Substrate of ventricular tachycardia

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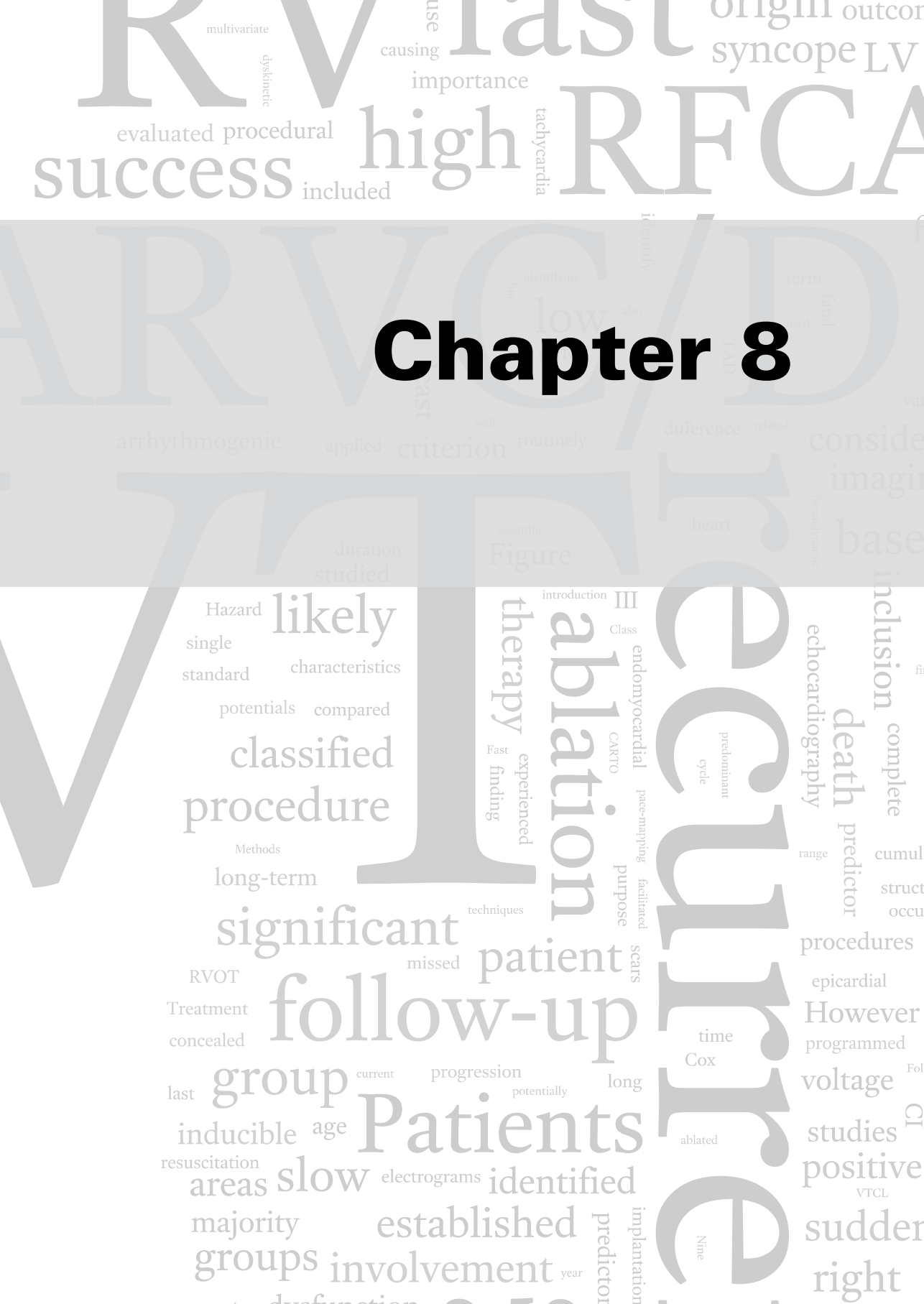
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Patients with scar-related right ventricular tachycardia: determinants of long-term outcome

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Abstract

Introduction: Patients with established ARVC/D based on task force (TF) criteria and ventricular tachycardia (VT) are at risk of VT recurrence and sudden death. Data on patients with VT due to right ventricular (RV) scar not fulfilling TF criteria are lacking. The purpose of this study was to assess the long-term arrhythmia recurrence rate and outcome in patients with scar-related right VT with and without a diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC/D).

Methods: Sixty-four patients (age 43.5±15yr, 49 male) presenting with non ischemic scar-related VT of RV origin were studied. Scar was identified by electroanatomical mapping, contrast-echocardiography and/or MRI. Patients were evaluated and treated according to a standard institute protocol.

Results: Twenty-nine (45%) patients were diagnosed with ARVC/D according to TF criteria (TF+) and 35 (55%) with RV scar of undetermined origin (TF-) at the end of follow-up (64±42 months). Patients were treated with anti-arrhythmic drugs, Radiofrequency catheter ablation and/or ICD implantation. VT recurrence-free survival for TF+ and TF- was 76% vs. 74% at 1yr and 45% vs. 50% at 4yr (p=ns). Patients with fast index VT (CL≤250ms, n=31) were more likely to experience a fast VT during follow-up than patients with a slow index VT (CL>250ms, n=33) (61% vs. 3%, p<0.001).

