Ventricular Dysrhythmias During Long-Term Follow-Up in Patients With Inherited Cardiac Arrhythmia

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Reports on development of frequent ventricular premature complexes (fVPC), (non)sustained ventricular tachycardias ([n]sVT), or ventricular fibrillation (VF) and their interrelationship in patients with different inherited cardiac arrhythmia (ICA) have sofar not been reported. The aim of this study is therefore to examine incidences and recurrences rates of sVT and VF ("malignant ventricular tachyarrhythmias, VTA") in addition to the incidence of fVPC and nsVT ("ventricular dysrhythmias, VDR") in patients with various ICA during long-term follow up. Patients (N = 167, 88 male, age 45 ± 15 years) with ICA including definite/borderline arrhythmogenic right ventricular cardiomyopathy (ARVC, N = 47), Brugada syndrome (BrS, N = 71), catecholaminergic polymorphic ventricular tachycardia (CPVT, N = 7), long QT syndrome (LQTS, N = 41) or short QT syndrome (SQTS, N = 1) who had frequent 24-hour Holter monitoring during a follow-up period of 4.6 ± 4.4 years. During the initial screening visit, 15 patients had a history of malignant VTA. fVPC and nsVT was observed in respectively 19% (OHCA/VF/sVT: N = 9) and 13% (OHCA/VF/sVT: N = 4) of all patients. Compared with the ARVC group, patients with BrS and LQTS had less frequent fVPC and nsVT (fVPC: odds ratio [OR] 0.20, 95% confidence interval [CI] 0.08 to 0.49, p <0.000 and OR 0.09, 95% CI 0.02 to 0.33, p <0.000; nsVT:OR 0.17, 95% CI 0.06 to 0.50, p = 0.001 and OR 0.09, 95% CI 0.02 to 0.46, p = 0.003). The recurrence rate of malignant VTA was 33%. In conclusion, variety of VDR and malignant VTA were found during long-term follow-up in patients with ICA. During nearly a 5 years follow-up period, the recurrence rate of malignant VTA was considerable. fVPC, nsVT, and malignant VTA were most often found in patients with an ARVC. **© 2019 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;124:1436−1441)**

Inherited cardiac arrhythmias (ICA), including channelopathies and cardiomyopathies, are responsible for approximately 5% to 10% of all sudden death cases.[1,2] The clinical spectrum of ICA ranges from asymptomatic to SCD caused by life-threatening ventricular tachyarrhythmias (VTA).[3,4] Previous studies have attempted to identify ICA patients at high risk of SCD. Priori et al identified a history of syncope, spontaneous Brugada type I electrocardiogram (ECG), ventricular refractory period <200 ms, and QRS fragmentation as high-risk factors for development of VTA in patients with Brugada syndrome (BrS).[5] Most studies evaluate the risk of developing life-threatening VTA in populations with a specific ICA. Reports on development of frequent ventricular premature complexes (fVPC), nonstained ventricular tachycardias ([n]sVT) or ventricular fibrillation (VF) in patients with different ICA during long-term follow-up and their interrelationship are scarce. The aim of this study is therefore to examine incidences and recurrences rates of fVPC, (n)sVT and VF in patients with various ICA during a long-term follow-up period.

Methods

This retrospective, single center study is part of the "EvaluatioN of CardiOgenetic Disease and Effectiveness of scReening" (ENCODER) project, which was approved by the local ethics committee in the Erasmus Medical Center Rotterdam, the Netherlands (MEC-2014-313). Informed consent was not required because all data, including patient characteristics and test outcomes, were collected from patients' medical records.

Patients older than 18 years who visited the cardiology outpatient clinic between 2004 and 2015 for cardiogenetic evaluation were included. They had survived VF/an out of hospital cardiac arrest (OHCA), had episodes of either nsVT or sustained VT (sVT), complaints with suspicion of ICA, were family members of a patient with (suspicion of) an ICA or were referred by the department of clinical genetics (mutation carriers). Patients with myocardial ischemia, anatomical abnormalities and intoxications were excluded. In this study, we selected a subgroup of patients diagnosed with an ICA who had Holter monitoring during the initial cardiogenetic evaluation and yearly follow up visits. These patients visited the outpatient clinic once a year. Examinations included history taking, registration of surface ECGs and 24-hour Holter monitorings.

