Nonsustained ventricular tachycardia is independently associated with sustained ventricular arrhythmias in nonischemic dilated cardiomyopathy

Piers, S.R.; Androulakis, A.F.; Yim, K.S.; Rein, N. van; Venlet, J.; Kapel, G.F.; ... ; Zeppenfeld, K.

Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Nonsustained Ventricular Tachycardia Is Independently Associated With Sustained Ventricular Arrhythmias in Nonischemic Dilated Cardiomyopathy

Sebastiaan R. Piers, MD, PhD; Alexander F. Androulakis, MD; Kevin S. Yim, BS; Nienke van Rein, PharmD, PhD; Jeroen Venlet, MD; Gijsbert F. Kapel, MD, PhD; Hans-Marc Siebelink, MD, PhD; Hildo J. Lamb, MD, PhD; Suzanne C. Cannegieter, MD, PhD; Sum-Che Man, PhD; Katja Zeppenfeld, MD, PhD

BACKGROUND: Spontaneous nonsustained ventricular tachycardia (NSVT) on Holter, VT inducibility during electrophysiology study, and late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) have been associated with sustained ventricular arrhythmias (SVAs) in nonischemic dilated cardiomyopathy (DCM). This study aimed to analyze whether these parameters carry independent prognostic value for spontaneous SVA in DCM.

METHODS: Between 2011 and 2018, patients with the DCM clinical spectrum and documented SVA, suspected SVA, or considered to be at intermediate or high risk for SVA were enrolled in the prospective Leiden Nonischemic Cardiomyopathy Study. Patients underwent a comprehensive evaluation including 24-hour Holter, LGE-CMR, and electrophysiology study. Holters were assessed for the presence of NSVT (≥3 beats; rate, ≥120 bpm; lasting <30 s) and NSVT characteristics (coupling interval, duration, cycle length, morphology, regularity). Patients were followed at 6 to 12 monthly intervals.

RESULTS: Of all 115 patients (age, 59±12 years; 77% men; left ventricular ejection fraction, 33±13%; history of SVA, 36%; LGE in 63%; median LGE mass, 13 g; interquartile range, 8–23 g), 62 (54%) had NSVT on Holter, and sustained monomorphic VT was inducible in 34 of 114 patients (30%). NSVT was not associated with LGE on CMR or VT inducibility during electrophysiology study nor were its features (all $P>0.05$). During 4.0±1.8 years of follow-up, SVA occurred in 39 patients (34%). NSVT (HR, 4.47 [95% CI, 1.87–10.72]; $P=0.001$) and VT inducibility (HR, 3.08 [95% CI, 1.08–8.81]; $P=0.036$) were independently associated with SVA during follow-up. A bivariable model including only noninvasively acquired parameters also allowed identification of a high-risk subgroup (ie, those with both NSVT and LGE on CMR). The findings remained similar when only patients without prior SVA were included.

CONCLUSIONS: In patients with DCM, NSVT on Holter and VT inducibility during electrophysiology study predict SVA during follow-up independent of LGE on CMR. NSVTs may serve as an initiator, and sustained VT inducibility indicates the presence of the substrate for SVA in DCM.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01940081.

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

Key Words: death, sudden, cardiac ■ electrocardiography, ambulatory ■ follow-up studies ■ tachycardia, ventricular ■ ventricular fibrillation

Correspondence to: Katja Zeppenfeld, MD, PhD, Department of Cardiology (B4-P), Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, the Netherlands. Email k.zeppenfeld@lumc.nl

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCEP.121.009979.
For Sources of Funding and Disclosures, see page 124.

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

WHAT IS KNOWN?

- Spontaneous nonsustained ventricular tachycardia (VT) on Holter, VT inducibility during electrophysiology study, and late gadolinium enhancement on cardiac magnetic resonance have been associated with sustained ventricular arrhythmias during follow-up in nonischemic dilated cardiomyopathy.

WHAT THE STUDY ADDS

- Nonsustained VT on Holter and VT inducibility during electrophysiology study are powerful predictors of sustained ventricular arrhythmias, independent of late gadolinium enhancement on cardiac magnetic resonance.
- Nonsustained VTs in nonischemic dilated cardiomyopathy are typically short, predominantly irregular, slower than induced and spontaneous sustained VTs, and not related to late gadolinium enhancement on cardiac magnetic resonance, suggesting that nonsustained VTs are a different entity and not merely a short version of sustained monomorphic VTs.

Nonstandard Abbreviations and Acronyms

CMR	cardiac magnetic resonance
DCM	nonischemic dilated cardiomyopathy
EPS	electrophysiology study
ICD	implantable cardioverter defibrillator
IQR	interquartile range
LGE	late gadolinium enhancement
LV	left ventricle
LVEF	left ventricular ejection fraction
NSVT	nonsustained ventricular tachycardia
NT-proBNP	N-terminal pro-B-type natriuretic peptide
SVA	sustained ventricular arrhythmia

Nonsustained ventricular tachycardia (NSVT) on Holter and VT inducibility during electrophysiology study (EPS) have been associated with an increased risk for ventricular arrhythmias and sudden cardiac death in nonischemic dilated cardiomyopathy (DCM).[1–5] Similarly, the presence of myocardial scar, as assessed by late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging, has been demonstrated to predict appropriate implantable cardioverter defibrillator (ICD) therapy, sudden cardiac death, and all-cause mortality in patients with DCM.[6–9]

Sustained monomorphic VTs have been attributed to reentrant activity in areas with myocardial scar, which is based on VT ablation studies that have localized critical VT isthmus sites to areas with LGE on CMR.[10] It is unclear whether NSVTs are similar (but shorter) reentrant tachycardias related to the presence of LGE on CMR or a distinct phenomenon not related to confluent area of fibrosis detectable by LGE-CMR but which may initiate sustained reentrant VT.

In the Leiden Nonischemic Cardiomyopathy Study, patients with DCM underwent a comprehensive evaluation including a 24-hour Holter, transthoracic echocardiography, LGE-CMR, exercise testing, blood sampling, invasive EPS, endomyocardial biopsy, and genetic analysis of 55 cardiomyopathy-related genes.

This study aimed to (1) compare the characteristics of NSVT on Holter, inducible sustained VTs during EPS, and sustained ventricular arrhythmias (SVAs) during follow-up and (2) to analyze whether NSVT on Holter, VT inducibility during EPS, and LGE on CMR have independent prognostic value for spontaneous SVA in DCM.

METHODS

Patients

The Leiden Nonischemic Cardiomyopathy Study is a single-center prospective cohort study designed to analyze substrates and mechanisms of ventricular arrhythmias in DCM (https://www.clinicaltrials.gov; unique identifier: NCT01940081). Between October 2011 and September 2018, a total of 148 patients aged 18 to 80 years with the idiopathic DCM clinical spectrum[11] and documented SVA, suspected SVA (eg, because of out-of-hospital cardiac arrest, palpitations, or syncope), or considered to be at intermediate or high risk for SVA were enrolled. The DCM clinical spectrum includes both dilation/nondilation and hypokinetic/nonhypokinetic phenotypes.[11] A high risk of SVA was defined as a left ventricular ejection fraction (LVEF) of ≤35%; an intermediate risk was defined as an LVEF of 36% to 50% and late enhancement on LGE-CMR. Exclusion criteria were inability to understand the nature and risks of the study procedures, inability to comply with the protocol owing to hemodynamic instability, pregnancy, and other cardiomyopathies (eg, previous myocardial infarction, tachycardiomyopathy, cardiac sarcoidosis, infiltrative cardiac disease such as amyloidosis, Chagas cardiomyopathy, arrhythmogenic RV cardiomyopathy, hypertrophic cardiomyopathy, noncompaction cardiomyopathy, and congenital heart disease).