Conclusions: Scar-related RV VTs have a high recurrence rate in TF+ and TF- patients. Patients presenting with a fast index VT are at high risk for fast VT recurrence and may benefit most from ICD therapy.

Introduction

Patients with scar-related ventricular tachycardia (VT) of right ventricular (RV) origin are at risk for VT recurrence and sudden cardiac death. RV scar can be due to various diseases, such as ischemic heart disease, viral myocarditis, sarcoidosis, and genetically determined diseases. Subtle forms of RV involvement may not always be detected and classified by clinical evaluation including echocardiography, heart catherization, MRI and endomyocardial biopsy which may have important diagnostic and therapeutic implications. An important cause of RV scar is arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), a progressive and most likely genetic disease. In more than 50% of affected patients no familial occurrence[1] or disease specific genetic mutations[2] are found, therefore diagnosis of ARVC/D is based on criteria proposed by a generally accepted consensus report by an international task force (TF).[3]

Prognosis and risk factors for arrhythmia recurrence and sudden cardiac death in patients with ARVC/D have been studied. Class III antiarrhythmic drugs may be effective to control arrhythmia[4]. Radiofrequency catheter ablation (RFCA) is acutely effective in selected patients but hampered by a high recurrence rate during follow-up perhaps due to progression of the disease or subepicardial substrate.[5, 6] ICD implantation for secondary prevention has shown a high incidence of appropriate ICD therapy of 70% to 74%.[7, 8]

Data on patients presenting with scar-related left bundle branch block (LBBB) type VT without an established diagnosis of ARVC/D according to TF criteria are lacking.

The purpose of this study is to compare the clinical presentation, arrhythmia recurrence and outcome in patients with ARVC/D versus TF negative patients with scar-related LBBB type VT's during long term follow-up.

Methods

Patient population

Data from 64 patients referred to the Leiden University Medical Center with non-ischemic scar-related LBBB type VT, defined as predominant S-wave in precordial lead V1 were studied.

Patients had to meet the following criteria for inclusion in the study: documentation of sustained LBBB type VT and evidence of RV scar. RV scar was defined as (1) akinetic or dyskinetic wall motion abnormalities and/or severe right ventricular dilatation with dysfunction[3] on echocardiography[9, 10] or MRI [11-14] and/or (2) as regions of adjacent, fragmented, prolonged (≥3 positive deflections, ≥40ms signal duration) and low amplitude bipolar electrograms (≤1.5 mV) [15, 16] on catheter mapping. Patients with (1) idiopathic LBBB VT without evidence of RV scar, (2) with extensive left ventricular (LV) scar or dysfunction

(LV ejectionfraction <45%) and (3) with significant symptomatic coronary artery disease (defined as positive exercise test and >50% diameter stenosis in one or more coronary arteries) were excluded.

Diagnostic Evaluation

All patients underwent standard invasive and non-invasive testing for ARVC/D according to the criteria defined by the Task Force (TF) of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology[3]. In these guidelines major and minor TF criteria have been established encompassing structural, histological, electrocardiographical, clinical and familial aspects of ARVC/D (Table 1).

A 12-lead surface electrocardiogram (ECG) was obtained to determine the presence of T-wave inversion beyond lead V_2, a QRS duration ≥110ms in leads V_1-V_3, the presence of an epsilon wave[3] and terminal activation delay (TAD) >55ms[17]. QRS durations were measured at 100mm/s. Two-dimensional echocardiography with emphasis on wall motion abnormalities and function of the RV and LV with and without intravenous contrast was performed. Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis, two-chamber and four-chamber images).

MRI studies were obtained using a 1.5 T MRI system (Philips Medical Systems, Best, The Netherlands). To evaluate regional cardiac function, ECG- triggered multislice, multi-phase gradient-echo MR imaging of the heart was performed encompassing both ventricles with 10-12 imaging planes. MRI studies were evaluated by an experienced cardiac radiologist. Evaluation by signal-averaged electrocardiography was not performed. Endomyocardial biopsies were not obtained routinely because of the well-known sampling error caused by the segmental nature of ARVC/D and the possible risk of perforating the thin walled RV in patients with ARVC/D.[18] All patients were classified according to TF criteria. The diagnosis of ARVC/D was established when at least 2 major criteria or 1 major plus 2 minor criteria or 4 minor criteria were fulfilled. TF negative patients who fulfilled 1 major and 1 minor criterion or 3 minor criteria were classified as 'probable' ARVC/D. In a second analysis the recently proposed TAD was included and considered as diagnostic class IV major criterion.

Arrhythmias

The cycle length (CL) of the index LBBB like VT was measured. In patients presenting with syncope or resuscitation the induced LBBB like VT was considered as index VT. Fast VT was defined as a VT with a CL≤250ms. Syncope without ECG documentation was considered as VT with hemodynamic compromise and registered as fast VT for analysis purpose. Slow VT was defined as VT with a CL>250ms. Electrical programmed stimulation was performed in all patients. The induction protocol consisted of 3 drive-cycle lengths (600, 500 and 400ms) and up to 3 ventricular extrastimuli from 2 right ventricular sites and burst pacing.