ARVC, BrS, LQTS, Short QT syndrome (SQTS), and catecholaminergic polymorphic VT (CPVT) were according to

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Table 1
Clinical characteristic

	All (N = 167)	ARVC (N = 47)	BrS (N = 71)	LQTS (N = 41)	CPVT (N = 7)	SQTS (N = 1)
Male	88 (53%)	23 (49%)	45 (63%)	17 (42%)	2 (29%)	1(100%)
Age (mean ± SD) years	45±15	48±16	45±15	45±15	27±14	26
Indication for cardiogenetic evaluation						
Documented VT	15 (9%)	11 (23%)	2 (3%)	1 (2%)	1 (14%)	–
Genetic screening, known diagnosis	44 (26%)	13 (28%)	23 (32%)	6 (15%)	2 (29%)	–
Genetic screening, unknown diagnosis	22 (13%)	6 (13%)	10 (14%)	4 (10%)	2 (29%)	–
Complaints suspected for ICA	50 (30%)	8 (17%)	33 (47%)	7 (17%)	1 (14%)	1(100%)
Carriers	17 (10%)	3 (6%)	2 (3%)	12 (29%)	–	–
VF/OHCA	6 (4%)	4 (9%)	1 (1%)	1 (2%)	–	–
Other diagnosis	13 (8%)	2 (4%)	–	10 (25%)	1 (14%)	–

ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; ICA = inherited cardiac arrhythmia; LQTS = long-QT syndrome; OHCA = out of hospital cardiac arrest; SQTS = short QT syndrome; VF = ventricular fibrillation; VT = ventricular tachycardia.

criteria defined in the 2015 ESC guideline for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.[6] Diagnosis is based on ECG abnormalities, family history or pathogenic mutations. ARVC is further differentiated into possible, borderline and definite ARVC but in this study we only included definite and borderline patients.[7]

In this study, VPC and nsVT were defined as ventricular dysrhythmias (VDR) and sVT and VF as "malignant" VTA. All 24-hour holter monitorings from every visit were

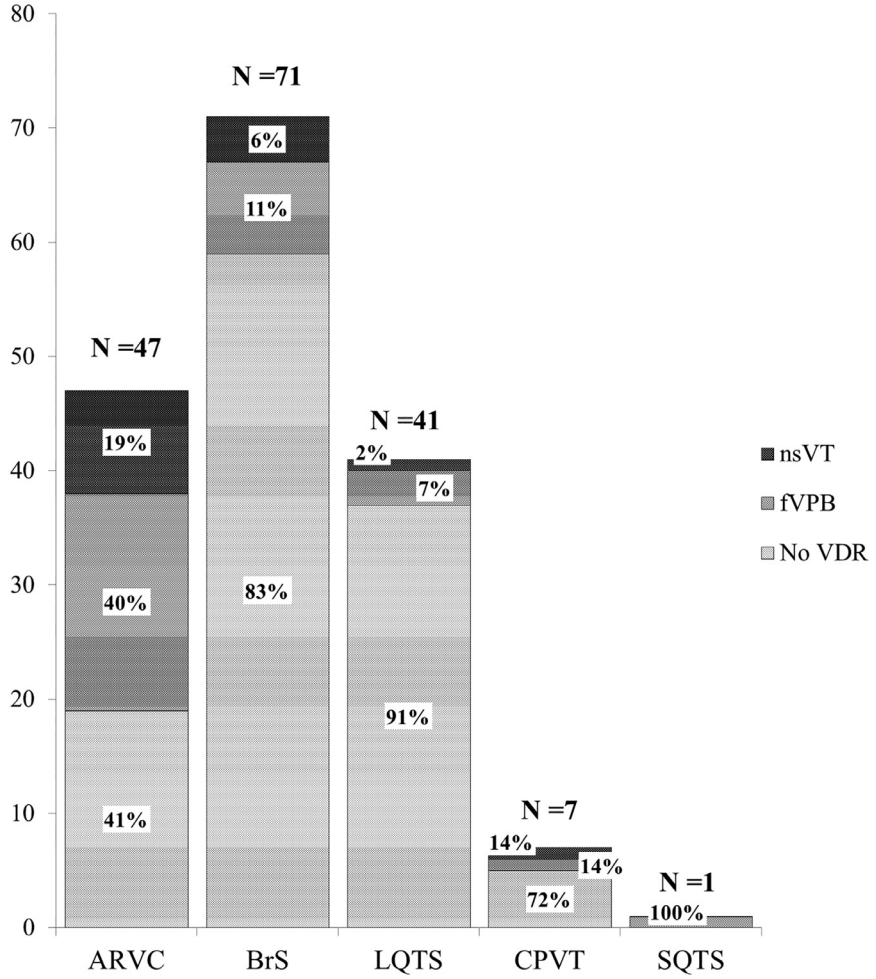

Figure 1. Bars demonstrating the percentage of patients presenting with frequent VPC and nsVT during initial screening in each group of patients. ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; fVPC = frequent ventricular premture complexes; LQTS = long-QT syndrome; nsVT = nonsustained ventricular tachycardia; SQTS = short QT syndrome; VDR = ventricular dysrhythmia.

