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ORIGINAL PAPER

Prognostic significance of ventricular tachycardia clustering after catheter ablation in non-ischemic dilated cardiomyopathy

Francesco Santoro[1,2] · Andreas Metzner[1] · Leonie Scholz[1] · Natale Daniele Brunetti[2] · Christian-H Heeger[1,3] · Andreas Rillig[1] · Bruno Reissmann[1] · Christine Lemeš[1] · Tilmann Maurer[1] · Thomas Fink[1] · Osamu Inaba[1] · Naotaka Hashiguchi[1] · Karl-Heinz Kuck[1] · Feifan Ouyang[1] · Shibu Mathew[1]

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Abstract

Background Ventricular tachycardia clustering (VTc) is associated with a worse clinical outcome in patients with non-ischemic dilated cardiomyopathy (NI-DCM) and implantable cardioverter defibrillator (ICD); however, its role after catheter ablation (CA) has still not been investigated. Aim of this study was to evaluate the prognostic significance of VTc after CA.

Methods 96 consecutive patients (59 ± 13 years, 82% males) with NI-DCM underwent CA for drug-refractory VT. After CA, patients with VT recurrence were divided into two groups: (1) patients that presented with VTc defined as the occurrence of three or more appropriate ICD interventions within 2 weeks, and (2) patients without VTc.

Results At 56-months follow-up after ablation 52/96 (54%) patients had recurrent VT, 28/52 (54%) patients experienced VTc and 24/52 (46%) no VTc. When comparing patients with VTc after CA with those without, no differences in terms of age, sex, ejection fraction and cardiovascular risk factors were found. However, patients with VTc showed higher mortality rates at follow-up (54% vs 21% $p = 0.04$; log-rank $p \leq 0.01$). No survival differences were found between patients without VT recurrence and those with VT recurrence but without VTc (29% vs 21% $p = 0.77$). Predictors of VTc were LVEF < 30% at follow-up and endo–epicardial scar at 3D voltage mapping. At stepwise multivariate analysis VTc and NHYA class were the only independent predictors of death (respectively, RR 3.4, CI 95% 1.16–10.3, $p = 0.02$; RR 4.18, CI 95% 1.3–12.6, $p = 0.01$).

Conclusions VTc after CA is an independent predictor of survival and is associated with reduced LVEF at follow-up and endo–epicardial scar at 3D voltage mapping.

Keywords Ventricular tachycardia · Non-ischemic dilated cardiomyopathy · Clustering · DCM · Follow-up · Survival

Introduction

Catheter ablation (CA) of ventricular tachycardia (VT) is a therapeutic option for patients with non-ischemic dilated cardiomyopathy (NI-DCM) [1]. Recent data showed that freedom from VT is associated with improved survival among patients with structural heart disease [2] VT clustering (VTc) has been defined as three or more episodes of VT/VF within two weeks adequately treated with implantable cardioverter defibrillator (ICD) intervention. VTc has been mainly investigated after ICD implantation and was associated with impaired survival [3]. However, no study investigated VT recurrence features after CA and its potential implication at follow-up. Aim of this study was to evaluate incidence, predictors and prognostic features of VTc after CA in NI-DCM patients.

Methods

Study population

Between September 2000 and August 2013, 96 consecutive patients with NI-DCM were admitted for CA of VT

Francesco Santoro and Andreas Metzner contributed equally and should both be considered as first authors.

✉ Francesco Santoro
dr.francesco.santoro.it@gmail.com

[1] Department of Cardiology, Asklepios Klinik, St Georg, Lohmühlenstraße 5, 20099 Hamburg, Germany

[2] Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy

[3] University Heart Center Lübeck, Lübeck, Germany

at Asklepios Klinik St. Georg, Hamburg, Germany. All patients had evidence of left ventricular (LV) dilation and LV systolic impairment [LV ejection fraction (LVEF) < 50%] persistent for at least 9 months despite optimal medical treatment after the initial diagnosis. Patients with coronary artery disease, congenital heart disease, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC/D), LV non-compaction, restrictive cardiomyopathy, (sub)acute myocarditis, cardiac sarcoidosis, toxic cardiomyopathy or primary valvular abnormalities were excluded.

