Pleomorphic ventricular tachycardia in dilated cardiomyopathy predicts ventricular tachycardia recurrence after ablation independent from cardiac function: comparison with patients with ischemic heart disease

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ORIGINAL ARTICLE

Pleomorphic Ventricular Tachycardia in Dilated Cardiomyopathy Predicts Ventricular Tachycardia Recurrence After Ablation Independent From Cardiac Function: Comparison With Patients With Ischemic Heart Disease

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BACKGROUND: In dilated cardiomyopathy (DCM), outcome after catheter ablation of ventricular tachycardia (VT) is modest, compared with ischemic heart disease (IHD). Pleomorphic VT (PL-VT) has been associated with fibrotic remodeling and end-stage heart failure in IHD. The prognostic role of PL-VT in DCM is unknown.

METHODS: Consecutive IHD (2009–2016) or DCM (2008–2018) patients undergoing ablation for monomorphic VT were included. PL-VT was defined as ≥1 spontaneous change of the 12-lead VT-morphology during the same induced VT episode. Patients were followed for VT recurrence and mortality.

RESULTS: A total of 247 patients (86% men; 63±13 years; IHD n=152; DCM n=95) underwent ablation for monomorphic VT. PL-VT was observed in 22 and 29 patients with IHD and DCM, respectively (14% versus 31%, *P*=0.003). In IHD, PL-VT was associated with lower LVEF (28±9% versus 34±12%, *P*=0.02) and only observed in those with LVEF<40%. In contrast, in DCM, PL-VT was not related to LVEF and induced in 27% of patients with LVEF>40%. During a median follow-up of 30 months, 79 (32%) patients died (IHD 48; DCM 31; *P*=0.88) and 120 (49%) had VT recurrence (IHD 59; DCM 61; *P*<0.001). PL-VT was associated with mortality in IHD but not in DCM. In IHD, VT recurrence was independently associated with LVEF, number of induced VTs, and procedural noncomplete success. Of note, in DCM, PL-VT (HR, 2.62 [95% CI, 1.47–4.69]), pathogenic mutation (HR, 2.13 [95% CI, 1.16–3.91]), and anteroseptal VT substrate (HR, 1.75 [95% CI, 1.00–3.07]) independently predicted VT recurrence.

CONCLUSIONS: In IHD, PL-VT was associated with low LVEF and mortality. In DCM, PL-VT was not associated with mortality but a predictor of VT recurrence independent from LVEF. PL-VT in DCM may indicate a specific arrhythmic substrate difficult to control by current ablation techniques.

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

Key Words: catheter ablation ■ dilated cardiomyopathy ■ ischemic heart disease ■ left ventricular ejection fraction ■ pleomorphic ventricular tachycardia

Catheter ablation (CA) has emerged as an effective treatment option for ventricular tachycardia (VT) in ischemic heart disease (IHD) and dilated cardiomyopathy (DCM). Compared with IHD, DCM patients show higher VT recurrence rates.[1] The worse outcome has been attributed to a dominant intramural

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WHAT IS KNOWN

- In dilated cardiomyopathy, the outcome of catheter ablation of ventricular tachycardia is modest, compared with ischemic heart disease.
- Pleomorphic ventricular tachycardia has been related to end-stage heart failure in patients with ischemic heart disease.

WHAT THE STUDY ADDS

- In ischemic heart disease patients referred for radiofrequency catheter ablation, Pleomorphic ventricular tachycardia was associated with low left ventricular ejection fraction and high mortality, whereas in dilated cardiomyopathy patients. Pleomorphic ventricular tachycardia was not related to cardiac function and mortality.
- Pleomorphic ventricular tachycardia was independently associated with ventricular tachycardia recurrence only in dilated cardiomyopathy patients and was the most decisive predictor of ventricular tachycardia recurrence.
- Pleomorphic ventricular tachycardia may indicate an arrhythmic substrate difficult to control by current ablation techniques in dilated cardiomyopathy.

Nonstandard Abbreviations and Acronyms

CA	catheter ablation
DCM	dilated cardiomyopathy
ICD	implantable cardioverter defibrillator
IHD	ischemic heart disease
IQR	interquartile range
PL-VT	pleomorphic ventricular tachycardia

scar location,[2–6] preserved wall thickness,[7] and disease progression.[8] Despite novel ablation techniques to improve transmural lesion formation, up to 50% of DCM patients experience VT recurrence early after CA.[9,10] Histological studies have demonstrated remarkable differences between IHD and DCM. While in IHD compact scars are surrounded by a borderzone of inhomogeneous fibrosis of variable size, fibrosis patterns in DCM are typically diffuse and patchy.[11–13]

Electrophysiological characteristics related to unfavorable outcomes also differ between etiologies. DCM patients show a lower frequency of late potentials,[14,15] and for the majority of mappable VTs a critical VT isthmus cannot be identified.[16] These findings may be explained by a deep intramural substrate location or a specific pattern of fibrosis.

Pleomorphic VT (PL-VT), defined as VT showing an abrupt morphological change of the 12-lead VT morphology during an ongoing VT episode has been first reported in IHD.[17,18] Of interest, patients with IHD and PL-VT had more dilated LV, poorer function, and a rapid progression to end-stage heart failure and death within weeks.[19] Diffuse fibrosis, as part of maladaptive cardiac remodeling, may contribute to PL-VT in IHD.[20] However, as diffuse fibrosis is the dominant pattern in DCM, PL-VT may occur in the absence of advanced heart failure and may indicate a VT substrate difficult to control by CA.