reviewed for the occurrence of VDR and malignant VTA. fVPC are defined as VPCs with a frequency of more than 10 per hour or more than 240 VPCs per 24 hours.[8] If patients had an implantable cardioverter defibrillator (ICD), we evaluated the approriateness of every shock using the ICD printouts.

Continuous variables were expressed as mean ± standard deviation. The Shapiro-Wilk or Kolmogorov-Smirnov test was applied to evaluate whether continuous variables were normally distributed. Categorical data were denoted by percentages. A binary logistic model was used to compare the risks of developing VDR between the different ICA. A p value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS, version 21 (IBM, Armonk, NY).

Results

Characteristics of the 167 selected patients are summarized in Table 1. The majority of patients had definite/boderline ARVC, BrS, or LQTS. Twenty-one patients were initially referred with documented VT (sVT: N = 9, nsVT: N = 6) or they were VF/OHCA (N = 6) survivors. During follow-up, 52 (37%) patients received an ICD; ICD indications were either primary (N = 37) or secondary prevention (N = 15).

FVPC were found in 32 (19%) patients during the initial screening at the outpatient clinic; 6 of them were referred for previous sustained VT and 3 patients were VF/OHCA survivors. Figure 1 shows that fVPC during the initial Holter monitorings were most often observed in the ARVC group compared with the CPVT, BrS, and LQTS group.

NsVT was present in 21 (13%) patients during the initial screening. Comparable to fVPC, Figure 1 shows that nsVT also occurred more frequently in ARVC patients followed by BrS, CPVT and LQTS. In the latter 3 groups, none of these patients had a history of malignant VTA.

Median duration of the follow-up period was 5 years (IQR 5 years). Figure 2 shows the development of various VDR over time. In the entire study population, malignant VTA only developed in patients with an ICD. Out of 52 patients with an ICD, 15 patients experienced appropriate shocks (AS), as shown in Figure 3. Five of them were referred with a history of malignant VTA. Thus, the recurrence rate of malignant VTA is 33%. Inappropriate shocks (IS) were detected in 5 patients and were caused by supraventricular tachycardia (N = 4) or dysfunction of the RV lead (N = 1).

Table 2 shows that BrS (odds ratio [OR] 0.20, 95% confidence interval [CI] 0.08 to 0.49, p <0.000) and LQTS (OR 0.09, 95% CI 0.02 to 0.33, p <0.000) patients are less likely to develop fVPC than ARVC patients. Similary, Table 3 shows that BrS (OR 0.17, 95% CI 0.06 to 0.50, p = 0.001) and LQTS patients (OR 0.09, 95% CI 0.02 to 0.46, p = 0.003) are also less likely to experience nsVT compared with ARVC patients. Patients with CPVT and SQTS were not included in the analysis because of the small number of patients.

Discussion

A variety of VDR and malignant VTA were found during long-term follow-up in patients with ICA. The recurrence rate of malignant VTA was as high as 33%.