Written informed consent was obtained from each patient prior to the procedure.

The current study complies with the Declaration of Helsinki and was approved by the local ethics committee (WF-07/16 Ärztekammer Hamburg).

Catheter ablation

Electrophysiological study and catheter ablation were performed under deep sedation utilizing midazolam, fentanyl and continuous infusion of propofol or under general anesthesia at operator's discretion. The ablation procedures were performed as previously described [4, 5].

The primary ablation end point was elimination of the clinical VT(s) and all mappable inducible VT(s). All patients underwent bipolar substrate mapping (scar defined as voltage < 1.5 mV for the endocardium; voltage < 1.0 mV for the epicardium [6]). Endocardial mapping was performed in all patients and epicardial mapping was performed if: (1) the 12-lead ECG of the VT suggested an epicardial origin; (2) there was evidence of epicardial substrate on imaging studies (eg, cardiac magnetic resonance imaging); (3) in the presence of unipolar electrogram abnormality (< 8.3 mV) with or without minimal bipolar (< 1.5 mV) electrogram abnormality; (4) in case of failure of endocardial ablation (either early VT recurrence or persistent inducibility of clinical VT) (Fig. 1).

Ablation was performed at the site of diastolic potentials during VT in case of stable VT and good post-pacing intervals after entrainment of the VT or guided by pace mapping at the substrate area with fractionated or late potentials (Fig. 2). For hemodynamically unstable VTs, substrate modification was performed with cluster/linear lesions targeting abnormal electrograms.

Irrigated radio-frequency current was delivered in power-controlled mode, power 30 to 40 W, irrigation 17 to 30 ml/min, and temperature limit 43 °C. At the end of the procedure programmed ventricular stimulation was always re-performed to evaluate inducibility of VT. The stimulation protocol consisted of programmed ventricular stimulation from the RV apex and RVOT (right ventricle outflow tract) at 2 drive cycle lengths with up to 3 extrastimuli and incremental burst pacing at a cycle length up to 250 ms. Acute procedural success was defined as the absence of any inducible VT (clinical or not) after programmed ventricular stimulation, at the end of the procedure.

Follow-up and definition of ventricular tachycardia clustering

Post-ablation care and follow-up prior to discharge included transthoracic echocardiography (TTE) to rule out pericardial effusion, as well as 12-lead ECG and ICD interrogation. The primary endpoint was all-cause mortality, recurrence of sustained VT documented by 12-lead ECG, ICD, Holter ECG or rhythm strip was defined as a secondary end point. VT recurrences after CA were classified into VTc if three or more sustained episodes of VT or VF (requiring ICD intervention with either DC shock or

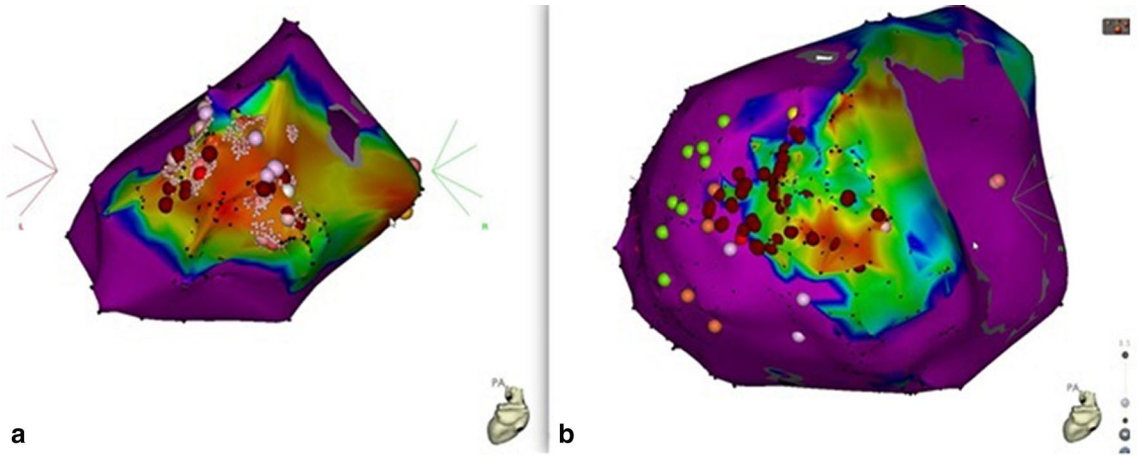

Fig. 1 Endo–epicardial electroanatomic map of the left ventricle showing a clear substrate in lateral-basal segments of both endocardium (**a**) and epicardium (**b**)