Patients underwent a comprehensive evaluation including transthoracic echocardiography, LGE-CMR, ambulatory 24-hour Holter monitoring, exercise testing, blood sampling, invasive EPS, endomyocardial biopsy, iodine-123 metaiodobenzylguanidine scan, and genetic analysis of ≥55 cardiomyopathy-related genes. Targeted next-generation sequencing of these 55 genes, a list of which is provided in the Supplemental Methods, was performed analyzing 151-bp paired-end reads on an Illumina MiSeq sequencer, as described previously.[12]

Premature ventricular contraction or VT ablation and ICD implantation were performed if clinically indicated. In the present study, all patients who underwent ambulatory 24-hour Holter at baseline were included.

The study protocol was approved by the local ethics committee and by the appropriate national ethics committee. All

patients provided written informed consent. Patients who refused endomyocardial biopsy or metaiodobenzylguanidine scans but agreed with all other study procedures were allowed to participate. To maintain patient confidentiality, data and study materials will not be made available to other researchers for purposes of replicating the results.

Holter Acquisition and Analyses

Ninety-five of 115 patients (83%) underwent ambulatory 24-hour Holter at the Leiden University Medical Center using SEER Light Compact Digital Holter Systems (General Electric Healthcare, Chicago, IL), which provides a 3-lead ECG recording based on 7 electrodes. These digital Holter data allowed a detailed evaluation of NSVT and its characteristics. The remaining 20 of 115 patients (17%) underwent 24-hour Holter monitoring at the referring center. These Holter recordings were not digitally available and were, therefore, only evaluated for the presence of any NSVT.

The Leiden University Medical Center Holter data were digitally stored and analyzed using MARS V8 SP5 ambulatory ECG analysis system (General Electric Healthcare). Episodes with ≥3 consecutive ventricular beats were automatically classified as ventricular runs. The ventricular runs were manually reviewed in all patients up to a maximum of 22 runs per patient, including the fastest and longest run. If the total number of runs exceeded 22 (fastest, longest, >20 other runs), 20 runs were randomly selected using a random number generator. All selected runs were manually reviewed and classified as NSVT, accelerated idioventricular rhythm, or other (eg, supraventricular arrhythmia, aberrancy, paced beats, noise). Nonsustained VT was defined as ≥3 consecutive beats arising below the atrioventricular node with a rate ≥120 beats per minute and lasting <30 seconds. Accelerated idioventricular rhythm was defined as ≥3 consecutive beats arising below the atrioventricular node with a rate <120 beats per minute.

The following features were reported for each NSVT:

1. Coupling interval of the first beat, measured from the onset of the previous QRS complex to the onset of the first NSVT beat
2. Coupling interval exceeding QT interval, in ms
3. Duration, in number of beats
4. Cycle length, in ms
5. Morphology, classified as monomorphic, pleomorphic (defined as 2 QRS morphologies), or polymorphic (defined as continuously changing morphology).
6. NSVT regularity (regular defined as ≤10% versus >10% beat-to-beat variability).

Patients were categorized as having predominantly regular or irregular and predominantly monomorphic NSVTs if ≥75% of episodes fulfilled the criterion.

It was not possible to use ICD interrogation data to corroborate Holter data, as device-recorded NSVT definitions (both duration and rate) vary among manufacturers and models, and the majority of tracings was not available or overwritten.

LGE-CMR Acquisition and Analysis

CMR imaging included cine and LGE images in long and short axes. Left ventricular (LV) and RV volumes were assessed and indexed to body surface area. Myocardial scar was considered to be present only if LGE was visible in 2 orthogonal views. LGE was defined by signal intensity ≥35% of the maximal myocardial signal intensity and subdivided into core (≥50% of the maximal signal intensity) and border zone (35%–50% of the maximal signal intensity).[13] Details are provided in the Supplemental Methods.

Heart Failure Severity

The severity of heart failure was quantified using (1) the New York Heart Association functional class, (2) maximal oxygen consumption during exercise test, (3) NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels, and (4) CMR-derived LV and RV volumes and ejection fraction.

Electrophysiology Study

Antiarrhythmic drugs were discontinued for at least 5 half-lives, if possible. Programmed electrical stimulation consisted of 3 drive trains of 8 beats (cycle length, 600, 500, and 400 ms) with 1 to 3 ventricular extrastimuli (coupling interval, 350 ms, down to the ventricular effective refractory period) and burst pacing at twice diastolic threshold from the RV apex and the RV outflow tract. If no SVA was induced, stimulation was repeated with isoprenaline (2–10 µg/min). Sustained monomorphic VT was defined by similar beat-to-beat QRS morphology and duration >30 seconds or the requirement for termination because of hemodynamic compromise.

Follow-Up and Outcomes

Follow-up started directly following the EPS. Patients were followed at the outpatient clinic, and devices were interrogated at 6 monthly intervals. Devices were programmed to include a monitor zone (from 150–170 to 188–200 beats per minute), fast VT zone with antitachycardia pacing and shocks (from 188–200 to 220–231 beats per minute), and ventricular fibrillation zone with antitachycardia pacing before or during charging and shocks (>220–231 beats per minute). All SVAs, defined as lasting >30 seconds or terminated by antitachycardia pacing or ICD shock, were classified as sustained monomorphic VT or polymorphic VT/ventricular fibrillation based on far-field electrogram morphology and cycle length stability (<30 ms in monomorphic VT). The following events were analyzed: (1) any SVA, (2) sustained monomorphic VT, and (3) a combined end point of heart failure mortality, cardiac transplantation, or LV assist device implantation. Patients were followed until the occurrence of the event of interest, death, or the end of the study period (July 19, 2019). Echocardiography and LGE-CMR were not routinely repeated during follow-up.

Statistical Analysis

All analyses using the presence or absence of NSVT on Holter included all 115 patients. All analyses of NSVT details (eg, cycle length, coupling interval, morphology) included only the 95 patients who underwent the Holter at the Leiden University Medical Center. Categorical variables are expressed as number (percentage) and continuous variables as mean±SD or median (interquartile range [IQR]). Categorical variables were compared using the χ^2 test or the Fisher exact test. Continuous variables were compared using the Mann-Whitney *U* test or the Student *t* test. Details of NSVT episodes were first aggregated per patient by calculating a percentage for dichotomous and

categorical variables and a mean or median, minimum, and maximum for continuous. Cycle lengths of NSVT on Holter, induced sustained monomorphic VTs, and sustained monomorphic VTs during follow-up were compared using the Wilcoxon signed-rank test.

The cumulative incidence of each individual event was estimated by the competing-risk method, in which death from other causes was considered a competing risk. Comparisons between exposure groups used the Gray test.[14] Univariable Cox proportional hazard analyses were performed to identify predictors for the studied events. The following predefined parameters were analyzed: age, sex, history of SVA, NSVT on Holter, LV end-diastolic volume index on CMR, LVEF on CMR, LGE on CMR, inducibility of sustained VT, and the presence of a pathogenic mutation. Multivariable Cox proportional hazard analyses were performed to analyze the independent predictive value of NSVT, adjusting for other predictors with $P<0.10$ in the univariable analyses. Cumulative incidence function analyses were performed using R, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). All other analyses were performed with SPSS, version 25 (IBM, Somers, NY). All tests were 2 sided, and P values <0.05 were considered statistically significant.