The aims of the current study are (1) to investigate the prevalence of PL-VT among induced VT in patients with IHD and DCM referred for VT ablation, (2) to assess the relation between PL-VT and cardiac function, (3) to determine the association between PL-VT and the acute and long-term outcomes after ablation.

METHODS

Patient Population

Consecutive patients with IHD or DCM referred to the Leiden University Medical Center for ablation of sustained monomorphic VT (SMVT) between January 2009 and February 2016 (IHD patients) and between January 2008 and August 2018 (DCM patients) were included. The diagnosis of IHD was based on the presence of wall motion abnormalities, nonreversible perfusion defects and/or subendocardial or transmural late gadolinium enhancement areas in the perfusion territory of a significant stenotic coronary artery (>75 %). Patients with DCM had dilated or hypokinetic nondilated LV and/or evidence of myocardial scar consistent with a nonischemic pathogenesis on cardiac imaging (echocardiography and/or contrast-enhanced magnetic resonance imaging) and/or on electroanatomical voltage mapping without any evidence for significant coronary artery disease.[21] Patients with arrhythmogenic right ventricular cardiomyopathy, congenital heart disease, hypertrophic or restrictive cardiomyopathy, biopsy-proven myocarditis, cardiac sarcoidosis, LV noncompaction or primary valvular disease were excluded. All patients provided preprocedural informed consent for the procedure. The study was approved by the Dutch local ethical committee (G21.119) and adhered to the Declaration of Helsinki. To maintain patient confidentiality, data and study materials will not be made available to other researchers for purposes of replicating the results.

Preprocedural Evaluation

In all patients, a comprehensive clinical evaluation was performed. Medical records were reviewed for the documentation of spontaneous ventricular arrhythmias on 12-lead ECG, Holter recordings and/or implantable cardioverter defibrillator (ICD) interrogation tracings. All patients underwent (contrast) echocardiography for cardiac function and exclusion of intracardiac thrombus. Echocardiography and/or contrast-enhanced magnetic resonance imagings were reviewed for scar distribution. In patients with IHD, data on ischemic events, acute reperfusion therapy and prior revascularization were collected. In patients with DCM, genetic testing by combined next-generation and Sanger sequencing of ≥55 cardiomyopathy related genes was performed as previously described.[22] In case of epicardial ablation, electrocardiography-gated CT derived images were used for procedural integration as previously described.[5] All AADs (except for amiodarone) were discontinued before the ablation.

Procedural Strategy

Endocardial electroanatomical mapping was performed in all patients and epicardial mapping in case of prior endocardial ablation failure and/or evidence of epicardial scar on echocardiography and/or contrast-enhanced magnetic resonance imaging. Epicardial access was not attempted in patients with prior cardiac surgery or in the presence of a basal, anteroseptal substrate for VT due to the anticipated limited substrate accessibility related to overlying anatomical structures.[23] If a combined percutaneous endo- and epicardial ablation remained ineffective in controlling VT, bailout strategies were applied including bipolar ablation, transcoronary ethanol ablation with mechanical circulatory support or surgical cryo-ablation.

Electrophysiological Study

The procedure was performed under conscious sedation, deep sedation or general anesthesia, when indicated. Programed ventricular stimulation (PVS) was conducted (3–4 drive cycle lengths [600, 500, 400, 350 ms], 3–4 extra's [≥200 ms]) from 2 right ventricular (RV) and ≥1 left ventricular (LV) sites and from the epicardium, if required for induction. Positive endpoint of stimulation was induction of a sustained VT lasting >30 s or requiring termination because of hemodynamic compromise.

PVS started with basic cycle length of 600 ms (S1) and 1–3 extrastimuli (S2–S4), with a coupling interval of 350 ms, down by 10 ms to 200 ms or refractoriness. If VT was not inducible, the protocol was repeated with S1 of 500 and 400 ms and S2–S4 and thereafter S1 of 350 ms and 4 extrastimuli (S2–S5). A stimulus strength of twice diastolic threshold was used for stimulation, and a pause of 3–5 seconds between trains of ventricular pacing was applied. The positive endpoint of stimulation was an induction of a sustained VT lasting >30 s or requiring termination because of hemodynamic compromise. The entire protocol was repeated from 2 right ventricular (RV) and ≥1 LV sites, and from the epicardium if required for induction until the positive endpoint was reached. Once modification of substrate was thought to be completed, the entire induction protocol was repeated. If monomorphic VT was induced and was considered to be clinically relevant, PVS was repeated after additional ablation.

Induced sustained VTs were categorized as:

1) Monomorphic VT: VT with a similar QRS configuration from beat to beat during the VT episode.[17,18]
2) Multiple monomorphic VTs (MM-VT): Induction of >1 morphologically distinct monomorphic VT episodes without spontaneous changes.[18]
3) PL-VT: A VT that fulfilled the following 3 criteria:
   (1) More than 1 morphologically distinct QRS complexes during the *same* VT episode but the QRS was not continuously changing[17,18]
   (2) Each QRS morphology lasted for ≥6 consecutive beats[19]
   (3) The change of morphology occurred spontaneously. VTs with changing morphology during RF application, overdrive pacing attempts or by catheter manipulation were not considered as PL-VT. A representative example of a PL-VT is shown in Figure 1.
4) Polymorphic VT: VT with continuously changing QRS configuration from beat to beat.[17]

Induced VTs were also classified as described before[24]: clinical VT, 12/12 lead ECG match and a difference in VTCL ≤30 ms with a previously documented VT; presumptive clinical VT, a difference in VTCL ≤30 ms with an ICD-recorded VT; or nonclinical VT, if the previous criteria were not fulfilled.