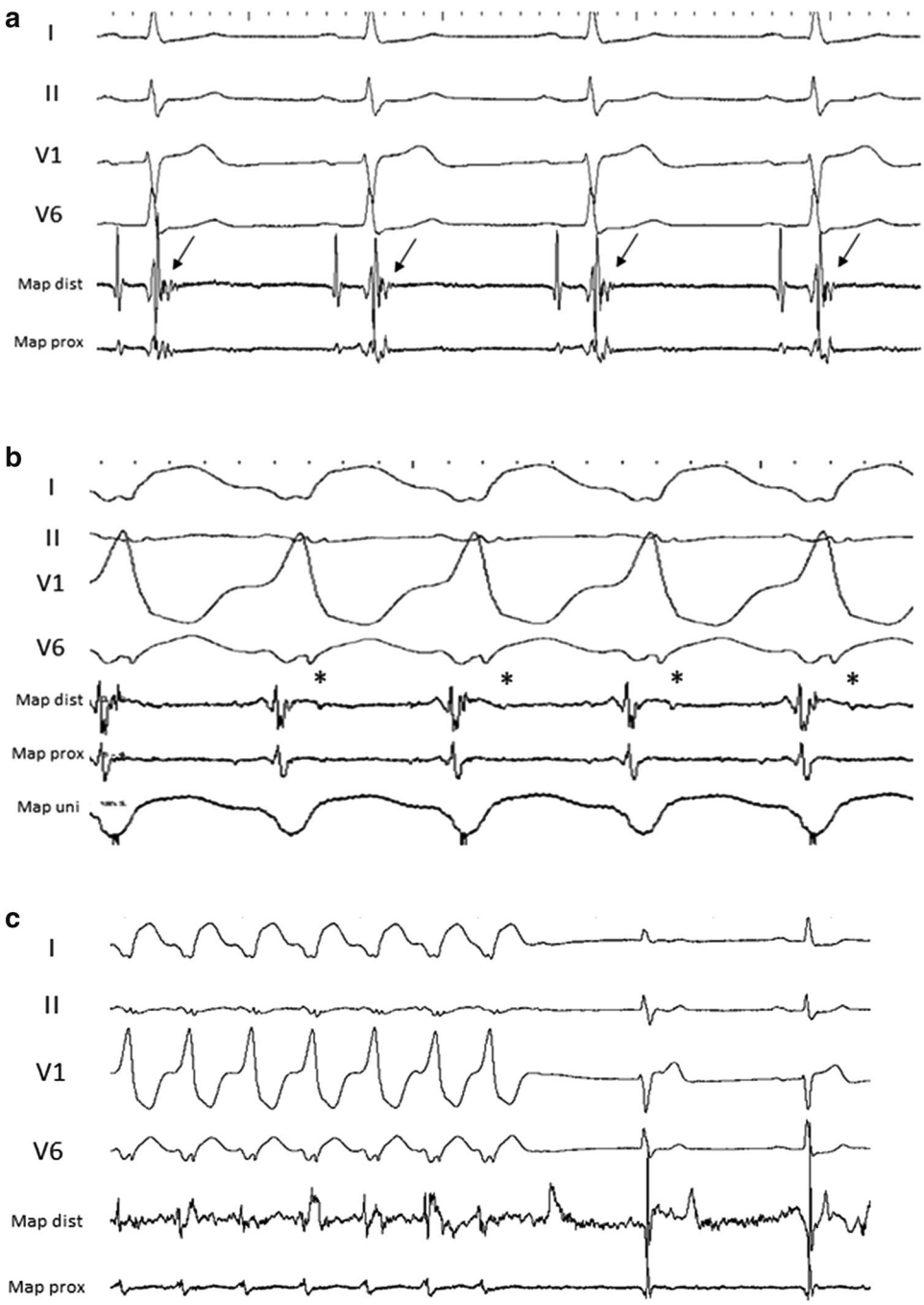

Fig. 2 **a** Surface ECG and intracardiac recordings from mapping catheter in the left ventricle in the lateral segment of the epicardium, with delayed and fractionated potentials (arrows) during sinus rhythm (**b**) evidence of mid-diastolic potential (*) during ventricular tachycardia on mapping catheter located in the same area (**c**) termination of ventricular tachycardia during catheter ablation in this area