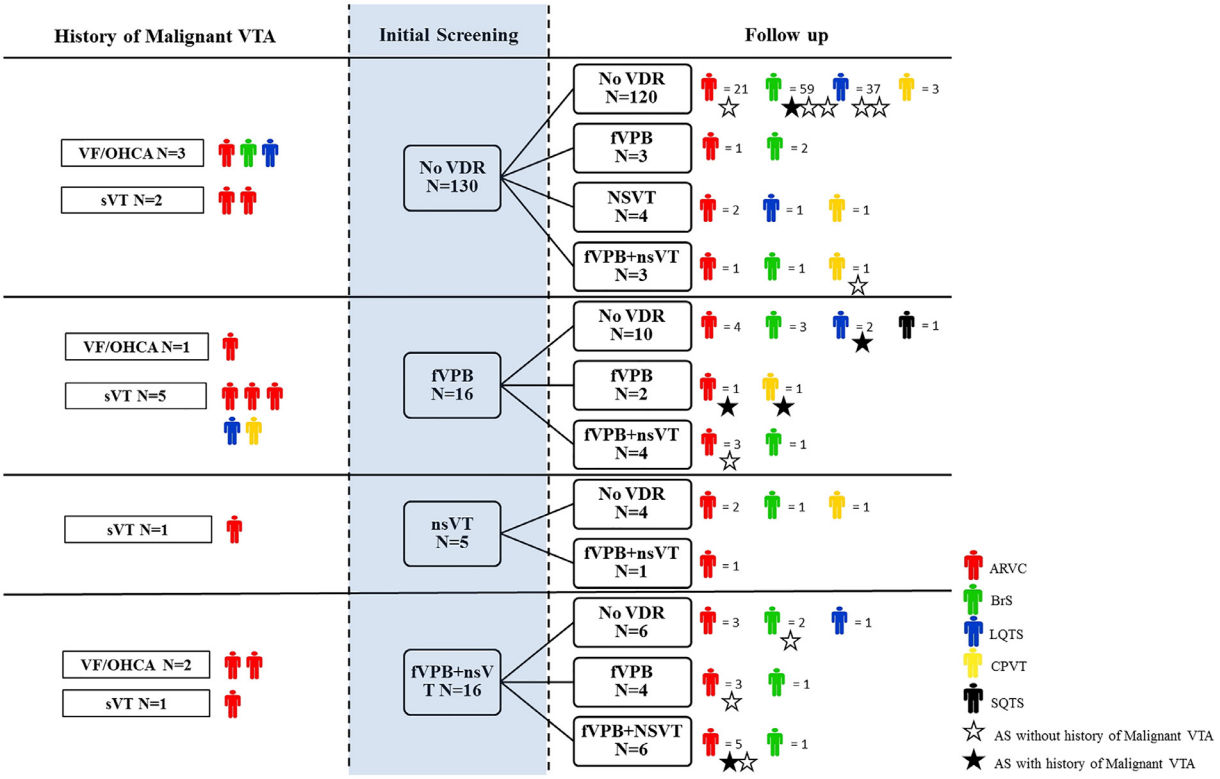

Figure 2. Flowchart demonstrating the development of various VDR during long term follow up.

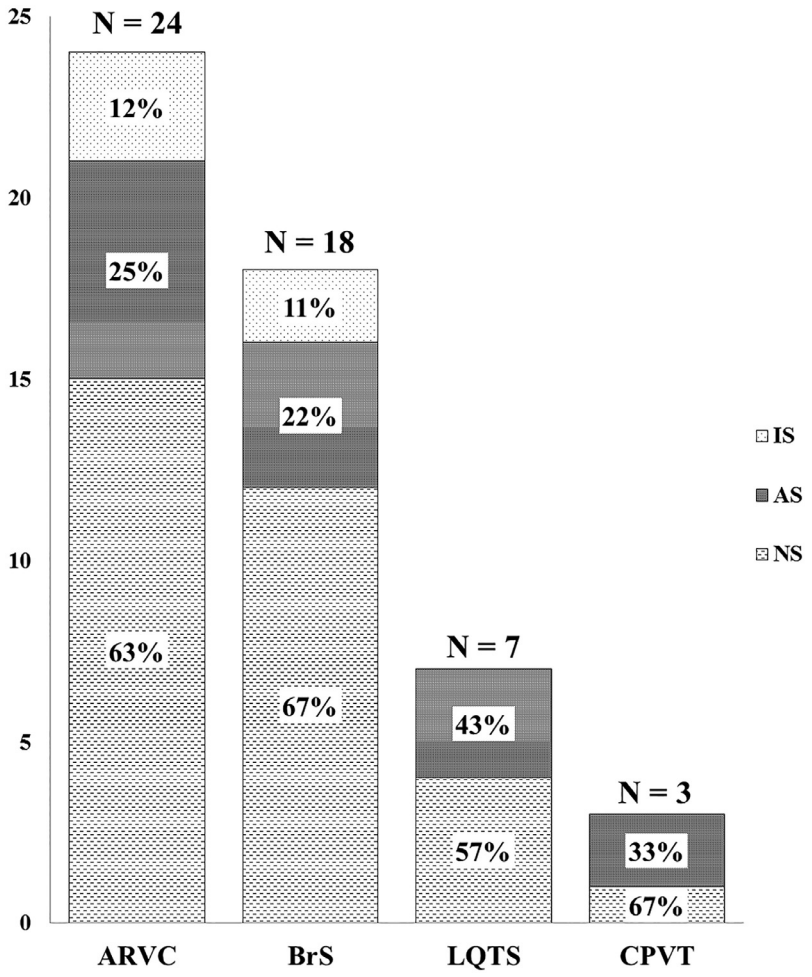

Figure 3. Bars demonstrating the distribution of shocks in patients with ICD. AS = appropriate shock; ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; IS = inappropriate shock; LQTS = long-QT syndrome; NS = no shock; SQTS = short QT syndrome.