The mapping and ablation procedure was continuously recorded for off-line analysis. All VT induction attempts were analyzed. The 12-lead ECGs of all sustained VTs were reviewed by 2 experienced electrophysiologists (Y.K., M.D.R.) blinded to the outcome data.

VT Substrate Identification and Ablation

All patients underwent Endocardial electroanatomical mapping of the LV endocardium. In addition, the RV and/or the epicardium were mapped when deemed appropriate. Bipolar voltage maps were created using a 3.5-mm irrigated-tip catheter (NaviStar Thermocool, Smarttouch, Biosense Webster Inc., CA) and the CARTO (Biosense Webster) system. Electrograms were filtered at 30 to 400 Hz (bipolar) and 1 to 240 Hz (unipolar). Standard cut-off bipolar voltage values of 1.5 mV for low voltage area, 0.5 mV for dense scar, and 0.5 to 1.5 mV for the border zone were applied in IHD. In DCM, 1.5 mV and 8.01 mV were used to define bipolar and unipolar LVAs.[23] Low voltage area with abnormal EGMs consistent with conduction delay (split, late, or fragmented potentials) were considered as potential substrate for VT. Hemodynamically tolerated VTs were approached by activation and/or entrainment mapping. For nonmappable VTs, pace-mapping was performed in addition to substrate mapping to select ablation target sites. Radiofrequency energy was delivered between 35 and 50W with a temperature limit of 43 °C and a flow rate of 20–30 mL/min until high-output pacing (≥10 mA/2 ms) failed to capture.

Acute Procedural Outcome

After the ablation, the entire induction protocol was repeated. Noninducibility of any SMVT or PL-VT was considered as complete acute success. Abolition of the clinical VT but persistent inducibility of any nonclinical VT after ablation was defined as partial success. Inducibility of the (presumed) clinical VT after ablation was considered as procedural failure. If multiple procedural attempts for arrhythmia control were required, acute and long-term outcomes were assessed after the last procedure.

Follow-Up and Outcomes

Patients were followed at the outpatient clinic 2 months after ablation and at 6-month intervals thereafter including ICD interrogation. VT recurrence was defined as occurrence of any sustained VT requiring ICD therapy, recorded within the ICD monitor lasting >30 s or documented on 12-lead ECG, including VTs that occurred before discharge from the hospital. ICD tracings of recurrent VT were analyzed by 2 experienced observers. For patients not followed at our center, the referring cardiologist was contacted for VT recurrence and mortality.

Statistical Analysis

Categorical variables are reported as numbers (percentages). Continuous variables are presented as mean ± standard deviation (SD) when normally distributed or median with interquartile rage (IQR) when not normally distributed. Continuous variables

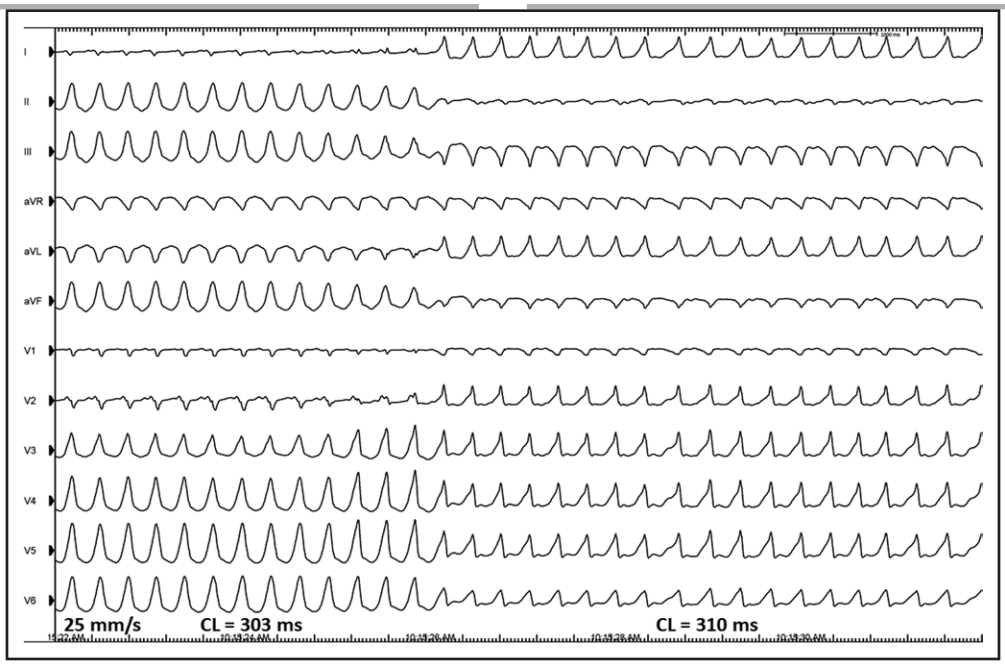


Figure 1. Representative example of pleomorphic ventricular tachycardia (VT).
CL indicates cycle length.