anti-tachycardia pacing) were documented within 2 weeks, or into VT without clustering if less than three episodes of VT or VF were documented within 2 weeks. VT/VF storm was defined as three or more sustained episodes of VT or VF documented within 24 h. Follow-up was performed at 3 and 6 months post-ablation, and in 6-month intervals thereafter. Post-discharge follow-up included ICD interrogation at all visits as well at least one TTE to assess for LV thrombus formation and LVEF. Discontinuation of anti-arrhythmic drugs was recommended 3 months post-ablation.

Statistical methods

Continuous variables are expressed as mean ± standard deviation and compared with Student's t test or Mann–Whitney *U* test as appropriate. Categorical variables are presented as percentages and compared with χ^2 or Fisher test as required.

Kaplan–Meier survival plots and log-rank test were used to evaluate the prognostic significance of VTc after CA regarding event-free survival. Multiple Cox' analysis was used to identify predictors for survival probability and for correcting bias of principal confounders, Relative risk as well as 95% confidence intervals (CI) were calculated. A $p < 0.05$ was considered as statistically significant.

Results

Baseline features

Ninety-six consecutive patients with NI-DCM (age 59 ± 13 years, 82% male) underwent CA for drug-refractory VT. Their baseline features are reported in Table 1. Thirty-three out of 96 (34%) patients presented with appropriate ICD intervention with DC shock, 8/96 (8%) patients with VT/VF storm, and 8/96 (8%) patients with symptomatic VT treated by anti-tachycardia pacing (ATP). Twenty-one out of 96 patients (22%) received a previous ablation in another institution.

Procedural data and outcome

At the beginning of the index procedure clinical VT was inducible in 79/96 (82%) patients and a mean of 2.2 ± 1.5 VT morphologies were induced (mean cycle length 395 ± 90 ms.). Acute procedural success was achieved in 68/96 (70%) patients. Among these patients clinical and non-clinical VTs were not inducible at the end of the procedure (Table 2).

Table 1 Baseline characteristics of patients with non-ischemic dilated cardiomyopathy and ventricular arrhythmias

Num. Pat, *n*	96
Age (years)	59 ± 13
Male, *n* (%)	79 (82%)
NHYA class	2 ± 1
Hypertension, *n* (%)	48 (50%)
Diabetes, *n* (%)	13 (13%)
Chronic obstructive pulmonary disease, *n* (%)	7 (7%)
Chronic kidney disease, *n* (%)[a]	31 (32%)
ARB/ACE, *n* (%)	52 (54%)
Beta-blocker, *n* (%)	78 (81%)
Echocardiographic evaluation	
Left ventricular ejection fraction (%)	32 ± 11
LVED diameter (mm)	61 ± 7
Clinical presentation	
VT storm, *n* (%)	8 (8%)
ICD-DC shock therapy, *n* (%)	33 (34%)
ICD-ATP therapy, *n* (%)	6 (6%)

[a]Chronic kidney disease was defined as the presence of glomerular filtration rate < 60 ml/min/1.73 m^2 for 43 months

One hundred forty-two procedures were performed in 96 patients (mean 1.5 ± 1; range 1–7 per patient). Twenty-five (27%) patients received a second procedure and 10 (10%) patients received three or more procedures. VT-free survival rate after a single procedure was 46% and first recurrence occurred within a median of 21 months.