RESULTS

Patients

Of all 148 patients included in the Leiden Nonischemic Cardiomyopathy Study, 115 (78%; age, 59±12 years; 96% White; 77% men) underwent an ambulatory 24-hour Holter registration and were included in the present study. Forty-four of these patients (38%) were included because of documented or suspected SVAs and 71 (62%) because of intermediate to high risk for SVAs. Baseline parameters are shown in Table 1. Thirty-four patients (30%) had a history of sustained monomorphic VT, 7 (6%) had a history of out-of-hospital cardiac arrest with a shockable rhythm (2 had both), and 76 (66%) did not have any history of SVA. Ninety-seven patients (84%) underwent cine CMR, and in 97 (84%), LGE images were acquired. Based on CMR or, if not available, echocardiography, LVEF was 33±13% and LV end-diastolic volume index was 121±43 mL/m^2. LVEF was depressed in 108 patients (94%) and indexed LV end-diastolic volume was increased in 91 patients (79%) compared with published normal values.[15,16] LGE was observed in 61 of 97 patients (63%), with a median LGE mass of 13 g (IQR, 8–23 g). An EPS was performed in 114 patients (99%), and sustained monomorphic VT was inducible in 34 of 114 patients (30%), including 28 of 33 patients (85%) with a history of spontaneous sustained monomorphic VT and 6 of 81 patients (7%) without prior sustained VT. In 21 patients, only one distinct sustained monomorphic VT morphology was induced; in 13 patients, ≥2 distinct VT morphologies were induced. The median cycle length of all induced VTs was 299 ms (IQR, 270–360 ms), the median cycle length of the fastest VT was 283 ms (IQR, 258–330 ms), and the median cycle length of the slowest VT was 330 ms (IQR, 270–415 ms). Genetic analysis was performed in 113 patients (98%) and revealed a (likely) pathogenic mutation (class IV or V mutation) in 30 of 113 patients (27%; titin in 8 patients [7%], lamin A/C in 6 [5%], phospholamban in 3 [3%], and other genes in

Table 1. Baseline Characteristics

	All patients (n=115)
Age, y	59±12
Ethnicity, White	110 (96%)
Men	88 (77%)
BMI, kg/m^2	27±4
Diabetes	14 (12%)
Hypertension	42 (37%)
NYHA functional class	
I	41 (36%)
II	57 (50%)
III	17 (15%)
History of atrial fibrillation/atrial flutter	36 (31%)
ECG	
PR interval, ms	190±53
QRS duration, ms	130±32
eGFR MDRD, mL/min per 1.73 m^2	84±22
NT-proBNP, ng/mL	841 (211–1731)
Exercise test, n=102 (89%)	
Peak oxygen consumption, mL/kg per min	20 (16–24)
CMR cine, n=97 (84%)	
LVEDVi, mL/m^2	124±42
LVESVi, mL/m^2	87±44
LVEF, %	33±14
RVEDVi, mL/m^2	80±22
RVESVi, mL/m^2	51±19
RVEF, %	37±13
Echocardiography, if cine CMR not available, n=18 (16%)	
LVEDVi, mL/m^2	102±42
LVESVi, mL/m^2	74±37
LVEF, %	31±11
CMR LGE images, n=97 (84%)	
LGE present	61 (63%)
LGE mass, g	13 (8–23)
LGE core mass, g	6 (2–11)
LGE border zone mass, g	8 (4–14)
Genetic testing, n=113 (98%)	
Pathogenic mutation (class IV or V)	30 (27%)

BMI indicates body mass index; CMR, cardiac magnetic resonance; eGFR, estimated glomerular filtration rate; LGE, late gadolinium enhancement; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; MDRD, Modification of Diet in Renal Disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; and RVESVi, right ventricular end-systolic volume index.

13 [12%]). Forty-two of 115 patients (37%) underwent PVC or VT ablation at baseline (28 VT ablation and 14 PVC ablation); 10 of these patients underwent Holter monitoring before ablation, and the other 32 underwent Holter monitoring after the ablation.

Nonsustained VT During the 24-Hour Holter

During the 24-hour Holter, 93 of 115 patients (81%) were on β-blocker, 11 (10%) on sotalol, 13 (11%) on amiodarone, and 5 (5%) on class I antiarrhythmic drugs. NSVT was observed during Holter in 62 of 115 patients (54%). In the subset of 95 patients who underwent a Holter at the Leiden University Medical Center, a total of 617 Holter episodes in 68 patients (72%) were classified as ventricular runs by the Holter analysis software, with a median of 5 episodes per patient (IQR, 1–21 episodes). After manual review, 244 episodes (40%) were classified as NSVT, 288 (47%) as accelerated idioventricular rhythm, 69 (11%) as supraventricular arrhythmia or aberrancy, 6 (1%) as junctional rhythm, 8 as artifacts (1%), and 2 as other (<1%). The median number of NSVTs per patient was 2 (IQR, 1–7). Eight patients (8%) had ≥10 NSVTs. NSVTs were short (median, 4 beats; IQR, 3–5 beats), slow (median cycle length, 420 ms; IQR, 392–459 ms), irregular (predominantly irregular in 46% of patients, mixed in 31%, and predominantly regular in 23%), and monomorphic (predominantly monomorphic in 75%). The median fastest NSVT cycle length was 385 ms (IQR, 335–436 ms). None of the patients had any NSVT with cycle length ≤250 ms, and only 4 patients (8%) had ≥1 fast NSVT (cycle length, 251–300 ms). The coupling interval exceeded the QT interval by a median of 174 ms (IQR, 112–272 ms), with the shortest coupling interval exceeding the QT interval by a median of 104 ms (IQR, 47–211 ms).

Nonsustained VT and History of Sustained VT, Late Enhancement on CMR, and Inducibility of Sustained VT During EPS

NSVT on Holter was not associated with a history of spontaneous sustained monomorphic VT (56% in patients with a history of sustained VT versus 52% without; *P*=0.72), nor were its features (all *P*>0.05; Table 2). NSVT on Holter was also not associated with the inducibility of sustained VT during EPS or with the presence of LGE on CMR, nor were any of the NSVT features (Tables 3 and 4). The LGE mass was comparable in patients with and without NSVT (median, 12 [IQR, 8–21] versus 16 [IQR, 6–23] g, respectively; *P*=0.65). The findings remained similar when only patients who were off sotalol and amiodarone during Holter monitoring were included in the analysis (data not shown).

Nonsustained VT and Heart Failure

The NT-proBNP level was higher in patients with versus without NSVT on Holter (median, 957 [IQR, 275–2068] versus 637 [IQR, 134–1309] ng/L; *P*=0.025; Table 5) and the RVEF was lower in patients with versus without NSVT (34±12% versus 41±14%; *P*=0.013). The New York Heart Association class, VO2max, LV end-diastolic volume index, LVEF, and RVEDV index did not differ between groups (all *P*>0.05).

Table 2. NSVT on Holter and History of Sustained Monomorphic VT

	History of sustained VT (n=27)	No history of sustained VT (n=68)	*P* value
NSVT occurrence	14 (52%)	38 (56%)	0.72
NSVT number of episodes	2 (1–7)	2 (1–7)	0.93
NSVT cycle length, ms	424 (407–460)	413 (382–460)	0.29
NSVT regularity			0.65
Predominantly irregular	7 (50%)	17 (45%)	
Mixed	5 (36%)	11 (29%)	
Predominantly regular	2 (14%)	10 (26%)	
NSVT duration in beats	4 (3–6)	4 (3–5)	0.98
NSVT coupling interval of first beat, ms	572 (522–642)	566 (495–698)	0.77
NSVT coupling interval exceeding QT in ms, average	181 (116–249)	173 (111–280)	0.82
NSVT coupling interval exceeding QT in ms, shortest	111 (46–209)	104 (43–221)	0.74
Any NSVT with onset within QT	2 (14%)	6 (16%)	0.89
NSVT predominantly monomorphic	6 (43%)	23 (61%)	0.26
β-Blocker during Holter	21 (78%)	56 (82%)	0.61
Sotalol during Holter	5 (19%)	3 (4%)	0.026
Amiodarone during Holter	6 (22%)	2 (3%)	0.003

NSVT indicates nonsustained ventricular tachycardia; and VT, ventricular tachycardia.