were compared with the student *t* test or the Mann-Whitney U test and categorical variables with χ^2 or Fisher exact test when applicable. Survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test. If mortality was considered as a competing risk event for analyzing VT recurrence rates, the cumulative incidences of the VT recurrence was estimated using the Fine and Gray competing risks approach. Univariable Cox proportional hazard analysis was used to test the association between the outcome event (VT-recurrence) and baseline covariates. Independent predictors of VT recurrence were analyzed with multivariable models using a backward stepwise selection. Variables with $P<0.10$ were initially included. At each step, the least significant variable was removed from the model until all variables reached $P<0.20$. All tests were 2-sided, and a P value <0.05 was considered as statistically significant. The proportional hazard assumption was tested by plotting log-minus-log curves. For the comparison of the prevalence of PL-VT between IHD and DCM patients, a propensity score matching analysis was also performed to account for baseline differences between the 2 groups. To estimate the propensity score, logistic regression was used, including the following covariates: age, sex, LVEF, prior VT ablation, VT storm or incessant VT, and amiodarone use. Matching was performed by the nearest neighbor method, one-to-one (1:1) ratio. Analyses were conducted in the unmatched and matched cohorts. Analyses were performed using JMP Pro 13.2.1 (SAS Institute, Inc, Cary, NC) or STATA version 16.

RESULTS

Baseline Characteristics According to the Etiologies

A total of 247 patients (86% men, age 63±13 years), 152 with IHD (62%) and 95 with DCM (38%) who underwent catheter ablation of SMVT were included. Baseline characteristics according to the etiologies are shown in Table 1. Compared with patients with DCM, patients with IHD were older, had lower LVEF, presented more often with VT storm/incessant VT, and had undergone less frequently a previous VT ablation attempt.

Prevalence of PL-VT

A total of 503 and 381 VTs were induced in patients with IHD and DCM, respectively (IHD, median 3 per patient, [IQR, 1–5]; DCM, median 3 per patient, [IQR, 1–5]). Of those, 32 (6%) and 76 (20%) VTs were classified as PL-VT in 22/152 and 29/95 patients with IHD and DCM, respectively (14% versus 31%; $P=0.003$; Table 1). The percentage of patients inducible for any SMVT, clinical/presumptive clinical VT, or MM-VT did not differ between IHD and DCM patients, following the same and uniform induction protocol.

Propensity score was matched in 120 patients (Table S1). The distribution of the propensity probabilities is shown in Figure S1. Of importance, in PS-matched cohort, the prevalence of PL-VT was 4 times higher in DCM patients Compared with matched IHD patients (7% versus 28%, $P=0.003$).

Clinical Characteristics According to PL-VT Inducibility

Baseline characteristics according to inducibility of PL-VT are shown in Table 2. IHD patients with PL-VT (PL-VT(+)) had a lower LVEF than those without

Table 1. Baseline Characteristics and Procedural Data According to Pathogenesis

	Overall (N=247	IHD (N=152	DCM (N=95	*P* value
Baseline characteristics				
Age	63±13	68±9	56±15	<0.001
Male sex	212 (86)	132 (87)	80 (84)	0.57
Hypertension	92 (37)	61 (40)	31 (33)	0.24
Diabetes	35 (14)	23 (15)	12 (13)	0.58
Renal failure	74 (30)	51 (34)	23 (24)	0.11
History of AF	80 (32)	46 (30)	34 (36)	0.37
LVEF, %	35±12	33±11	39±12	<0.001
Prior VT ablation	49 (20)	22 (14)	27 (28)	0.008
VT storm/incessant VT	78 (32)	41 (27)	37 (39)	0.05
Amiodarone	105 (43)	63 (41)	42 (44)	0.67
Procedural data				
SMVT	235 (95)	144 (95)	91 (96)	0.77
Mean CL of induced VTs, ms	347±80	357±81	331±76	0.02
Clinical/presumptive clinical VT	207 (84)	131 (86)	76 (80)	0.20
MM-VT	187 (76)	120 (79)	67 (71)	0.14
PL-VT	51 (21)	22 (14)	29 (31)	0.003
Acute complete success	94 (38)	59 (39)	35 (37)	0.76

Results are expressed as a number (%), mean ± SD, or median (IQR). AF indicates atrial fibrillation; CL, cycle length; DCM, nonischemic cardiomyopathy; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MM-VT, multiple monomorphic ventricular tachycardias; PL-VT, pleomorphic ventricular tachycardia; RF, radiofrequency; SMVT, sustained monomorphic ventricular tachycardia; and VT, ventricular tachycardia.

PL-VT (PL-VT(−)) (28±9% versus 34±12%, *P*=0.02). In contrast, LVEF was not significantly different in DCM patients with and without PL-VT (37±11% versus 40±12%, *P*=0.18). In addition, among 80 patients with a preserved LVEF >40%, none of 39 IHD patients but 11 of 41 (27%) DCM patients had PL-VT (*P*<0.001). In patients with DCM, a pathogenic genetic mutation was more often found in PL-VT(+) (52% versus 30% in PL-VT(-), *P*=0.048). Table S2 provides details of likely pathogenic or pathogenic variants.

Electroanatomical Substrates and Procedural Outcome

Procedural data are provided in Table 3. Among patients with IHD, PL-VT(+) patients had significantly larger endocardial bipolar low voltage area, larger core scar and borderzone areas than PL-VT(−) patients. DCM patients with PL-VT had significantly larger endocardial bipolar and unipolar low voltage area than PL-VT(−) patients. In addition, in DCM patients, a dominant anteroseptal substrate was more frequently observed in PL-VT(+) patients (69% versus 42%, *P*=0.03). Interestingly, PL-VT was associated with worse acute procedural outcome in IHD but not in DCM (complete procedural success: IHD, PL-VT(+) 18% versus PL-VT(-) 42%, *P*=0.03; DCM, PL-VT(+) 38% versus PL-VT(-) 36%, *P*=0.88).