VT clustering incidence, features and predictors

Considering VT recurrence features after index procedure, 28/52 (54%) patients experienced VTc and 24 /52 patients (46%) suffered from VT without clustering. Patients with VTc were not different from those without in terms of age, sex, cardiovascular risk factors and LVEF at admission (Table 2). Moreover, there were no differences in terms of VT inducibility before and after CA (Table 2). All patients had an ICD implantation before or immediately after CA and CRT device was present in 46% and 36% among patients with and without VTC ($p = 0.55$). Among patients with VTc, 20/28 (72%) patients received appropriate ICD shock and 8/28 (28%) patients ATP therapy. In patients without VTc, 4/24 (16%) patients received appropriate ICD shock and 7/24 (29%) patients ATP therapy. Mean number of CA procedures in patients with or without VTc was 2.1 ± 2 and 2 ± 0.9 ($p = 0.88$).

Patients of both groups received similar drug treatment during follow-up apart from amiodarone which was prescribed at a higher rate in patients of the VTc group (82% vs 36% $p = 0.03$).

Eighteen out of 28 (64%) patients presented with VTc before CA, meanwhile 10/28(36%) patients suffered from VTc after index VT ablation. A trend toward an increased number of VTc over years of follow-up was observed. During first year after CA mean number of VTc was 1.25 and at fifth year of follow-up it was 2.14 (p for trend < 0.05, Fig. 3).

Predictors of VTc were LVEF at 6 months FU ≤ 30% (30 ± 9% vs 38 ± 13 $p \leq 0.01$) and endo–epicardial scar at 3D left ventricle voltage mapping (32% vs 7% $p \leq 0.01$).

Prognostic significance of VTc

Patients with VTc had a statistically higher mortality rate during follow-up when compared to those without VTc (54% vs 21% $p = 0.04$, Log rank $p \leq 0.01$). However, no differences in terms of mortality were found between patients with VT recurrence without clustering and those without VT recurrence (21% vs 29% $p = 0.77$) (Fig. 4).

In the VTc group 15 out of 28 (54%) patients died at long-term FU. Eight out of 15 (53%) patients died due to cardiovascular causes. Of those, 6 patients had end-stage heart failure and 2 patients untreatable electrical VT storms.

Table 2 Baseline features and events at follow-up among patients with and without VT clusters

	Patients with VT cluster		Patients without VT cluster		*P* value
	Mean	SD	Mean	SD	
NUM. of patients	28		24		
Age	61	±9	55	±13	0.10
Male	77%		87%		0.38
Class of heart failure					
NHYA class I	26%		6%		0.17
NHYA class II	33%		40%		0.98
NHYA class III	33%		46%		0.87
NHYA class IV	8%		6%		0.98
Crt device	46%		36%		0.55
CV risk factors					
Hypertension	41%		47%		0.68
Diabetes	14%		10%		0.69
Chronic kidney disease	36%		37%		0.98
Echocardiogram findings					
Admission LVEF%	30%	±10	31%	±12	0.83
Admission LVEDD (mm)	62	±6	60	±10	0.24
LVEF after CA	30%	±9	35	±11	0.09
LVEDD (mm) after CA	62	±6	61	±11	0.56
ICD intervention at follow-up					
ICD-DC shock	72%		16%		<0.01
ICD ATP	28%		29%		0.98
VT/VF storm	14%		0%		0.12
VT inducibility before and after ablation	91% 35%		93% 33%		0.98 0.99
VT cycle length	370±95 msec		360±95 msec		0.81
Num. of ablations	2.1	±2	2	±0.9	0.88
Medication at discharge					
Class I-AA	14%		9%		0.67
Beta-blocker	75%		87%		0.30
Sotalol	4%		0		0.88
Amiodarone	68%		38%		0.05
ACE-I/ARB	61%		55%		0.78
Medication at follow-up					
Class I-AA	17%		9%		0.56
Beta-blocker	82%		95%		0.78

Table 2 (continued)

	Patients with VT cluster		Patients without VT cluster		*P* value
	Mean	SD	Mean	SD	
Sotalol	10%		0		0.78
Amiodarone	82%		36%		0.03
ACE-I/ARB	61%		55%		0.78

Moreover, 4 patients were listed for heart transplantation. One of them received heart transplant, meanwhile another 2 patients underwent left ventricular assistance device (LVAD) implantation. In the VT recurrence group without VTc, 5 out of 24 (21%) patients died. Four out of 5 (80%) patients died for cardiovascular causes (end-stage heart failure) and no patient underwent heart transplantation or LVAD implantation. Among patients without VT recurrence 13 out of 44 patients (29%) died. Six out of 13 (46%) patients died for cardiovascular causes and 3/13 (27%) of them for heart failure.