Table 1. Diagnostic Criteria

	Definition	TF+ n=29	TF- n=35
Class I Dysfunction and structural alterations			
Major	Severe dilatation and reduction of RV ejection fraction with no (or mild) LV impairment and/or localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging)	**25**(86)	**6**(17)
Minor	Mild global RV dilatation and/or ejection fraction reduction with normal LV and/or mild segmental dilatation of the RV and/or regional RV hypokinesia	**3**(10)	**14**(40)
Class II Tissue characterization of walls			
Major	Fibrofatty replacement of myocardium on endomyocardial biopsy	-	-
Class III Repolarization abnormalities			
Minor	Inverted T waves in right precordial leads (V2 and V3) (age> 12 yr; in absence of right bundle branch block)	**17**(58)	**1**(3)
Class IV Depolarization abnormalities			
Major	Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V1-V3)	**17**(58)	**1**(3)
	Terminal activation duration (TAD) ≥55ms*	**17**(58)	**6**(17)
Minor	Late potentials (signal-averaged ECG)	-	-
Class V Arrhythmias			
Minor	Left bundle branch block type ventricular tachycardia and/or frequent ventricular extrasystoles	**29**(100)	**35**(100)
Class VI Family history			
Major	Familial disease confirmed at necropsy or surgery	**0**(0)	**0**(0)
Minor	Familial history of premature sudden death due to suspected right ventricular dysplasia and/or familial history (clinical diagnosis based on present criteria)	**0**(0)	**1**(3)

Diagnostic criteria for ARVC/D as defined by McKenna et al.(3) The number (%) of patients fulfilling each criterion is given for patients with (TF+) and without (TF-) diagnosis of ARVC/D. *Recently proposed diagnostic criteria for ECG depolarisation abnormalities[17], not included to classify patients into TF+ and TF-.

Treatment

Patients were treated according to the routine clinical protocol. The protocol included class III antiarrhythmic drugs (preferably sotalol) in all patients and RFCA if feasible. Patients who were not inducible after RFCA and/or on class III antiarrhythmic drugs were discharged without ICD and antiarrhythmic drug therapy was maintained. Patients who were resuscitated and patients who remained inducible despite AAD received an ICD. In the later course of the study also patients who present with spontaneous or inducible fast VT received an ICD regardless of the results of electrical programmed stimulation and an established diagnosis of ARVC/D.

Hemodynamically tolerated VT were mapped and ablated during VT. Target sites for ablation were sites with an isolated middiastolic potential, and/or sites where pacing entrained the VT with concealed fusion and a postpacing interval within 30ms of the VT cycle length. For fast and hemodynamically untolerated VT the mapping approach was based on the presence of electrograms with low amplitude fragmented signals, double potentials and/or isolated late potentials during sinus rhythm. At these sites pace-mapping was performed. A paced QRS morphology similar to the VT QRS morphology and stimulus to QRS delay >40ms was used to identify target sites for ablation. Ablation for slow and fast VT's was initially performed using roving catheter techniques and later facilitated by electroanatomical mapping (EAM) (CARTO XP EP system, Biosense Webster Inc, Diamond Bar, CA, USA or RPM™ system, Boston Scientific, Natick, MA, USA).

Complete procedural success was defined as the absence of any inducible monomorphic VT at the end of the ablation procedure. Partial success was defined as successful ablation of the clinical tachycardia and ablation failure if the clinical VT could not be successfully ablated.

Follow-up

All patients were followed routinely at our clinic. During visits a detailed history with regard to arrhythmia recurrence was taken. Progression of disease was defined as progressive de- or repolarization abnormalities on ECG, progression of RV dilatation and new a- and dyskinetic areas on echocardiography and/or MRI.

Arrhythmia recurrence was defined as not-otherwise explained syncope or documented VT on 12-lead ECG, 24-hour holter registration, event monitor and/or ICD.

All patients were reevaluated and classified according to TF criteria at last visit.

Statistical Analysis

Continuous variables are expressed as mean±SD, and categorical variables as frequency(%). Comparison of data was performed using the Student's *t*-test. The probability of remaining event free was analyzed by the Kaplan-Meier method, and differences in event-free survival were evaluated with the log-rank test. Multivariate analysis was performed with the use of

Cox regression analysis and variables that were found statistically significant in univariate analysis.

Twenty-one out of 49 patients in the study population underwent more than one ablation procedure because of VT recurrence. In order to judge the long-term effect of RFCA, subsequent procedures were included in the survival analysis using a delayed entry approach, with time from inclusion as analysis time scale. Individuals who had more than one procedure reentered the survival analysis after their initial recurrence. Since multiple occurrences of the same patient are based on disjoint time intervals, correction for dependence is not needed in this approach. For all tests a p-value <0.05 was considered significant.

Results

Study population

The studied population consisted of 49 males and 15 females. Median age at referral was 39yr (range 15–79yr). Thirty-three (52%) patients were younger than 40yr. At presentation 25 patients were diagnosed with ARVC/D according to TF criteria. At the end of follow-up 29 patients fulfilled TF criteria for ARVC/D (TF+) and 35 patients did not fulfill TF criteria (TF-). Nine of the 35 TF- patients were classified as probable ARVC/D. The diagnosis of ARVC/D was based on at least 2 major TF criteria in 11 and at least 1 major and 2 minor TF criteria in 18 patients. In TF- group 14 patients fulfilled only 1 minor, 12 patients fulfilled 2 minor, 2 patients fulfilled 3 minor and 7 patients fulfilled 1 major and 1 minor TF criterion (Table 1). If the newly proposted TAD criterion was applied only one additional patient would have been classified TF+.