Table 3. NSVT on Holter and Inducibility of Sustained VT During EP Study

	Sustained VT inducible (n=26)	No sustained VT inducible (n=68)	*P* value
NSVT occurrence	13 (50%)	38 (60%)	0.61
NSVT number of episodes	2 (1–12)	3 (1–6)	0.65
NSVT cycle length, ms	429 (411–467)	407 (382–458)	0.17
NSVT regularity			0.30
Predominantly irregular	5 (39%)	19 (50%)	
Mixed	6 (46%)	9 (24%)	
Predominantly regular	2 (15%)	10 (26%)	
NSVT duration in beats	3 (3–5)	4 (3–5)	0.57
NSVT coupling interval of first beat, ms	608 (485–704)	561 (510–640)	0.45
NSVT coupling interval exceeding QT in ms, average	183 (31–300)	174 (117–249)	0.91
NSVT coupling interval exceeding QT in ms, shortest	79 (6–200)	109 (53–221)	0.57
NSVT with onset within QT	3 (23%)	4 (11%)	0.26
NSVT predominantly monomorphic (≥75% of episodes)	7 (54%)	21 (55%)	0.93
β-Blocker during Holter	21 (81%)	55 (81%)	0.99
Sotalol during Holter	4 (15%)	4 (6%)	0.14
Amiodarone during Holter	6 (23%)	2 (3%)	0.002

NSVT indicates nonsustained ventricular tachycardia; and VT, ventricular tachycardia.

Nonsustained VT and Cardiac Events During Follow-Up

At discharge, 97 (84%) of 115 patients were on β-blocker, 13 (11%) on sotalol, 14 (12%) on amiodarone, and 5 (4%) on class I antiarrhythmic drugs. Forty-one patients (36%) were discharged with a biventricular ICD, 45 (39%) with a single- or dual-chamber ICD, 1 (1%) with an implantable loop recorder, and the remaining 28 patients (25%) without an implantable cardiac device. No patient was lost to follow-up. During a median of 4.0 years of follow-up (IQR, 2.6–5.3 years), an additional 10 patients (9%) received an ICD, so that 97 of 115 patients (84%) had an ICD or implantable loop recorder at the end of follow-up. During follow-up, 39 (34%) had any SVAs, 31 (27%) had sustained monomorphic VTs, and 9 (8%) had polymorphic VT/ventricular fibrillation. The median sustained monomorphic VT cycle length during follow-up was 287 (IQR, 241–319) ms, the median fastest VT cycle length was 247 (IQR, 210–284) ms, and the median slowest VT cycle length was 311 (IQR, 263–368) ms.

Table 4. NSVT on Holter and LGE on Cardiac Magnetic Resonance

	LGE present (n=47)	LGE absent (n=34)	*P* value
NSVT occurrence	27 (57%)	16 (47%)	0.36
NSVT number of episodes	2 (1 to 6)	1 (1 to 4)	0.22
NSVT cycle length, ms	414 (397 to 462)	421 (384 to 449)	0.87
NSVT regularity			0.33
Predominantly irregular	13 (48%)	7 (44%)	
Mixed	9 (33%)	3 (19%)	
Predominantly regular	5 (19%)	6 (38%)	
NSVT duration in beats	4 (3 to 4)	3 (3 to 6)	0.93
NSVT coupling interval of first beat, ms	564 (480 to 624)	592 (520 to 752)	0.32
NSVT coupling interval exceeding QT in ms, average	171 (75 to 244)	193 (121 to 320)	0.24
NSVT coupling interval exceeding QT in ms, shortest	79 (−16 to 183)	126 (50 to 320)	0.14
Any NSVT with onset within QT	7 (26%)	1 (6%)	0.11
NSVT predominantly monomorphic	15 (56%)	9 (56%)	0.97
β-Blocker during Holter	39 (83%)	26 (77%)	0.47
Sotalol during Holter	3 (6%)	2 (6%)	0.93
Amiodarone during Holter	3 (6%)	2 (6%)	0.93

LGE indicates late gadolinium enhancement; and NSVT, nonsustained ventricular tachycardia.

Table 5. NSVT on Holter and Heart Failure

	NSVT	No NSVT	*P* value
NYHA class			
I	22 (36%)	19 (36%)	0.21
II	34 (55%)	23 (43%)	
III	6 (10%)	11 (21%)	
VO2 max, mL/min per kg	19 (16–24)	21 (16–25)	0.70
NT-proBNP, ng/L	957 (275–2068)	637 (134–1309)	0.025
CMR			
LVEDVi, mL/m²	130±43	118±41	0.16
LVESVi, mL/m²	92±46	81±41	0.21
LVEF, %	32±14	35±14	0.35
RVEDVi, mL/m²	82±26	78±19	0.43
RVESVi, mL/m²	54±21	47±16	0.041
RVEF, %	34±12	41±14	0.013

CMR indicates cardiac magnetic resonance; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; NSVT, nonsustained ventricular tachycardia; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume index; and VO2 max, maximal oxygen consumption.

A total of 18 patients (16%) died, including 12 heart failure deaths, 2 sudden deaths, and 4 noncardiac deaths. One patient (1%) underwent cardiac transplantation, and 2 patients (2%) underwent LV assist device implantation.

NSVT was associated with a higher rate of sustained monomorphic VT and any SVA during follow-up (Figure 1; Table 6). Similarly, inducibility of sustained VT during EPS and LGE on CMR were both associated with sustained monomorphic VT and any SVA during follow-up (Figures 2 and 3; Table 6). Inducibility of sustained VT and LGE were interrelated: LGE on CMR was present in 83% of patients with inducible VT compared with 56% of patients without inducible VT (P=0.015), and if present, the LGE mass was numerically larger in patients with versus without inducible VT (LGE mass: median, 16 [IQR, 11–43] versus 11 [IQR, 6–20] g, respectively; P=0.058).

In a multivariable model including history of SVA, NSVT on Holter, inducibility of sustained VT during EPS, and LGE on CMR, both NSVT on Holter and sustained VT inducibility remained independently associated with sustained monomorphic VT and any SVA during follow-up (all P<0.05; Table 6). Bivariable models with (1) NSVT and VT inducibility and (2) NSVT and LGE on CMR are provided as alternative bivariable prediction models that include invasively and only noninvasively acquired parameters, respectively (Table 6). Importantly, patients with both NSVT and VT inducibility or with both NSVT and LGE on CMR had a high rate of SVA during follow-up (Figure 4).

In patients with NSVT on Holter, neither the cycle length of the fastest NSVT nor the number of NSVT episodes (1 versus 2–5 versus >5 episodes) were associated with SVAs during follow-up (P=0.27 and P=0.63, respectively). In patients who had both NSVT on Holter and sustained VT during follow-up, the cycle length of NSVTs on Holter was significantly longer than the cycle length of sustained VTs during follow-up (P<0.001; Figure 5). In contrast, no significant difference was found between the cycle length of induced sustained VTs during EPS and the cycle length of sustained VTs during follow-up (P=0.61).