At univariate and multivariate analysis including patients with VT recurrence (both VTC and single VT), VTC and NHYA class (RR 3.46 95% CI 1.1–3.4 $p=0.02$; RR = 4.18 95% CI 0.92–0.97 $p=0.01$, respectively) were the only statistically significant predictors for mortality at long-term follow-up (Table 3).

Discussion

To the best of our knowledge, this is the first study that evaluated the role of VTc after CA in patients with NI-DCM. The main findings of this study are the following:

1. VTc after CA is associated with an increased risk of mortality and, together with NHYA class, are the only independent predictors of mortality;
2. No difference in terms of mortality is assessed when comparing patients with VT recurrence without clustering and those without VT recurrence;
3. Predictors for VTc after CA are LVEF < 30% at 6 months FU, and endo–epicardial substrate at 3D left ventricular voltage mapping.

VTc in NI-DCM has been investigated only among patients with previous ICD implantation due to mainly primary prevention. We report incidence, predictors and prognostic significance of VTc among NI-DCM patients after VT ablation.

Incidence of VT clustering

In the present study, we report a VTc incidence of 54% after CA in patients with NI-DCM, which is higher than described in previous studies which only evaluated patients that did not undergo CA. Indeed, Baensch et al. reported an incidence of 28.3% among patients with ICD implantation after 33 months FU [3] and Lunati et al. 52% among heart failure patients with a biventricular ICD and after 19 months