Long-Term Outcome

Median time of follow-up after ablation was comparable for IHD and DCM patients (31 [20–47] months versus 29 [20–49] months, *P*=0.84). During follow-up, 79 patients (32%) died and 120 patients (49%) had VT recurrence (Table S3). Heart failure was the main cause of death in both IHD and DCM patients (Table S4).

IHD and DCM patients had similar mortality rates, whereas DCM patients had more often VT recurrence (freedom from VT-recurrence after 2 years: 102/152 [67%] versus 46/95 [48%], Log-rank, *P*=0.002, Figure S2).

Impact of PL-VT on Mortality and VT Recurrence

Kaplan-Meier analyses showed a significant association between PL-VT inducibility and mortality (all-cause death and cardiovascular death) only for patients with IHD (Figure 2A, 2B, 2D, and 2E). In contrast, inducibility of PL-VT was associated with higher VT-recurrence rates in both IHD and DCM patients (Figure 2C and 2F). The higher rate of VT-recurrence in PL-VT (+) was confirmed if mortality was considered as a competing risk event. Of importance, in DCM patients, inducibility of PL-VT was associated with higher VT recurrence rates regardless of the LVEF (Figure S3).

In patients with IHD, inducibility of PL-VT was associated with higher rates of VT recurrence in univariable analysis. In multivariable analysis, only LVEF,

Table 2. Baseline Characteristics According to Inducibility of PL-VT

	IHD			DCM		
	PL-VT (+) (N=22	PL-VT (–) (N=130	*P* value	PL-VT (+), (N=29	PL-VT (–), (N=66	*P* value
Age	70±7	68±9	0.26	57±14	56±15	0.68
Men	21 (95)	111 (85)	0.31	25 (86)	55 (83)	1.00
Hypertension	9 (41)	52 (40)	1.00	10 (34)	21 (32)	0.80
Diabetes	4 (18)	19 (15)	0.75	6 (21)	6 (9)	0.18
Renal failure	10 (48)	41 (32)	0.16	11 (38)	12 (18)	0.04
History of AF	8 (36)	38 (29)	0.62	9 (31)	25 (36)	0.64
LVEF, %	28±9	34±12	0.02	37±11	40±12	0.18
Anterior MI	11 (50)	52 (40)	0.38	–	–	–
Time since MI	19±8	19±9	0.78	–	–	–
MI acute reperfusion	4 (18)	24 (18)	1.00	–	–	–
Prior CABG	8 (36)	50 (38)	1.00	–	–	–
Prior PCI	9 (41)	50 (38)	0.82	–	–	–
(Likely-) pathogenic genetic variant	–	–	–	15 (52)	20 (30)	0.048
ICD present before ablation	23 (85)	83 (66)	0.07	25 (86)	52 (79)	0.57
Prior VT ablation	4 (18)	18 (14)	0.53	9 (31)	18 (27)	0.81
VT storm/Incessant VT	6 (27)	35 (27)	1.00	14 (48)	23 (35)	0.22
Amiodarone	13 (59)	50 (38)	0.07	17 (59)	25 (38)	0.06

Results are expressed as a number (%) or mean ± SD. CABG indicates coronary artery bypass surgery; MI, myocardial infarction; and PCI, percutaneous coronary intervention. See Table 1 for the other abbreviations.

the number of induced VT, and acute procedural outcome were independent predictors of VT recurrence (Table 4). In contrast, in patients with DCM, PL-VT remained the strongest independent predictor of VT recurrence during follow-up (HR, 2.62 [95% CI, 1.47–4.69]; $P<0.001$; Table 4). All variables significant in the multivariable analyses fulfilled the proportional hazard assumption.

VT Recurrence Based On Acute Procedural Outcome and PL-VT Inducibility in DCM

In DCM patients, inducibility of PL-VT during the procedure had important prognostic implications (Figure 3). While patients with acute complete success and no PL-VT inducible had a favorable freedom of VT recurrence at 2 years of 78% [95% CI, 60%–95%], 2-year VT free rate was only 27% [95% CI, 1%–53%] in those

Table 3. Procedural Data and Acute Outcome

IHD	Overall (N=152	PL-VT (+) (N=22	PL-VT (-) (N=130	*P* value
Mean CL of induced VTs, ms	357±81	399±78	350±80	0.009
Number of induced VTs	3 (2–5)	5 (3–7)	2 (1–4)	<0.001
Low bipolar voltage (<1.5 mV) area, cm^2	61 (38–86)	81 (61–108)	58 (35–82)	0.01
Scar core (<0.5 mV) area, cm^2	24 (8–43)	43 (22–65)	22 (7–39)	0.004
Scar border (0.5–1.5 mV) area, cm^2	36 (23–49)	47 (40–57)	34 (22–46)	<0.001
Epicardial RF energy application	12 (8)	4 (18)	8 (6)	0.07
Complete procedural success	59 (39)	4 (18)	55 (42)	0.03
DCM	**Overall (N=95)**	**PL–VT (+) (N=29)**	**PL–VT (–) (N=66)**	***P* value**
Mean CL of induced VTs, ms	330±76	364±86	315±66	0.0 04
Number of induced VTs	3 (1–5)	5 (2–10)	2 (1–4)	<0.001
Low bipolar voltage (<1.5 mV) area, cm^2	5 (0–14)	11 (2–33)	2 (0–9)	0.002
Low unipolar voltage (<8.01 mV) area, cm^2	43 (12–85)	76 (38–102)	34 (11–75)	0.007
Dominant anteroseptal substrate	48 (51)	20 (69)	28 (42)	0.03
Epicardial RF energy application	43 (45)	11 (38)	32 (48)	0.34
Complete procedural success	35 (37)	11 (38)	24 (36)	0.88

Results are expressed as a number (%), mean±SD, or median (IQR). See Table 1 for abbreviations.