Nonsustained VT on Holter was not associated with the combined end point of cardiac transplantation, LV assist device implantation, or mortality due to heart failure (HR, 2.05; P=0.24; Figure 1).

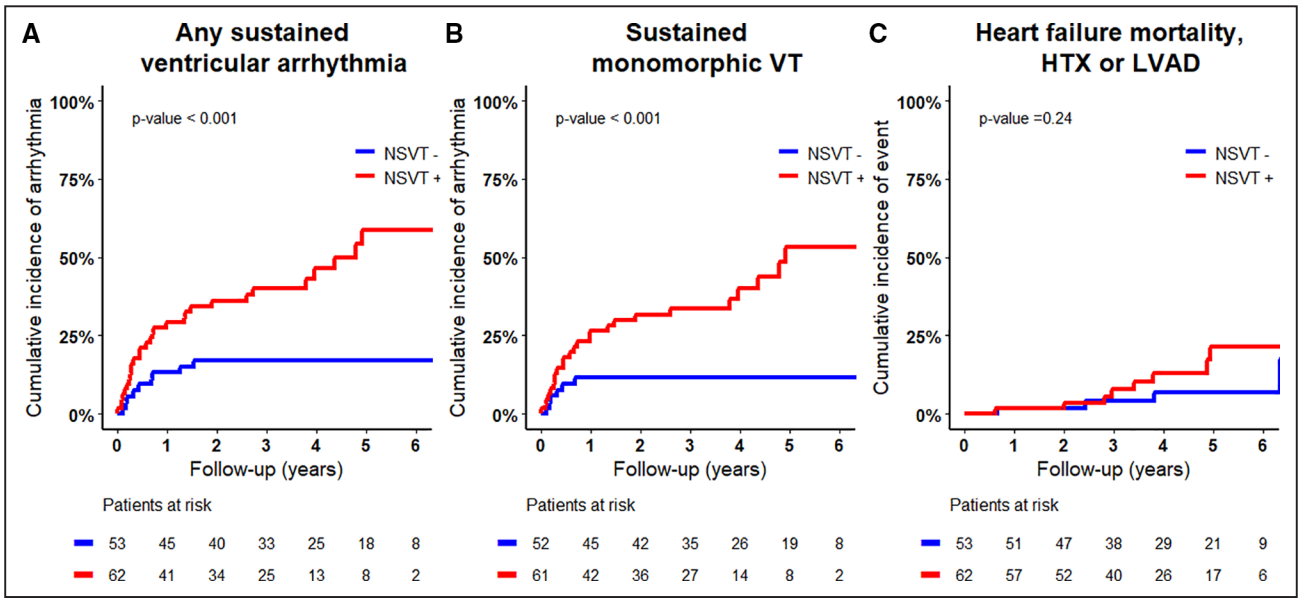

Figure 1. Association between nonsustained ventricular tachycardia (NSVT) on 24-h Holter and events during follow-up. **A–C** show the association between NSVT and events during follow-up. HTX indicates cardiac transplantation; LVAD, left ventricular assist device implantation; and VT, ventricular tachycardia.

Table 6. Predictors of Ventricular Arrhythmias During Follow-Up

	Any sustained ventricular arrhythmia		Sustained monomorphic VT	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Univariable				
Age, per y	1.01 (0.98–1.04)	0.58	1.01 (0.98–1.04)	0.62
Male sex	2.16 (0.84–5.53)	0.11	3.03 (0.92–9.97)	0.068
History of SVA	4.68 (2.42–9.02)	<0.001	7.00 (3.17–15.43)	<0.001
NSVT on Holter	3.73 (1.76–7.92)	0.001	4.48 (1.83–10.99)	0.001
LVEDVi on CMR, per mL	1.00 (0.99–1.01)	0.63	1.01 (1.00–1.01)	0.24
LVEF on CMR, per %	1.00 (0.98–1.03)	0.75	1.01 (0.98–1.04)	0.61
RVEF on CMR, per %	0.98 (0.96–1.01)	0.27	0.98 (0.95–1.02)	0.28
LGE on CMR	2.09 (0.90–4.85)	0.088	3.08 (1.05–9.01)	0.040
NT-proBNP >median 841 ng/L	0.76 (0.40–1.47)	0.42	0.77 (0.38–1.59)	0.49
Sustained VT inducibility	4.78 (2.52–9.10)	<0.001	7.52 (3.49–16.18)	<0.001
Pathogenic mutation	1.57 (0.80–3.08)	0.19	1.70 (0.81–3.57)	0.16
Multivariable				
Male sex			2.14 (0.47–9.71)	0.33
History of SVA	1.87 (0.69–5.08)	0.22	2.61 (0.81–8.44)	0.11
NSVT on Holter	4.47 (1.87–10.72)	0.001	6.35 (2.09–19.35)	0.001
Sustained VT inducibility	3.08 (1.08–8.81)	0.036	3.05 (0.88–10.51)	0.078
LGE on CMR	1.23 (0.50–3.07)	0.65	1.49 (0.46–4.88)	0.51
Bivariable, invasive				
NSVT on Holter	4.33 (2.03–9.26)	<0.001	5.35 (2.16–13.25)	<0.001
Sustained VT inducibility	5.38 (2.81–10.31)	<0.001	8.56 (3.93–18.61)	<0.001
Bivariable, noninvasive				
NSVT on Holter	3.79 (1.62–8.87)	0.002	5.05 (1.72–14.87)	0.003
LGE on CMR	1.98 (0.85–4.60)	0.11	2.78 (0.95–8.16)	0.062

CMR indicates cardiac magnetic resonance; HR, hazard ratio; LGE, late gadolinium enhancement; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RVEF, right ventricular ejection fraction; SVA, sustained ventricular arrhythmia; and VT, ventricular tachycardia.

All findings remained similar when only the 76 patients without a history of SVA were analyzed (Table S1), when only the 83 patients who did not undergo PVC or VT ablation before Holter were analyzed (Table S2), or when only the 88 patients who were discharged off sotalol or amiodarone were analyzed (Table S3).

In patients without a history of SVA, the cumulative incidence of any SVA at 4 years was 32% (95% CI, 11%–52%) for those who had all 2 or 3 risk factors (NSVT on Holter, VT inducibility or LGE on CMR), compared with 16% (95% CI, 3%–29%) for patients who had 1 risk factor, and 7% (95% CI, 0%–21%) for patients who had none of these 3 risk factors.

DISCUSSION

The present study is the first to systematically perform Holter, electrophysiology studies, and LGE-CMR in a prospective cohort of patients with DCM. It is demonstrated that NSVT on Holter and VT inducibility during EPS are powerful predictors of ventricular arrhythmias during follow-up in patients with a DCM, independent of LGE on CMR. Importantly, a bivariable model including only noninvasively acquired parameters also allows identification of a high-risk subgroup (ie, those with both NSVT and LGE on CMR). NSVTs were short, predominantly irregular, and slower than both induced sustained VTs and spontaneous SVAs during follow-up, and not associated with LGE, suggesting that NSVTs are a different entity and not merely a short version of sustained monomorphic VTs.