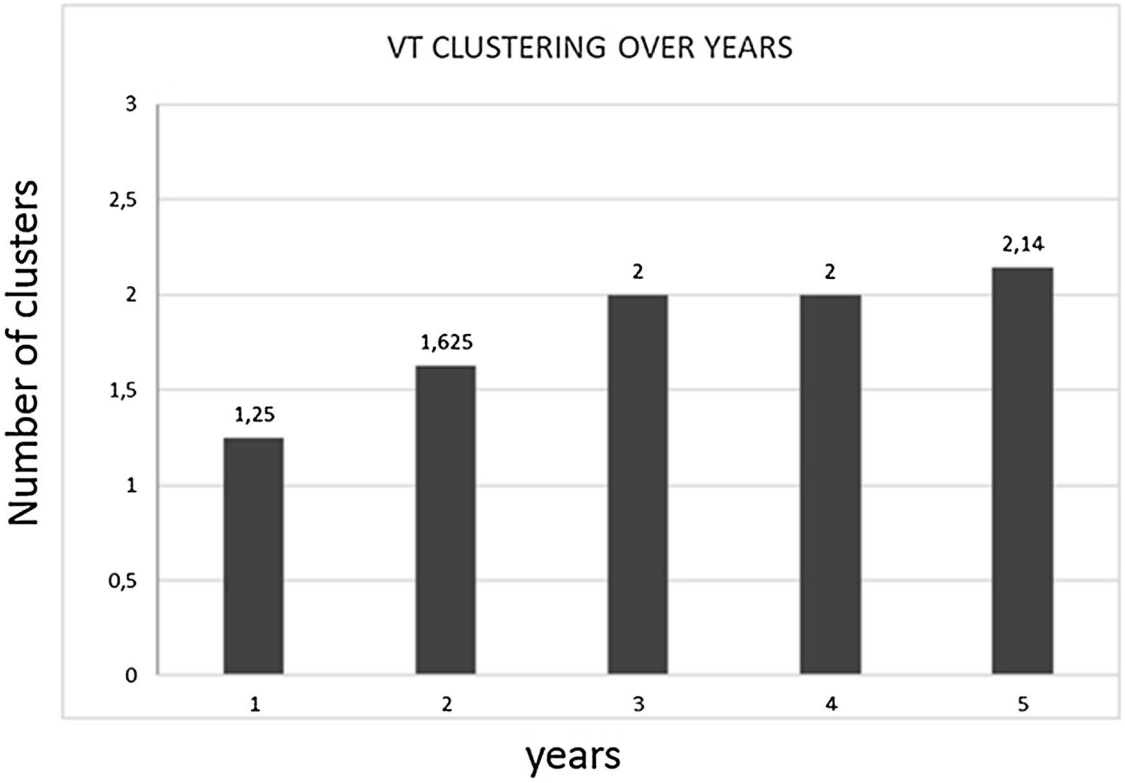

Fig. 3 Mean ventricular tachycardia (VT) clustering episodes experienced during follow-up after catheter ablation of VT

FU [7]. However, the present cohort is a subset of high-risk patients with a previous history of VT.

Some differences may be related to VTc definition, which consists of three VT/VF episodes treated within 24 h in some studies [3, 8] and within 2 weeks in others [9]. In the present study, VTc has been defined as three ventricular arrhythmia episodes treated with appropriate ICD intervention within 2 weeks, because, as reported by Wood et al., VTc has a non-random distribution and 78% of VTc episodes occur within 5 days since the first VT episode [10]. VTc has a circadian presentation with a morning and afternoon peak [11]; most of them happen in association with an increase in monthly temperature range and also during working hours and working days [12].

Predictors of clustering

In previous studies predictors of VTc were heart failure before ICD implantation, occurrence of monomorphic VT, EF < 40%, and thyroid dysfunction [3, 6, 7]. We found two predictors of VTc: reduced EF at 6-month FU (< 30%) and endo–epicardial scar at 3D left ventricular voltage mapping. This study remarks the importance of endo–epicardial voltage mapping to predict the prognosis among NI-DCM patients. Indeed, transmural substrate involvement may imply an advanced disease with mid-myocardial scarring [13]. Cardiac MRI may be a valid surrogate to investigate this feature and allow for non-invasive risk stratification. Piers et al. found that transmural myocardial scar, as assessed by late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) imaging, was able to predict monomorphic VT in 87 patients with NI-DCM and ICD [14]. Moreover, Gulati et al. found that midwall fibrosis with LGE at CMR imaging is an independent prognostic predictor beyond LVEF in patients with NI-DCM [15].

CA ablation of VT in NI-DCM has a lower success rate when compared to ischemic cardiomyopathy because of the complexity of substrate in these patients [16]. A complete abolishment of all pathological electrical potentials found in both endocardium and epicardium could provide better results in terms of VT recurrence and rehospitalization [17]. In addition, intramural substrates cannot be reached from both the endo- and epicardium in some patients.

Prognostic implication

This study shows that VTc after CA of VT is an independent predictor of mortality in addition to NHYA class,