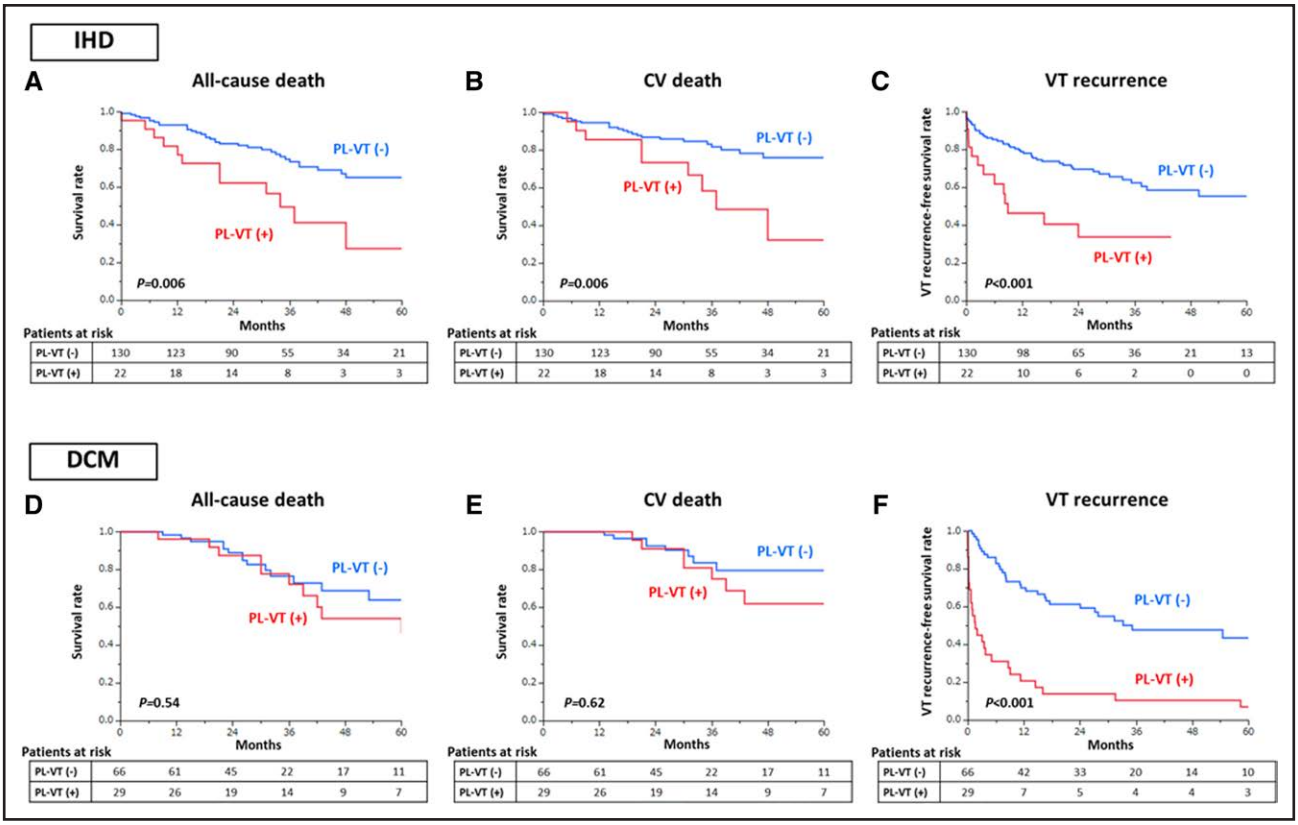


Figure 2. Survival according to pleomorphic ventricular tachycardia (PL-VT) inducibility.
A through **C**, ischemic heart disease (IHD) (**A**: all-cause death, **B**: cardiovascular death, **C**: 2-year VT recurrence), **D** and **E**, Nonischemic cardiomyopathy (DCM) (**D**: all-cause death, **E**: cardiovascular death, **F**: 2-year VT recurrence). CV indicates cardiovascular.

with complete procedural success but with documented PL-VT during the procedure. Patients with PL-VT who remained inducible for VT at the end of the procedure had a very poor prognosis, with a 2-year VT free rate of only 6% [95% CI, 0–16%].

DISCUSSION

Main Findings

This is the first study to evaluate the prevalence of inducible PL-VT, its relation to disease severity and its impact on outcome after CA of SMVT in patients with IHD and DCM. The major findings of the study can be summarized as follows: (i) PL-VT was significantly more frequently induced in DCM than in IHD. After matching for disease severity, the prevalence of PL-VT was 4 times higher among DCM patients. (ii) In IHD, PL-VT was strongly associated with a low LVEF, all-cause/cardiovascular mortality and worse procedural outcome. In contrast, in DCM, PL-VT was not related to cardiac function, mortality, or acute procedural outcome. (iii) PL-VT was an independent predictor of VT recurrence after CA in DCM but not in IHD.

These data suggest that induction of PL-VT is a marker of advanced heart failure in patients with IHD, whereas it indicates an arrhythmic substrate difficult to control by CA independently from LV function in patients with DCM.