NSVT on Holter, LGE on CMR, and Ventricular Arrhythmias During Follow-Up

NSVT on Holter was a powerful predictor of SVAs during follow-up in the present study, and importantly, its predictive value is independent of VT inducibility during EPS and LGE on CMR. Several prior studies have found associations between NSVT and an increased risk for ventricular arrhythmias and sudden cardiac death in DCM,[1–4] but none have also systematically performed CMR. Two prior studies have also performed electrophysiology studies but only in patients with NSVT on Holter and have found

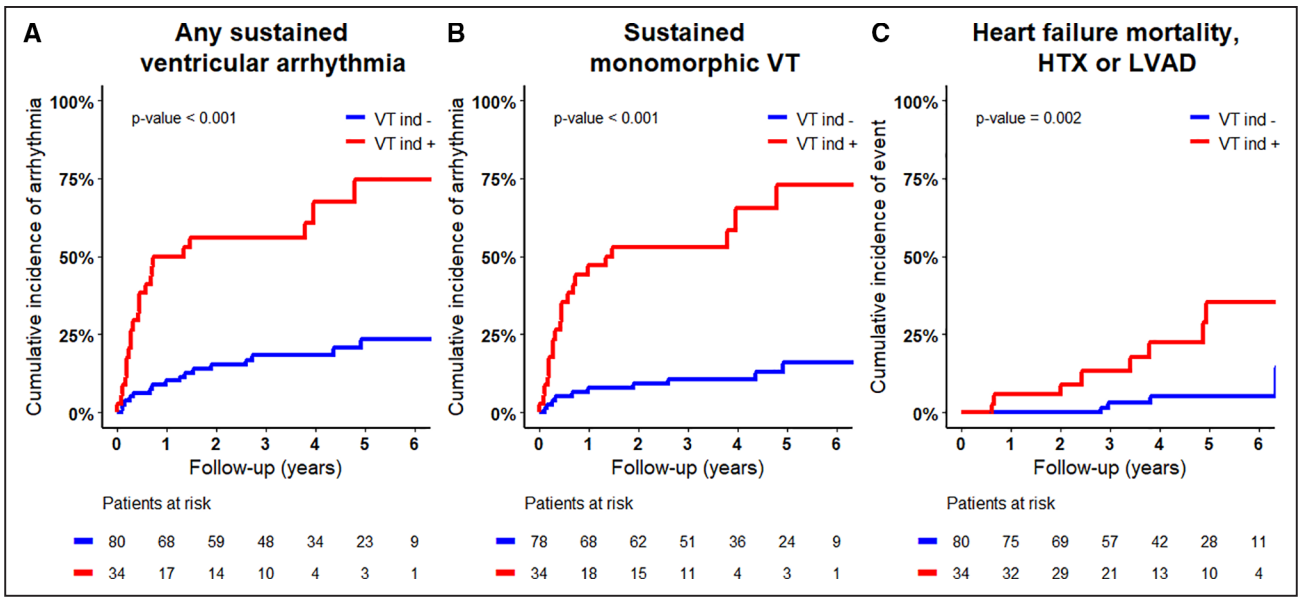

Figure 2. Association between ventricular tachycardia (VT) inducibility during electrophysiology study and events during follow-up.
HTX indicates cardiac transplantation; and LVAD, left ventricular assist device implantation.

low rates of sustained VT inducibility (ie, 7%–13%).[1,17] In the present study, we could demonstrate that NSVT is neither associated with inducibility of sustained VT nor with LGE on CMR.

In a multivariable model, LGE on CMR was not an independent predictor for SVAs during follow-up, which may, in part, be explained by the fact that VT inducibility and LGE on CMR were interrelated. Since electrophysiological studies are not routinely performed in potential ICD recipients in most hospitals, a bivariable model including only NSVT and LGE on CMR is also provided and allows identification of a subgroup with both NSVT and LGE on CMR who are at a particularly high risk for SVA during follow-up. However, an invasive electrophysiological study may be beneficial for risk stratification, as VT inducibility was a stronger predictor for SVA than LGE on CMR.

Of note, NSVTs on Holter were slower than induced sustained VTs (NSVT cycle length, 413±51 ms versus induced VT cycle length, 317±65 ms), nonshort coupled, and predominantly irregular. The cycle length of NSVTs was also substantially longer than the cycle length of induced VTs during electrophysiology studies and SVAs during follow-up. Of interest, the cycle length of the

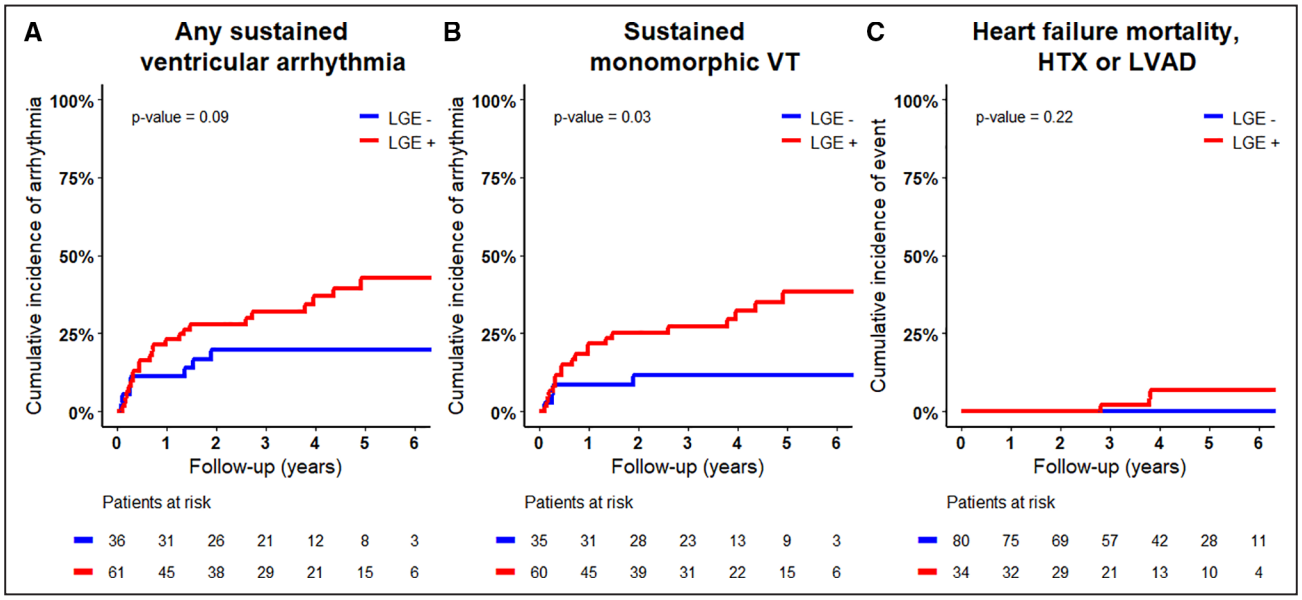

Figure 3. Association between late gadolinium enhancement on cardiac magnetic resonance and events during follow-up.
HTX indicates cardiac transplantation; LVAD, left ventricular assist device implantation; and VT, ventricular tachycardia.