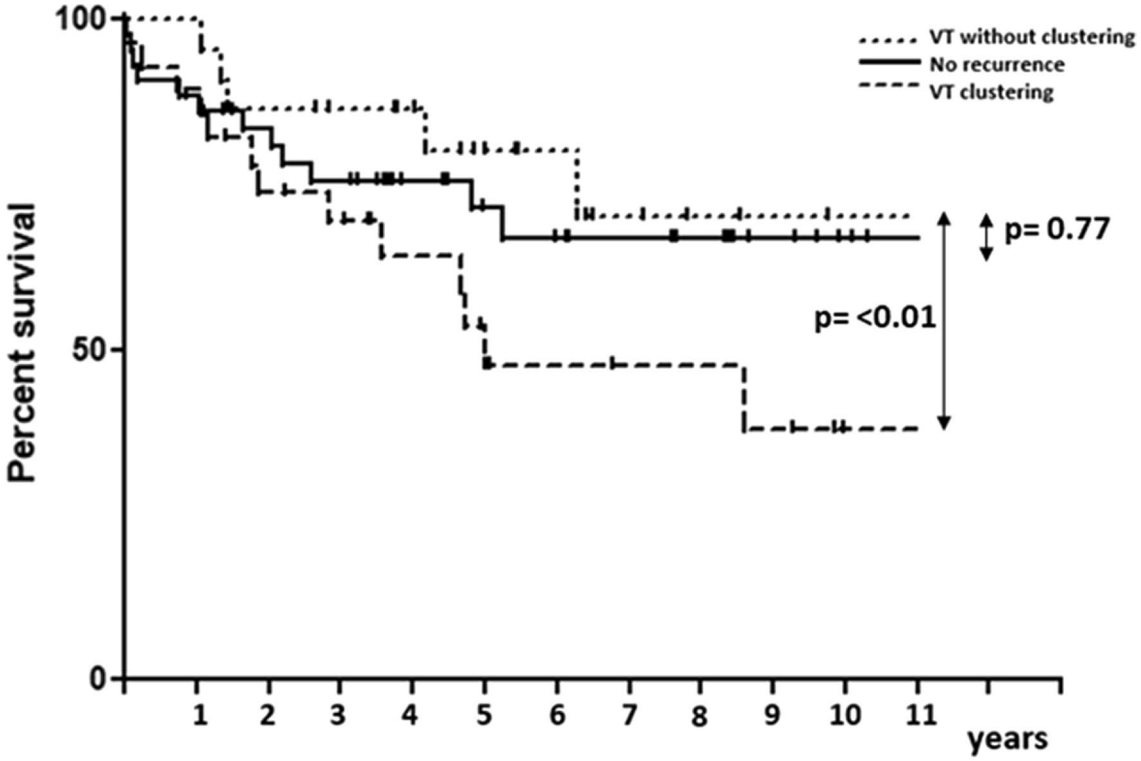

Fig. 4 Kaplan–Meier curve of survival after catheter ablation in patients without ventricular tachycardia (VT recurrence), with VT recurrence with clustering, and VT recurrence without VT clustering

Table 3 Univariate and multivariate analysis of predictors of mortality including patients with VT recurrence (both VTc and single VT)

Variable	Univariate analysis			Multivariate analysis		
	RR	95% CI	*P* value	RR	95% CI	*P* value
Age	1.01	0.97–1.05	0.45			
Male	0.29	0.04–2.20	0.23			
Admission LVEF	0.97	0.93–1.01	0.16			
VT cluster	2.93	1.05–8.18	**0.04**	3.46	1.1–3.4	**0.02**
NHYA class	3.97	1.33–11.84	**0.01**	4.18	0.92–0.97	**0.01**

Bold *p* values statistically significant

while, instead, VT recurrence without clustering has no prognostic implication. Therefore, ICD monitoring after CA is crucial to clearly identify the presence of VTc. Indeed, these patients have a worse prognosis and may require a strict cardiological evaluation. Patients with VTc had a higher rate of ICD shocks at FU, which could be associated with an increased risk of mortality. Villacastin et al. compared patients with multiple appropriate ICD-DC shocks vs those with only single shock and found that the first group had a higher mortality rate [19]. Moreover, in the same study, no survival differences were present among patients with a single ICD shock vs those without. LVEF was the only independent predictor of multiple ICD shock [18]. NHYA class III combined with reduced LVEF has been also associated with an increased risk of multiple ICD shocks [19].

Although catheter ablation is an important therapeutic strategy for symptoms improvements (i.e., reduction of ICD shocks), no randomized study has shown mortality reduction after VT ablation [20, 21].

Moreover, the diagnosis of NI-DCM is still based on exclusion criteria and identification of sub-types with different evolution and prognosis is crucial to provide early treatment to high-risk patient. VTc after CA may represent an important indicator of advanced disease and patients

with VTc should be referred to heart failure and electrophysiology clinics.

Limitations

Some limitations have to be considered for the present investigation. First, this is a single-center retrospective study with its typical limitations. Second, 22% of patients received a previous ablation procedure at other institutions. Third, cardiac MRI was not routinely performed and there was not a cardiac imaging protocol before ablation. Fourth, all procedures were performed in a tertiary high-volume center with extensive ablation experience and therefore results cannot be generalized. Fifth considering a large enrolling period (from September 2000 to August 2013), there might be some differences regarding ICD programming that could influence also mortality in this population.

Conclusions

VTc after CA in NI-DCM is an independent predictor of mortality and is associated with reduced LVEF and presence of endo–epicardial scar at voltage mapping.

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