Pleomorphic VT and LV Function

Data on pleomorphic VTs in IHD and DCM are scarce. The first report on PL-VT came from a small series of patients with sustained VT, the majority with IHD and LV aneurysm, who underwent PES. In 4 out of 14 patients *spontaneous* alterations of the VT morphology were observed.[25] In a sub-study of the DATAS trial, also including mainly patients with IHD, PL-VT documented on ICD read-outs was associated with all-cause and cardiac mortalities. Of importance, the time from the development of PL-VT to death was remarkably short (median, 1.5 months),[19] suggesting that occurrence of PL-VT may indicate progression to end-stage heart failure in IHD. In line with these data, PL-VT was significantly related to a lower LVEF, and higher mortality, mainly due to end-stage heart failure and restricted to patients with an EF<40% in our IHD cohort.

In contrast, the present study showed that DCM patients with and without PL-VT had a similar LVEF and mortality. Of note, PL-VT was observed in 27% of patients with a preserved LV function (LVEF >40%).

Table 4. Cox Regression Analysis for Predictors of VT Recurrence

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
IHD						
Age, per 1 year increase	0.98	0.96–1.01	0.18			
Men	2.68	0.99–11.0	0.053	2.70	0.84–8.68	0.10
Acute reperfusion therapy	0.74	0.35–1.42	0.39			
Prior CABG	0.84	0.48–1.42	0.52			
LVEF, per 5% increase	0.84	0.74–0.94	0.003	0.87	0.78–0.96	0.04
VT storm/incessant VT	1.31	0.72–2.27	0.37			
Amiodarone	1.62	0.96–2.72	0.07			
PL-VT	2.65	1.36–4.80	0.005			
Number of induced VTs, per 1 increase	1.31	1.19–1.43	<0.001	1.22	1.10–1.36	<0.001
Endocardial bipolar LVA, per 1 cm^2 increase	1.01	1.00–1.01	0.057			
Noncomplete success	3.45	1.84–7.06	<0.001	2.11	1.02–4.39	0.04
DCM						
Age, per 1 year increase	1.01	1.00–1.03	0.13			
Male sex	1.11	0.57–1.76	0.78			
LVEF, per 5% increase	0.88	0.79–0.98	0.02	0.92	0.81–1.05	0.19
(Likely-) pathogenic genetic mutation	2.80	1.63–4.82	<0.001	2.13	1.16–3.91	0.02
VT storm/incessant VT	1.11	0.65–1.85	0.70			
Amiodarone	1.89	1.13–3.18	0.02			
PL-VT	4.14	2.46–6.94	<0.001	2.62	1.47–4.69	<0.001
Number of induced VTs, per 1 increase	1.17	1.09–1.25	<0.001	1.08	0.99–1.17	0.06
Endocardial bipolar LVA, per 1 cm^2 increase	1.04	1.02–1.06	<0.001			
Endocardial unipolar LVA, per 1 cm^2 increase	1.02	1.01–1.04	<0.001	1.00	0.99–1.01	0.18
Dominant anteroseptal substrate	2.38	1.42–4.07	0.001	1.75	1.00–3.07	0.05
Noncomplete success	1.72	1.01–3.08	0.047	1.76	0.96–3.23	0.07

LVA indicates low voltage area. See Table 1 for other abbreviations.

Electroanatomical Findings

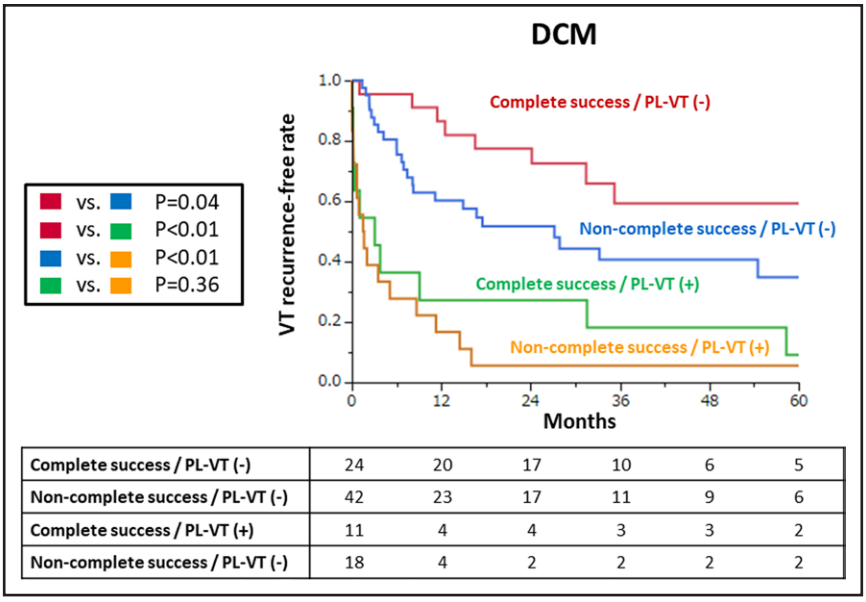
Our data suggest that, in IHD, the substrate for PL-VT is related to maladaptive, adverse cardiac remodeling. This is supported by the in particular larger electroanatomical scar border zone, as identified by BV mapping in IHD patients with PL-VT. The inhomogeneous fibrosis in the ischemic scar border zone may play an important role in the generation of VT pleomorphism.