RV scar was detected by imaging techniques in 44(69%) patients (TF+ 28 (97%) vs. TF- 16 (46%, p<0.001), in 20 (31%) TF- patients scar was only identified by EAM.

Severe RV dysfunction was present in 7 patients (TF+ 6 vs. TF- 1, p=0.02) and mild left ventricular (LV) involvement in 8 (TF+ 5 vs. TF- 3, p=0.29). In patients with severe RV dilatation and dysfunction the QRS duration was significantly longer as compared to patients with mild RV involvement (149±28ms vs. 110±24 respectively, p<0.001).

Low amplitude, fragmented electrograms were found in 42/49 patients (TF+ 81% vs. TF- 89%, p=0.28) who underwent RFCA. Patient characteristics are summarized in Table 2.

Presentation and treatment

Nine patients (14%) had been resuscitated and 12(19%) had experienced syncope, all of these patients were inducible for LBBB type VT at electrical programmed stimulation. A fast VT (CL ≤250 ms) was documented in 10 (17%) patients and a slow VT (CL>250 ms) in 33 (52%) patients at initial presentation. Forty-nine (72%) patients were treated with Class III antiarrhythmic drugs and 49 (72%) underwent at least one RFCA procedure. A total of 97

Table 2. Patient Characteristics

	TF+ n=29	TF- n=35	P=
Sex M/F	**26/3**	**23/12**	0.02
Age	**41**±13	**46**±18	0.21
Imaging			
Mild TVR	**14**(48)	**16**(46)	0.90
Moderate TVR	**5** (17)	**5**(14)	0.77
Mild PVR	**11**(38)	**19**(54)	0.12
Moderate PVR	**0**(0)	**2**(6)	0.19
Mild RV dilatation	**9**(31)	**3**(11)	0.06
Severe RV dilatation	**10** (34)	**3**(9)	0.011
Mild RV dysfunction	**7**(24)	**2**(6)	0.04
Severe RV dysfunction	**6**(21)	**1**(3)	0.02
LV involvement	**5**(19)	**3**(9)	0.27
Catheter mapping			
Low voltage fragmented electrograms	**17**(59)	**25**(71)	0.28
Located at 1 RV area			
RV outflow tract	**4**(24)	**11**(44)	0.22
RV apex	**1**(6)	**3**(12)	0.48
RV free wall	**0**	**2**(8)	0.24
Adjacent to Tricuspid Annulus	**2**(12)	**1**(4)	0.33
Located at ≥2 RV areas	**10**(59)	**8**(32)	0.07
Presentation			
Resuscitation	**4**(14)	**5**(14)	0.96
Syncope	**8**(28)	**4**(11)	0.09
Fast VT (CL≤250ms)	**6**(21)	**4**(11)	0.31
Slow VT (CL>250ms)	**11**(38)	**22**(63)	0.05
CL VT at baseline (ms)	**260**±55	**286**±67	0.10
Superior axis VT*	**14**(48)	**10**(29)	0.15
Multiple VT morphologies*	**9**(34)	**5**(14)	0.14

CL indicates cycle length; EPS, programmed extrastimulation;TVR, tricuspid valve regurgitation; PVR, pulmonary valve regurgitation; TF+, taskforce positive; TF-, taskforce negative, RV, right ventricular; LV, left ventricular; VT, ventricular tachycardia. * VT's Spontaneous at presentation or at first EPS. Data are expressed as absolute number (%) or mean±SD.

RFCA were performed with complete success in 17 (45%) of the procedures in TF+ patients and in 33 (56%) in TF- patients (p=0.25). Antiarrhythmic drug therapy was continued after RFCA in all patients. 3-Dimensional EAM of the RV was used to facilitate RFCA in 58(59%) procedures in 33 patients (CARTO system in 25 patients, RPM system in 8 patients). RFCA

Table 3. Treatment

	TF+ n=29	TF- n=35	p=
Medication			
Class III	**22**(76)	**27**(77)	0.68
Other	**5**(17)	**8**(23)	0.68
RFCA			
Patients	**21**(72)	**28**(80)	0.48
Number RFCA procedures	**38**	**59**	
Mean no RFCA	**1.31**±1.13	**1.69**±1.99	0.37
Complete success	**17**(45)	**33**(56)	0.25
Partial/No success	**21**(55)	**26**(44)	0.25
3-D EA mapping (% of patients)	**13**(62)	**20**(71)	0.22
ICD	**19**(66)	**7**(20)	<0.001

RFCA indicates radiofrequency catheter ablation; ICD, implantable cardioverter defibrillator; TF+, taskforce positive; TF-, taskforce negative; 3-D EA, 3 dimensional electroanatomical. Data are expressed as absolute number (%) or mean±SD.

success was not influenced by the use of 3-D EAM systems or the site of origin (RVOT vs. none RVOT) of the VT.

An ICD was implanted in 26 patients (41%), 66% of patients in group TF+ and in 20% of patients in TF- (p<0.001) (Table 3).