Table 2
Binary logistic regression model – predictors of fVPC in BrS and LQTS patients compared with ARVC patients

VPC >10	OR	CI 95%	p
BrS	0.20	0.08-0.49	0.000
LQTS	0.09	0.02-0.33	0.000

ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; fVPC = frequent ventricular premature complexes; LQTS = long-QT syndrome.

Table 3
Binary logistic regression model – predictors of nsVT in BrS and LQTS patients compared with ARVC patients

nsVT	OR	CI 95%	p
BrS	0.17	0.06-0.50	0.001
LQTS	0.09	0.02-0.46	0.003

ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; LQTS = long-QT syndrome; nsVT = nonsustained ventricular tachycardia.

Compared with BrS and LQTS, ARVC patients had more VDR and malignant VTA.

Although VPC are common in the general population[9,10] they are considered to be benign. Frequent ventricular ectopy may, however, induce a cardiomyopathy.[11,12] The Framingham Heart Study demonstrated that in men without apparent coronary artery disease, asymptomatic ventricular ectopy is associated with a twofold increase in risk for all-cause mortality.[13] Other studies also showed that fVPC increase the risk of SCD significantly in apparently healthy men (adjusted relative risk = 3.0; p <0.025).[14]. Previous studies have suggested that VPC may trigger VT episodes which in turn may progress into VF and asystole.[15-17] Although these findings could not be derived from our ICA patients, the presence of VPC or nsVT indicated a higher probability to develop malignant VTA.

Most patients with fVPC or nsVT in this study population were ARVC patients; and they were also more likely to develop fVPC and nsVT than BrS and LQTS patients. NsVT are well-known risk factor for sudden cardiac death in ARVC patients.[18] The combination of increased ventricular

ectopy and structural abnormalities in ARVC patients may explain why ARVC patients have a higher susceptibility to develop VDR and eventually malignant VTA. Patients with ARVC have regional fibrofatty replacements of ventricular myocardium which result in localized abnormalities in morphology, especially in the right ventricle (RV). However, as ARVC progresses, fibrofatty replacements extends to other RV areas and finally also the left ventricle (LV).[19]

In this study, only a few BrS patients had VDR or VTA during follow up. Similar observations were made in a Canadian study population of 105 BrS patients of whom only 6.7% had VF or monomorphic VT.[20] Likewise, Rodríguez-Mañero et al found that 4.2% (35 from 834 patients) of BrS patients with an ICD experienced VTA (monomorphic ventricular tachycardia).[21] However, apart from the ARVC group, BrS patients had more both VDR and malignant VTA compared with the remainder of the study population. Recent studies demonstrated that similar structural abnormalities found in ARVC are also present in the right ventricular outflow tract of patients with BrS.[22-25] There may also be an overlap in the pathophysiology between BrS and ARVC patients.[26-28] The presence of structural abnormalities could explain why BrS patients presented with more VDR and malignant VTA compared with other channelopathies in this study.

Mechanisms underlying development of VDR may not only differ between patients with various ICA but may also differ between patients with the same ICA. For example, both reentry and triggered activity due to delayed after depolarization have been suggested as the main mechanism of arrhythmias in patients with BrS.[29] On the other hand, different degrees of overlap could be present between group of diseases as mentioned above.

The small sample size in some ICA groups hampered comparison of development of VDR between all ICA groups. Selecting only patients with Holter recordings can produce a selection bias in this study. Also, not all patients had an ICD and were thus not continuously monitored which implies that episodes of fVPC and nsVT could have been missed. For that reason, we only reported the recurrence rate of malignant VTA.

Conclusion

In patients with ICA, the recurrence of malignant VTA was considerable during a nearly 5-year follow-up period. Compared with BrS and LQTS, fVPC, nsVT, and malignant VTA were most often found in patients with ARVC patients.

Disclosures

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