In contrast to IHD, PL-VT occurred independently from cardiac function in DCM, suggesting that in these patients, PL-VT may be due to a pathogenesis-specific pattern of fibrosis. In DCM, electroanatomical and histological scar patterns are fundamentally different,[26,27] and dense transmural scars are a rare finding. Accordingly, low bipolar voltage areas, consistent with transmural scars, were in general small in our DCM cohort.

Unipolar voltage mapping is considered as gold standard to identify nonischemic fibrosis. In a previous study comparing in-vivo voltage mapping with 3D histology of deceased DCM patients, we could demonstrate a reduction of unipolar voltage with increasing amounts of diffuse and patchy fibrosis.[12] In the current cohort, DCM patients with PL-VT showed remarkably larger unipolar low voltage areas compared with patients without PL-VT (76 versus 34 cm^2). This disease specific pattern of fibrosis can already occur in an early stage of the disease, hence in patients with a preserved ventricular function. Of interest, PL-VTs were more frequently observed in anteroseptal compared with inferolateral substrate locations (69% versus 42%). Anteroseptal VT substrates are known to be difficult to control by ablation even in early cardiomyopathies, due to a lack of abnormal EGMs,[28] which has been explained by an intramural substrate location.[23] However, the lack of abnormal EGMs may also be due to a diffuse, not well-demarcated, fibrotic pattern which may provide the substrate for PL-VT.[12]

Impact of PL-VT on Acute and Long-Term Ablation Outcome

Conflicting results have been published regarding the impact of LV function on acute ablation outcome in IHD.[29,30] In the present IHD cohort, patients with PL-VT,



Complete success / PL-VT (-)	24	20	17	10	6	5
Non-complete success / PL-VT (-)	42	23	17	11	9	6
Complete success / PL-VT (+)	11	4	4	3	3	2
Non-complete success / PL-VT (-)	18	4	2	2	2	2

Figure 3. Ventricular tachycardia (VT)-recurrence free survival according to acute procedural outcome and pleomorphic (PL)-VT inducibility.
See Table 1 for the abbreviations.

the majority with a severely impaired systolic LV function, were more likely to remain inducible after ablation compared with those without PL-VT (acute complete success 18% versus 42%). However, although PL-VT in IHD was associated with higher VT recurrence during follow-up in univariable analysis, it did not remain an independent predictor after correction for cardiac function and persistent inducibility after ablation.

In contrast to IHD, in DCM, complete procedural success was similar in patients with and without PL-VT. Of note, occurrence of PL-VT during the procedure was the strongest predictor of VT recurrence for patients with mild to moderately impaired (LVEF >40%) and for patients with severely impaired function (LVEF ≤40%), further supporting that PL-VT in DCM does not reflect poor cardiac function but indicates a DCM specific VT substrate.

PL-VT is not synonymous with induction of multiple monomorphic VT morphologies. Before the current definition of PL-VT was stated in the 2009 consensus document,[17] multiple monomorphic VT morphologies were sometimes referred in the literature as VT-pleomorphism and have been associated with higher VT recurrence in IHD and DCM patients. Of importance, in the present study, the number of induced VT morphologies was associated with VT recurrence in multivariable analysis only in IHD, and inducibility of PL-VT was the strongest independent predictor for VT recurrence in the DCM cohort.

It has been suggested that the higher VT recurrence rates in DCM compared with IHD may at least in part be explained by the presence of deep intramural substrates difficult to reach by conventional ablation in combination with disease progression. However, despite the use of bail-out techniques, such as bipolar and needle ablation, to increase lesion depth, VT recurrence has been reported to be frequent in the mid-term follow-up period (44%–52% in 6–12 months), suggesting incomplete substrate modification rather than disease progression.[9,10]

In the present study, a particularly high VT recurrence rate of 78% in 2-years follow-up was observed in DCM patients with PL-VT, compared with 22% in those without PL-VT, independently from the acute procedural result. This finding suggests that PES may not be the appropriate diagnostic and prognostic test for some nonischemic VT substrates.

Study Limitations

This study is limited by its retrospective observational nature. The sample size especially in the propensity score-matched analysis is limited. Moreover, a complete balance between the 2 groups was not achieved on all predictors included in the propensity score model. We report on data from a single center with expertise in complex arrhythmia management, which could arise a potential selection and referral bias towards more severely affected individuals. A multicenter and prospective study is needed to validate our findings. The antiarrhythmic medication after ablation was left at the discretion of the referring cardiologist and might have influenced the incidence of VT recurrence in some patients. Another limitation is that we do not have data on the number of VT induction attempts. We routinely perform PVS at least at the beginning and at end of the procedure, but if VTs that are considered clinically relevant remain inducible after CA, additional ablation followed by repeated PES is performed. Lastly, despite our systematic diagnostic approach, we cannot fully exclude inflammation or inflammatory as one underlying cause of PL-VT in all patients.

CONCLUSIONS

Pleomorphic VT was more frequently induced in DCM than in IHD patients. IHD patients with PL-VT had poorer cardiac function and a higher mortality but not higher VT recurrence rates than patients without PL-VT, suggesting that in IHD, PL-VT might be a marker of advanced heart failure. In contrast, DCM patients with PL-VT had similar cardiac function and mortality rates as patients without PL-VT but a higher chance of VT recurrence after ablation independent of the acute procedural result. These findings suggest that in DCM, PL-VT might indicate the presence of a complex, possibly pathogenesis-specific substrate difficult to control by current ablation techniques.

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Supplemental Material

Tables S1–S4
Figures S1–S3

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