Patient follow-up

The mean follow-up until last evaluation for VT recurrence was 64±42 months, range 1 to 166 months (TF+ 68±43 months vs. TF- 61±42 months, p=0.51). Follow-up between inclusion and last evaluation for the presence of TF criteria was 57±42 months. During follow-up VT recurrence occurred in 41 patients, (TF+ 20 (72%) and TF- 21 (60%) p=0.21). The cumulative VT recurrence-free survival after the index event was 76% and 74% at 1 year, 59% and 61% at 2 years and 45% and 50% at 4 years, for TF+ and TF- respectively. There was no significant difference in the VT recurrence-free interval between both groups (Figure 1). Within the TF- group (n=35) the VT recurrence free survival was comparable between patients with a probable ARVC/D (n=9) and patients with less than 1 major + 1 minor or 3 minor TF criteria (n=26) (respectively 53% and 49% at 4 years, p=0.54). Three patients died during follow-up (3 TF+).Two deaths were sudden, both occurred in patients without ICD during the early phase of the study when ICD's were not implanted routinely for patients presenting fast VT. One death was non-cardiac.

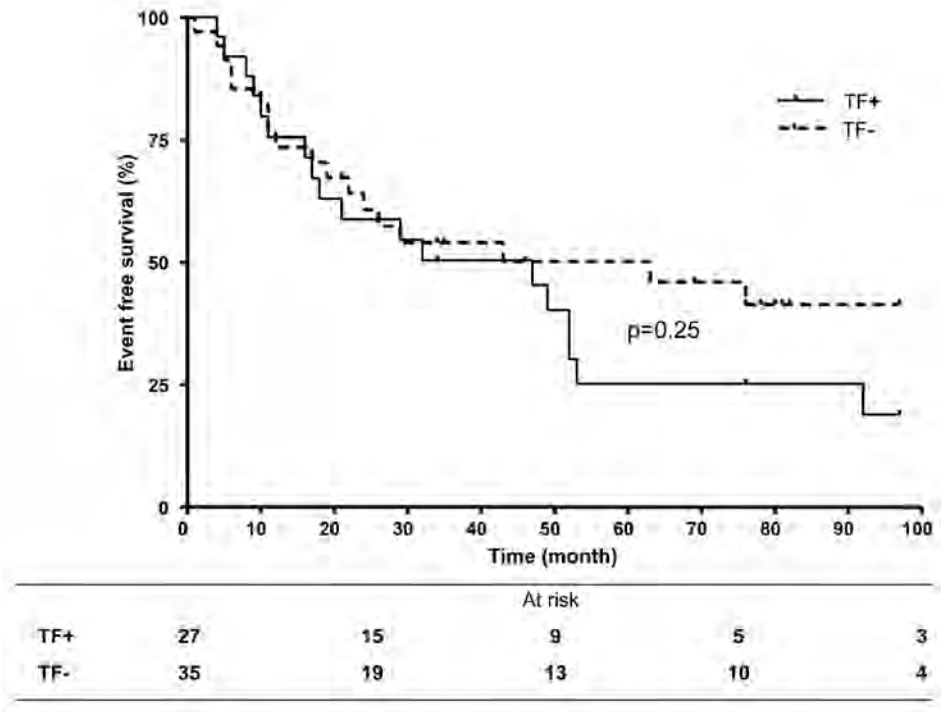

Figure 1. Survival analysis showing the cumulative event free survival for patients with (TF+) and without (TF-) diagnosis of ARVC/D after initial presentation. The table below the graph indicates the numbers of patients at risk.

Cycle length of the index VT

Patients with documented fast VT or syncope at inclusion had a significant lower cumulative recurrence-free interval (35% at 4 years) than patients with documented slow VT (60% at 4 years) (Figure 2). Except for one patient (TF+, index VT CL 260ms), no patient with slow VT at presentation experienced fast VT during follow-up. Figure 3 illustrates the shortest documented VTCL at inclusion and the shortest documented VTCL during follow-up for each individual patient.

Predictors of VT recurrence

Fast VT and/or resuscitation and/or syncope at inclusion and age≤40yr at referral were significant predictors for recurrence after univariate Cox regression analysis of the baseline characteristics. Diagnosis of ARVC/D (hazard ratio TF+ vs. TF- 1.41 (95% CI 0.77-2.62) and severe RV dilatation and RV dysfunction were not predictive for VT recurrence. After multivariate analysis fast VT and/or resuscitation and/or syncope were the only significant predictors for VT recurrence (Hazard Ratio 1.98, 95% CI 1.03-3.81, p=0.04).