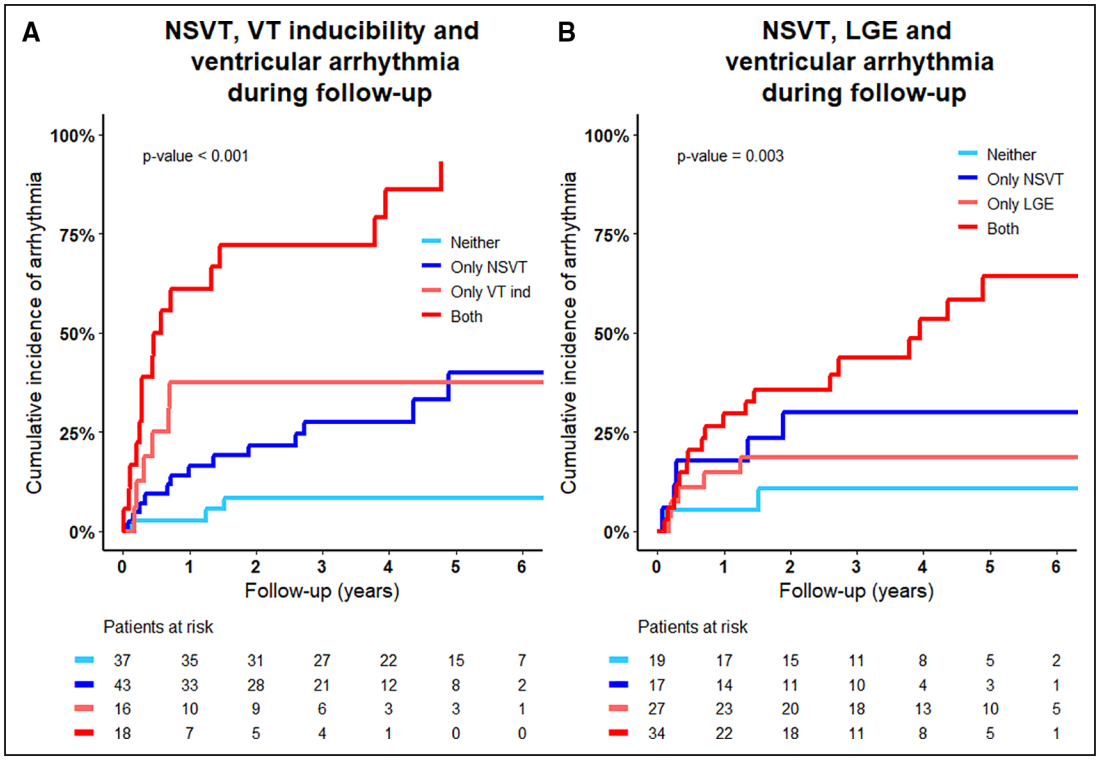

Figure 4. Association between nonsustained ventricular tachycardia (NSVT) on Holter, sustained ventricular tachycardia (VT) inducibility during electrophysiology study, late gadolinium enhancement (LGE) on cardiac magnetic resonance, and sustained ventricular arrhythmias during follow-up.

A and **B** show the association between NSVT, sustained VT inducibility, LGE on cardiac magnetic resonance and events during follow-up.

induced VTs was comparable to the cycle length of spontaneous VTs during follow-up. Although the mechanism and underlying substrate of the NSVT cannot be determined with certainty, the findings of this study may be consistent with abnormal impulse formation. Accordingly, the source and mechanism of the NSVT may be different from scar-related reentry as dominant underlying mechanism for induced and spontaneous sustained monomorphic VT in our DCM population. Considering the high rate of spontaneous SVAs during follow-up in patients who have NSVT and VT inducibility, it is appealing to speculate that NSVTs facilitate the initiation of scar-related reentry. The coexistence or absence of both may identify patients at a particular high or low risk for spontaneous ventricular arrhythmias.

Interaction Between Ventricular Arrhythmias and Heart Failure

NSVT has been associated with an increased risk of heart failure episodes[4] and death due to heart failure,[18] and it has been demonstrated that the number of NSVTs may decrease after initiation of β-blocker and angiotensin-converting enzyme inhibitors.[19] In the present study, NT-proBNP levels were higher, and RVEF was lower in patients with versus without NSVT, although New York Heart Association functional class, VO2max, and LVEF were all similar. As brain natriuretic peptides have been demonstrated to be released due to increased ventricular wall stress,[20,21] one may hypothesize that NSVTs are related to increased wall stress and thereby constitute a link between heart failure and SVAs in DCM. Together, these data support an important interaction between heart failure and ventricular arrhythmias in DCM.

Risk Stratification

The presence of NSVT has been largely abandoned as a criterion for ICD implantation, except for specific cardiomyopathies such as laminopathy.[22] The DANISH trial (The Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) has demonstrated low rates of sudden cardiac death and no reduction in all-cause mortality with prophylactic ICD implantation in patients with nonischemic systolic heart failure with LVEF ≤35%,[23] emphasizing the need for better risk stratification for sudden cardiac death in DCM. The current study demonstrates that NSVT on Holter and VT inducibility during EPS are independent predictors of SVAs. Of importance, patients who had 3 risk factors (NSVT, VT inducibility, and LGE on CMR) were at particularly high risk for events with a 100% rate of SVAs at 4 years of follow-up. A bivariable model including only noninvasively acquired parameters also allows identification of a high-risk subgroup (ie, those with both NSVT and LGE on CMR). Future trials may aim to evaluate the

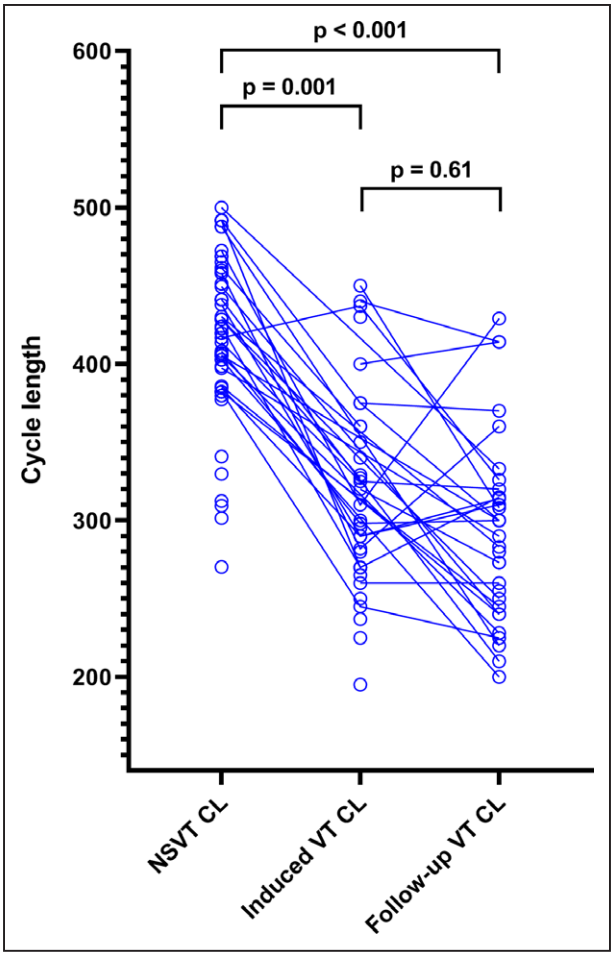

Figure 5. Median cycle lengths (CLs) of nonsustained ventricular tachycardia (NSVT) on Holter, induced sustained monomorphic ventricular tachycardia (VT) and sustained monomorphic VT during follow-up.

efficacy of risk stratification if the results of ambulatory Holter monitors, electrophysiology studies, and LGE-CMR are combined in larger cohorts of patients with DCM.

Limitations

The present findings require external validation. Ambulatory Holter monitoring was performed for only 24 hours, and the percentage of patients with documented NSVT may increase with increasing monitoring duration (from 35% in 1 day to 54% in 7 days in 1 study[24]). Inclusion of patients with a history of SVA and patients undergoing PVC and VT ablation may have affected some results, but analyses excluding patients with a history of SVA and those who underwent Holter after ablation resulted in similar findings, which makes it likely that our results are representative for the whole population. As 96% of the study participants were White, our findings may not be fully generalizable to other races. Like NSVT burden, LVEF and LGE burden are dynamic, and changes in these parameters were not captured because no routine and uniform follow-up imaging data were acquired.

