter-defibrillator patients. *J Am Coll Cardiol*. 2010;55:2769–2777. doi: 10.1016/j.jacc.2009.12.066
29. Lehrke S, Lossnitzer D, Schob M, Steen H, Merten C, Kemmling H, Pribe R, Ehlermann P, Zugck C, Korosoglou G, et al. Use of cardiovascular magnetic resonance for risk stratification in chronic heart failure: prognostic value of late gadolinium enhancement in patients with non-ischaemic dilated cardiomyopathy. *Heart*. 2011;97:727–732. doi: 10.1136/hrt.2010.205542
30. Neilan TG, Coelho-Filho OR, Danik SB, Shah RV, Dodson JA, Verdini DJ, Tokuda M, Daly CA, Tedrow UB, Stevenson WG, et al. CMR quantification

of myocardial scar provides additive prognostic information in nonischemic cardiomyopathy. *JACC Cardiovasc Imaging*. 2013;6:944–954. doi: 10.1016/j.jcmg.2013.05.013
31. Wu KC, Weiss RG, Thiemann DR, Kitagawa K, Schmidt A, Dalal D, Lai S, Bluemke DA, Gerstenblith G, Marban E, et al. Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. *J Am Coll Cardiol*. 2008;51:2414–2421. doi: 10.1016/j.jacc.2008.03.018
32. Purmah Y, Cornhill A, Lei LY, Dykstra S, Mikami Y, Satriano A, Labib D, Flewitt J, Rivest S, Sandonato R, et al. Mid-wall striae fibrosis predicts heart failure admission, composite heart failure events, and life-threatening arrhythmias in dilated cardiomyopathy. *Sci Rep*. 2022;12:1739. doi: 10.1038/s41598-022-05790-y
33. Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, Sheppard MN, Poole-Wilson PA, Pennell DJ. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol*. 2006;48:1977–1985. doi: 10.1016/j.jacc.2006.07.049
34. Muser D, Nucifora G, Castro SA, Enriquez A, Chahal CAA, Magnani S, Kumareswaran R, Arkles J, Supple G, Schaller R, et al. Myocardial substrate characterization by CMR T(1) mapping in patients with NICM and No LGE undergoing catheter ablation of VT. *JACC Clin Electrophysiol*. 2021;7:831–840. doi: 10.1016/j.jacep.2020.10.002
35. Pontico M, Brunotti G, Conte M, Corica F, Cosma L, De Angelis C, De Feo MS, Lazri J, Matto A, Montebello M, et al. The prognostic value of (123)I-mIBG SPECT cardiac imaging in heart failure patients: a systematic review. *J Nucl Cardiol*. 2022;29:1799–1809. doi: 10.1007/s12350-020-02501-w
36. Nagamatsu H, Momose M, Kobayashi H, Kusakabe K, Kasanuki H. Prognostic value of 123I-metaiodobenzylguanidine in patients with various heart diseases. *Ann Nucl Med*. 2007;21:513–520. doi: 10.1007/s12149-007-0062-7
37. Sood N, Al Badarin F, Parker M, Pullatt R, Jacobson AF, Bateman TM, Heller GV. Resting perfusion MPI-SPECT combined with cardiac 123I-mIBG sympathetic innervation imaging improves prediction of arrhythmic events in non-ischemic cardiomyopathy patients: sub-study from the ADMIRE-HF trial. *J Nucl Cardiol*. 2013;20:813–820. doi: 10.1007/s12350-013-9750-y
38. Barber MJ, Mueller TM, Henry DP, Felten SY, Zipes DP. Transmural myocardial infarction in the dog produces sympathectomy in noninfarcted myocardium. *Circulation*. 1983;67:787–796. doi: 10.1161/01.cir.67.4.787
39. Chen HS, Voortman LM, van Munsteren JC, Wisse LJ, Tofig BJ, Kristiansen SB, Glashan CA, DeRuiter MC, Zeppenfeld K, Jongbloed MRM. Quantification of large transmural biopsies reveals heterogeneity in innervation patterns in chronic myocardial infarction. *JACC Clin Electrophysiol*. 2023;9:1652–1664. doi: 10.1016/j.jacep.2023.04.021
40. Vaseghi M, Lux RL, Mahajan A, Shivkumar K. Sympathetic stimulation increases dispersion of repolarization in humans with myocardial infarction. *Am J Physiol Heart Circ Physiol*. 2012;302:H1838–H1846. doi: 10.1152/ajpheart.01106.2011
41. Yokoyama T, Lee JK, Miwa K, Opthof T, Tomoyama S, Nakanishi H, Yoshida A, Yasui H, Iida T, Miyagawa S, et al. Quantification of sympathetic hyperinnervation and denervation after myocardial infarction by three-dimensional assessment of the cardiac sympathetic network in cleared transparent murine hearts. *PLoS One*. 2017;12:e0182072. doi: 10.1371/journal.pone.0182072
42. Olivas A, Gardner RT, Wang L, Ripplinger CM, Woodward WR, Habecker BA. Myocardial infarction causes transient cholinergic transdifferentiation of cardiac sympathetic nerves via gp130. *J Neurosci*. 2016;36:479–488. doi: 10.1523/JNEUROSCI.3556-15.2016
43. Ieda M, Kanazawa H, Kimura K, Hattori F, Ieda Y, Taniguchi M, Lee JK, Matsumura K, Tomita Y, Miyoshi S, et al. Sema3a maintains normal heart rhythm through sympathetic innervation patterning. *Nat Med*. 2007;13:604–612. doi: 10.1038/nm1570
44. Vaseghi M, Yamakawa K, Sinha A, So EL, Zhou W, Ajijola OA, Lux RL, Laks M, Shivkumar K, Mahajan A. Modulation of regional dispersion of repolarization and T-peak to T-end interval by the right and left stellate ganglia. *Am J Physiol Heart Circ Physiol*. 2013;305:H1020–H1030. doi: 10.1152/ajpheart.00056.2013
45. Dajani AJ, Liu MB, Olaopa MA, Cao L, Valenzuela-Ripoll C, Davis TJ, Poston MD, Smith EH, Contreras J, Pennino M, et al. Heterogeneous cardiac sympathetic innervation gradients promote arrhythmogenesis in murine dilated cardiomyopathy. *JCI Insight*. 2023;8:e157956. doi: 10.1172/jci.insight.157956