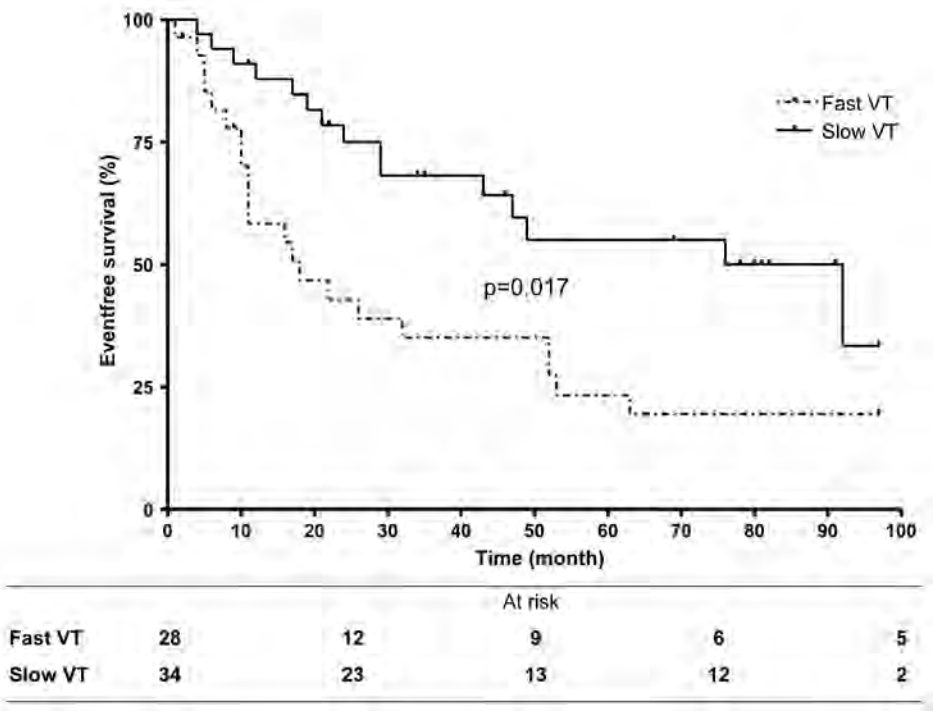

Figure 2. Survival analysis showing the cumulative recurrence free survival for patients presenting with fast VT (cycle length≤250ms) or resuscitation or syncope and patients presenting with a slow VT (cycle length>250ms). The table below the graph indicates the numbers of patients at risk.

Outcome after RFCA

In the subgroup of patients who underwent RFCA the cumulative VT recurrence free survival after a single RFCA procedure was 48% and 58% at 1 year, 31% and 36% at 2 years and 14% and 26% at 4 years, for group TF+ and group TF- respectively. The recurrence free survival was longer after complete success as compared to partial or no success of RFCA (Figure 4). In patients with a fast index VT complete success of RFCA was less likely (32%) than in patients presenting with a slow VT (71%) (p=<0.001). After multivariate analysis fast VT (Hazard Ratio 2.14, 95% CI 1.24-3.69) and incomplete or no success of RFCA were independent predictors of VT recurrence after a single RFCA procedure (Hazard Ratio 2.15, 95% CI 1.24-3.72).

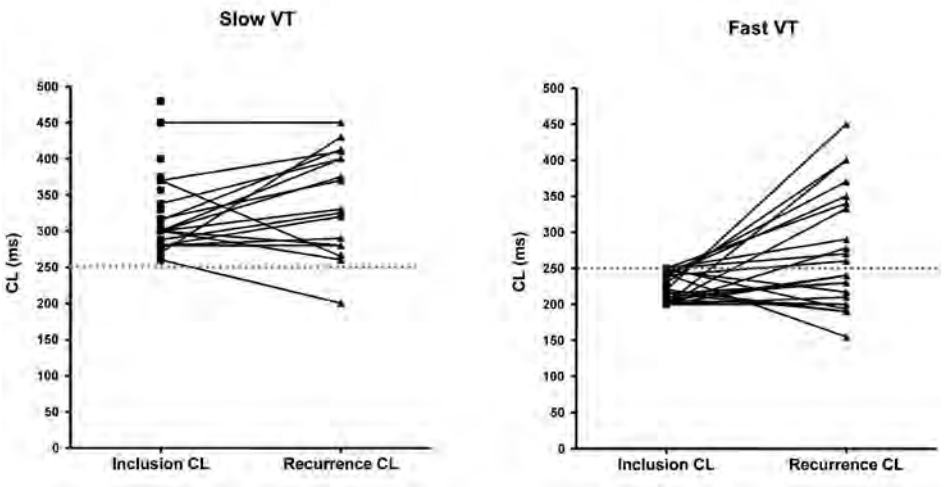

Figure 3. Chart showing the cycle length (CL) of VT at presentation and the shortest documented CL of recurrent VT during follow-up for each individual. Patients who presented with a slow VT (CL>250ms) are shown in the left panel, patients who presented with a fast VT (CL≤250/syncope) are shown in the right panel. Except for 1 patient none of those presenting with a slow VT experienced a fast VT during follow-up.

Discussion

The present study compares the long term clinical outcome of 64 patients presenting with scar-related LBBB type VT. The major finding is that the recurrence rate of ventricular arrhythmias is high in patients with an established diagnosis of ARVC/D and in patients with RV scar of undetermined origin. Patients presenting with a fast VT are at high risk for fast VT recurrence.

RV scar and TF criteria

ARVC/D is a progressive, often inherited cardiomyopathy, but to date molecular diagnosis is not feasible in the majority of cases. The clinical diagnosis is based on the Task Force criteria, however, patients with a confirmed ARVC/D causing mutation may remain TF negative and disease causing mutations are found in less than 50% of TF positive patients.[19-22]

EAM is a sensitive diagnostic modality capable of identifying RV involvement in concealed forms of ARVC/D that are not identified by imaging modalities.[23] In a small series of patients presenting with RVOT VT in the absence of RV dilatation or dysfunction on imaging low voltage areas on EAM correlated with fibrofatty myocardial replacement at biopsy.[23] However, different pathologies such as myocarditis or sarcoidosis may mimic ARVC/D.[24-26] Analysis of endomyocardial biopsies in ARVC/D TF positive patients with LBBB type VT identified myocarditis as underlying cause of RV scar in some of these patients.[25] Despite