CONCLUSIONS

NSVT on Holter and sustained VT inducibility during EPS are powerful independent predictors of SVAs during follow-up, independent of LGE on CMR. Two bivariable models including either invasively or only noninvasively acquired parameters both allow identification of a high-risk subgroup (ie, those with both NSVT and VT inducibility or with both NSVT and LGE on CMR). NSVTs may serve as initiator, whereas the inducibility of sustained reentrant VT during EPS and the presence of LGE on CMR may indicate the substrate required for VT maintenance. NSVT, LGE on CMR, and VT inducibility may thereby provide important complementary information in patients with DCM.

ARTICLE INFORMATION

Received March 18, 2021; accepted January 3, 2022.

Affiliation

Department of Cardiology, Willem Einthoven Center for Cardiac Arrhythmia Research and Management (S.R.P., A.F.A., K.S.Y., J.V., G.F.K., H.-M.S., S.-C.M., K.Z.), Department of Epidemiology (N.v.R., S.C.C.), and Department of Radiology (H.J.L.), Leiden University Medical Center, the Netherlands.

Sources of Funding

The Department of Cardiology from the Leiden University Medical Center receives unrestricted grants from Edwards Lifesciences, Biotronik, Medtronic, Boston Scientific, and Biosense Webster.

Disclosures

None.

Supplemental Material

Supplemental Methods
Tables S1–S3

REFERENCES

1. Becker R, Haass M, Ick D, Krueger C, Bauer A, Senges-Becker JC, Voss F, Hilbel T, Niroomand F, Katus HA, et al. Role of nonsustained ventricular tachycardia and programmed ventricular stimulation for risk stratification in patients with idiopathic dilated cardiomyopathy. *Basic Res Cardiol.* 2003;98:259–266. doi: 10.1007/s00395-003-0398-7
2. Clementy N, Bisson A, Challal F, Andre C, Pierre B, Fauchier L, Babuty D. Nonsustained ventricular tachycardia at the time of implantation predicts appropriate therapies on rapid ventricular arrhythmia in primary prevention patients with nonischemic cardiomyopathy: results from the very-high-rate registry. *JACC Clin Electrophysiol.* 2017;3:1338–1339. doi: 10.1016/j.jacep.2017.04.016
3. Grimm W, Christ M, Bach J, Müller HH, Maisch B. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: results of the Marburg Cardiomyopathy Study. *Circulation.* 2003;108:2883–2891. doi: 10.1161/01.CIR.0000100721.52503.85
4. Mittal S, Aktas MK, Moss AJ, McNitt S, Kutyifa V, Steinberg JS, Zareba W. The impact of nonsustained ventricular tachycardia on reverse remodeling, heart failure, and treated ventricular tachyarrhythmias in MADIT-CRT. *J Cardiovasc Electrophysiol.* 2014;25:1082–1087. doi: 10.1111/jce.12456
5. Gatzoulis KA, Vouliotis AI, Tsiachris D, Salourou M, Archontakis S, Dilaveris P, Gialernios T, Arsenos P, Karystinos G, Sideris S, et al. Primary prevention of sudden cardiac death in a nonischemic dilated cardiomyopathy population: reappraisal of the role of programmed ventricular stimulation. *Circ Arrhythm Electrophysiol.* 2013;6:504–512. doi: 10.1161/CIRCEP.113.000216
6. 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
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. Iles L, Pfluger H, Lefkovits L, Butler MJ, Kistler PM, Kaye DM, Taylor AJ. Myocardial fibrosis predicts appropriate device therapy in patients with implantable cardioverter-defibrillators for primary prevention of sudden cardiac death. *J Am Coll Cardiol.* 2011;57:821–828. doi: 10.1016/j.jacc.2010.06.062
9. 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
10. Piers SR, Tao Q, de Riva Silva M, Siebelink HM, Schalij MJ, van der Geest RJ, Zeppenfeld K. CMR-based identification of critical isthmus sites of ischemic and nonischemic ventricular tachycardia. *JACC Cardiovasc Imaging.* 2014;7:774–784. doi: 10.1016/j.jcmg.2014.03.013
11. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M, Duboc D, Gimeno J, de Groote P, Imazio M, et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. *Eur Heart J.* 2016;37:1850–1858. doi: 10.1093/eurheartj/ehv727
12. 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
13. Roes SD, Borleffs CJ, van der Geest RJ, Westenberg JJ, Marsan NA, Kaandorp TA, Reiber JH, Zeppenfeld K, Lamb HJ, de Roos A, et al. Infarct tissue heterogeneity assessed with contrast-enhanced MRI predicts spontaneous ventricular arrhythmia in patients with ischemic cardiomyopathy and implantable cardioverter defibrillator. *Circ Cardiovasc Imaging.* 2009;2:183–190. doi: 10.1161/CIRCIMAGING.108.826529
14. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat.* 1988;16:1141–1154.
15. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28:1.e14–39.e14. doi: 10.1016/j.echo.2014.10.003
16. Maceira AM, Prasad SK, Khan M, Pennell DJ. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. *J Cardiovasc Magn Reson.* 2006;8:417–426. doi: 10.1080/10976640600572889
17. Turitto G, Ahuja RK, Caref EB, el-Sherif N. Risk stratification for arrhythmic events in patients with nonischemic dilated cardiomyopathy and nonsustained ventricular tachycardia: role of programmed ventricular stimulation and the signal-averaged electrocardiogram. *J Am Coll Cardiol.* 1994;24:1523–1528. doi: 10.1016/0735-1097(94)90149-x
18. Yokoshiki H, Shimizu A, Mitsuhashi T, Furushima H, Sekiguchi Y, Manaka T, Nishii N, Ueyama T, Morita N, Okamura H, et al; Members of the Implantable Cardioverter-Defibrillator (ICD) Committee of the Japanese Heart Rhythm Society. Prognostic significance of nonsustained ventricular tachycardia in patients receiving cardiac resynchronization therapy for primary prevention: analysis of the Japan cardiac device treatment registry database. *J Arrhythm.* 2018;34:139–147. doi: 10.1002/joa3.12023
19. Zecchin M, Di Lenarda A, Gregori D, Merlo M, Pivetta A, Vitrella G, Sabbadini G, Mestroni L, Sinagra G. Are nonsustained ventricular tachycardias predictive of major arrhythmias in patients with dilated cardiomyopathy on optimal medical treatment? *Pacing Clin Electrophysiol.* 2008;31:290–299. doi: 10.1111/j.1540-8159.2008.00988.x
20. Kinnunen P, Vuolteenaho O, Ruskoaho H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: effect of stretching. *Endocrinology.* 1993;132:1961–1970. doi: 10.1210/endo.132.5.8477647
21. Iwanaga Y, Nishi I, Furuichi S, Noguchi T, Sase K, Kihara Y, Goto Y, Nonogi H. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. *J Am Coll Cardiol.* 2006;47:742–748. doi: 10.1016/j.jacc.2005.11.030
22. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, et al; ESC Scientific Document Group. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J.* 2015;36:2793–2867. doi: 10.1093/eurheartj/ehv316
23. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, et al; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med.* 2016;375:1221–1230. doi: 10.1056/NEJMoa1608029
24. Pastor-Pérez FJ, Manzano-Fernández S, Goya-Esteban R, Pascual-Figal DA, Barquero-Pérez O, Rojo-Alvarez JL, Martinez-Espejo MD, Chavarri MV, García-Alberola A. Comparison of detection of arrhythmias in patients with chronic heart failure secondary to non-ischemic versus ischemic cardiomyopathy by 1 versus 7-day Holter monitoring. *Am J Cardiol.* 2010;106:677–681. doi: 10.1016/j.amjcard.2010.04.027