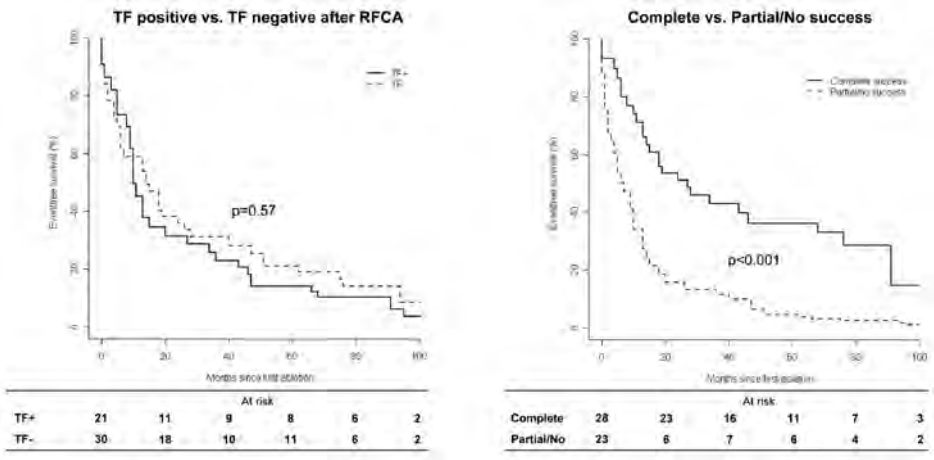

Figure 4. Survival analysis showing the cumulative recurrence free survival for patients with (TF+) and without (TF-) diagnosis of ARVC/D after the first RFCA procedure (left panel) and the cumulative recurrence free survival for patients with acute complete and partial/no success of RFCA (right panel). The table below the graph indicates the numbers of patients at risk.

the clinical importance of the TF criteria these findings highlight their limitations for identification of patients with scar related VT due to mild or early form of ARVC/D and for distinguishing ARVC/D from other potential arrhythmogenic diseases. To date, most available data on outcome and recurrence of scar-related RV VT are derived from TF positive patients or their relatives.

To our best knowledge this is the largest study reporting on long-term arrhythmia recurrence and treatment efficacy in patients with scar-related LBBB type VT of undetermined origin. Of importance, we included bipolar electrogram criteria to define scar and in 54% of the TF- patients scar was only detected by EAM implicating that some of these VT's may have been otherwise classified as idiopathic VT (Figure 5).

Long-term arrhythmia follow-up

ARVC/D is associated with a ventricular arrhythmia recurrence rate of 48 – 74%. [7, 8, 27] The results of the present study confirm the high VT recurrence rate in these patients despite drug therapy and RFCA. However, a remarkable finding is the high VT recurrence rate in patients with RV scar of undetermined origin of whom the majority had no or mild structural alterations of the RV on MRI and/or contrast echocardiography. This finding extends prior observations that localized RV scar, even if detected only by EAM, predispose to VT recurrence, and of importance, to a similar extend as in TF+ ARVC/D patients with obvious structural and functional alterations of the RV. These localized scars may be due to an early/mild form of ARVC/D. Since endomyocardial biopsy was not performed systematically in

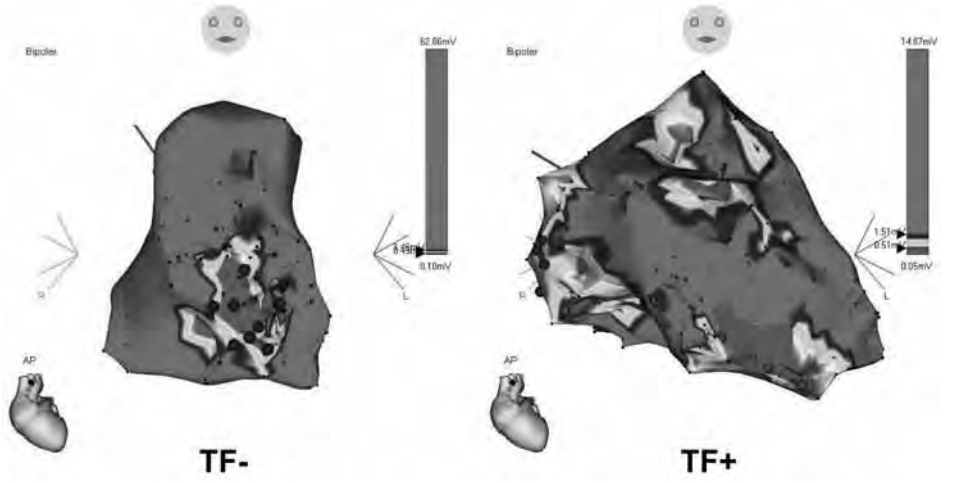

Figure 5. Right ventricular 3-D electroanatomical bipolar voltage maps of a TF- (left) and a TF+ (right) patient. Voltages are color-coded according to the corresponding color bar. Normal voltage is defined as electrogram amplitude >1.5mV displayed in purple. The TF- patient had recurrent VT's with different morphologies originating from a single small RV free wall scar area. Scar was only identified by voltage mapping. The TF+ patient had multiple low voltage areas. VT was successfully terminated at the lateral tricuspid annulus. **(for figure in color see page: 261)**

our patient population because of the predominant non-septal location of the scar areas other causes of RV scars can not be excluded.

Risk stratification

A fast index VT or syncope as presenting symptom, most likely due to a VT with hemodynamic compromise was the only independent predictor for VT recurrence in both groups. The event free survival in these patients was significantly shorter than in patients presenting with slow VT. Of importance, patients who presented with a fast index VT were also more likely to experience recurrence of fast and potentially fatal ventricular arrhythmias during follow-up perhaps identifying a subgroup of patients who benefit most from ICD therapy. This is in line with previous data demonstrating fast VT/VF at presentation as a predictor for potentially fatal VT recurrence in ARVC/D patients.[7, 27]

Several studies seeking risk factors for VT in patients with TF positive ARVC/D have identified younger age, severity of RV failure and LV involvement as factors with predictive value for arrhythmia recurrence. [7, 8, 27] In contrast to these studies severe RV enlargement and LV involvement was not found to be an independent predictor of VT recurrence, however this is likely due to the smaller number of ARVC/D patients with RV enlargement and the exclusion of patients with significant functional LV impairment.

Treatment

Treatment to prevent VT recurrence was similar in both groups. RFCA was offered to all patients and attempted in 49. There was no difference in acute procedural success between both groups. The low acute success rate of RFCA may be at least partly due to a subepicardial substrate typical for patients with ARVD/C, which may not be reachable by an endocardial approach. The recently introduced technique of epicardial mapping and ablation in patients with scar-related RVVT was applied in 4 patients with an unsuccessful endocardial ablation approach leading to complete ablation success in 2 patients. The acute success rate was lower in patients presenting with a fast VT compared to patients in whom a slow VT was targeted. In the latter mapping could be performed during VT which may explain the favourable result. The concept of substrate mapping and ablation during stable rhythm to target unstable VT's based on electrogram characteristics and pace-mapping has evolved during the course of the study. In addition the application of linear lesion to encircle low voltage areas and connect scars was only introduced recently[6]. This approach and the introduction of epicardial ablation is likely to further improve the acute results of RFCA for fast VT.

However, after adjustment fast VT and procedural failure remained independent predictors for VT recurrence. After RFCA the recurrence-free interval was remarkable short for both groups. The high VT recurrence rate in patients with ARVC/D in the first 4 years after ablation is in line with previous studies by Verma et al[6] and Dalal et al[5] and may be due to disease progression. Marchlinski et al.[28] reported a distinctly higher long-term procedural success of RFCA facilitated by EAM in ARVC/D patients. These findings seem to contradict the presented results. However, the current study reported the outcome of all RFCA procedures. In contrast, 68% of the patients reported by Marchlinski et al.[28] underwent a repeated ablation procedure suggesting a lower single procedure success rate. The high VT recurrence after RFCA in patients with RV scar of undetermined origin found in this study may indicate that the arrhythmogenic substrate in these patients is similar to that in patients with established ARVC/D and may be consistent with an early form of ARVC/D.

However, despite the long term follow-up RV involvement remained concealed in the majority of the patients if routine imaging modalities are applied.

In the current study TF+ ARVC/D patients were more likely to receive an ICD than TF- patients. Similar to the strategy that has been adopted for VT treatment and sudden death prevention in patients after myocardial infarction patients with scar related VT and a preserved RV function who did not meet diagnostic criteria for ARVC/D were considered to be at low risk for sudden cardiac death and VT recurrence after drug treatment and RFCA. Although no sudden death occurred in the TF- group during the follow-up period, the high recurrence rate of fast and therefore potential fatal VT's gives cause for concern.

The results of this study indicate that the diagnosis of ARVC/D based on TF criteria does not identify patients at risk for recurrence of RV scar-related VT. Careful decision making

for ICD implantation should include the type of the presenting arrhythmia rather than the definite diagnosis of ARVC/D.

Study Limitations

Our study has several limitations. Not all arrhythmia episodes necessitate hospitalization and episodes may have been missed particularly in patients without ICD.

Due to advances in catheter mapping and the introduction of endo- and epicardial high density 3-dimensional electroanatomical mapping during the course of the study, we can only provide data on the distribution of low voltage areas and not on the scar burden. The extend of the subendocardial and particular the subepicardial scar is likely underestimated in both groups and small low voltage areas may be missed due to the initially performed restricted EAM.

No signal averaged ECG were obtained in our patient population. Therefore a TF class IV minor criterion can be missed which is relevant for the TF- group. If hypothetically the SAECG in all TF- patients had shown late potentials 9 patients in this group would be diagnosed with ARVC/D according to TF criteria resulting in a TF+ group of 38 patients. Repeated analysis of these groups did not result in a significant difference in recurrence free survival between TF+(+9) and TF-(-9) patients. Furthermore univariate Cox regression did not identify a diagnosis of TF+(+9) as predictor for recurrence.

The majority of patients in this study was not evaluated for genetic mutations causing ARVC/D. Genotyping both TF+ and TF- patients is of the greatest relevance and would provide valuable information regarding the underlying cause of RV scar.

Conclusion

Scar-related RV VT are associated with high recurrence rates regardless if the patient was considered TF+ or TF-. In the majority of TF- patients RV scar was only identified by voltage mapping, which might be a diagnostic tool with important prognostic and therapeutic implications. Patients who present with fast VT are at high risk for fast VT recurrence despite intervention and may benefit most from ICD therapy.

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