Ablation Compared to Drug Therapy for Recurrent Ventricular Tachycardia in Arrhythmogenic Right Ventricular Cardiomyopathy; Results from a Multicenter Study

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Abstract

Background: The comparative efficacy of antiarrhythmic drug therapy (AAD) versus ventricular tachycardia (VT) ablation in arrhythmogenic right ventricular cardiomyopathy (ARVC) is unknown.

Objectives: We compared outcomes of AAD and/or beta blocker (BB) therapy to VT ablation (with AAD/BB) in ARVC patients with recurrent VT.

Methods: In a multicenter retrospective study, 110 ARVC patients (38±17 years, 83% male) with a minimum of 3 VT episodes were included; 77 (70%) were initially treated with AAD/BB and 32 (29%) underwent ablation. Subsequently, 43 of the 77 patients treated with AAD/BB-only also underwent ablation. Overall, 75 patients underwent ablation.

Results: When comparing initial AAD/BB therapy (n=77) and VT ablation (n=32) after ≥3 VT episodes, a single ablation procedure rendered 35% of patients free of VT at 3 years compared to 28% of AAD/BB-only treated patients (p=0.46). Of the 77 AAD/BB treated patients, 43 subsequently had ablation. For all 75 patients who had ablation, 56% were VT-free at 3 years after the last ablation. Epicardial ablation was used in 53% and was associated with lower VT recurrence after the last ablation (endocardial/epicardial vs. endocardial-only; 71% vs. 47% three-year VT-free survival, p=0.05). Importantly, there was no difference in survival free of death or transplantation between the ablation- and AAD/BB-only treated patients (p=0.61).

Conclusion: Amongst ARVC patients with a high VT burden, mortality and transplantation-free survival is not significantly different between drug- and ablation-treated patients. These patients have a high risk of recurrent VT despite drug therapy. Combined endocardial/epicardial ablation is associated with reduced VT recurrence compared to endocardial-only ablation.

Keywords: Arrhythmogenic right ventricular cardiomyopathy, ventricular tachycardia, catheter ablation

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Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by fibrofatty replacement of myocardial tissue.[1-4] ARVC is associated with an increased risk of ventricular tachycardia (VT) and sudden cardiac death.[5, 6] Implantable cardiac defibrillators (ICD) have been reported to improve long-term outcome in patients with ARVC and VT.[7] In a subset of patients with ICDs however, multiple shocks due to recurrent VT result in significant morbidity.[8, 9]

Over the past two decades, a number of studies have reported that VT ablation can reduce arrhythmia burden in ARVC, albeit with significant recurrence rates and a risk of procedural complications.[10-15] Catheter ablation has largely been reserved for patients with a high ICD shock burden despite antiarrhythmic drug (AAD) or beta blocker (BB) therapy, and the impact of adding ablation to AAD therapy relative to continuing or escalating AAD therapy is not well studied. Furthermore, it is now clear that for some patients epicardial ablation is more efficacious than endocardial ablation, but may expose the patient to additional procedural risks. In view of these considerations, the frequency of VT that warrants proceeding to catheter ablation is uncertain. A recent trial in patients with post infarction VT found that patients with 3 or more episodes of VT or who had received an ICD shock despite antiarrhythmic drug therapy had better composite outcomes with ablation rather than escalated antiarrhythmic drug therapy.[16]

The aim of this multicenter study was to compare outcomes of these treatment strategies in patients with ARVC who had recurrent VT (≥3 episodes). All patients were receiving AAD and or BB and we compared three groups: those who continued to receive only drug therapy, those who received adjunctive therapy with endocardial ablation, and those who received combined endocardial/epicardial ablation.

Methods

Patient population

Retrospectively identified ARVC patients were included from five tertiary cardiac centers between January 2000 and May 2015. All patients fulfilled the 2010 Task force criteria for a definite diagnosis of ARVC.[17] Taskforce criteria were evaluated at the time of inclusion into the study. An additional inclusion criterion was that all patients experienced either 1) ≥3 episodes of sustained VT (requiring either external DC cardioversion, ATP, ICD shock, or acute chemical cardioversion) resulting in separate presentations at distinct time points or, 2) ≥3 cumulative appropriate shocks for VT (either 3 consecutive shocks on the same presentation, i.e. VT storm, or 3 cumulative shocks over 2 separate presentations). The study was approved by the Institutional Review Boards at the respective institutions.

Electrophysiology study and catheter ablation

The decision to treat with AAD/BB or to perform VT ablation was at the treating physician's discretion. In the subset of patients that underwent VT ablation, endocardial mapping was performed in all patients. Epicardial mapping and ablation

was performed in selected patients, also at the physicians' discretion. A percutaneous subxyphoid approach was used to gain epicardial access.[18] Three dimensional electroanatomical substrate maps were created using either the Carto (Biosense Webster, Diamond Bar, CA) or NavX (St. Jude Medical, St Paul, Minnesota) mapping system. Normal bipolar voltage was defined as >1.5 mV; scar was defined as <0.5 mV; and scar border zones were defined as 0.5-1.5 mV.[19]

All monomorphic VTs that the treating physician thought were clinically relevant (based on cycle length/morphology matching clinically documented VT) were targeted during ablation, including all mappable VTs. Conventional entrainment and activation mapping techniques were used to identify critical target sites for mappable VTs. A substrate-based approach was used in patients with unmappable VTs. Substrate ablation targeted sites with low-amplitude electrograms with wide fractionation (usually multicomponent electrograms <0.5mV; >133ms), sites with late (usually >10 ms after end of QRS) and split potentials (usually isoelectric period of >30-50 ms between spikes) and sites with a paced QRS morphology matching a VT (usually with a stimulus to QRS interval of >40 ms).[20, 21] An example of a voltage map and potential targets for substrate ablation are illustrated in Figure 1. VT inducibility was assessed post-ablation with programmed stimulation using 3 extrastimuli (until refractoriness or a minimum cycle length of 200 ms was reached).

Follow-up

The follow-up period for the comparison between AAD/BB therapy and VT ablation began after the 3rd VT episode/3rd shock. The follow-up period for the comparison

between endocardial-only ablation and combined endocardial/epicardial ablation began after the last VT ablation procedure. In patients with ICDs, data from sequential ICD interrogations was documented. Failure of VT ablation or AAD/BB therapy was defined as a recurrence of sustained VT, including episodes terminated by ICD shocks, episodes treated with ATP, and monitored sustained VT episodes requiring DC cardioversion or chemical cardioversion.

Statistical analysis

Data analysis was performed with SPSS version 23.0 (IBM SPSS, Armonk, NY). Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR). Continuous variables were compared using the Student's t-Test or Mann-Whitney U test. Categorical variables were compared using the χ^2 test. The endpoints of freedom from sustained VT and freedom from death/heart transplantation were determined using Kaplan-Meier analysis. Only interventions after three VT episodes/shocks were included in the analysis (failure of VT ablations or AAD/BBs prior to three VT episodes were 'blanked').

Results

Patient population

The patient cohort comprised of 110 ARVC patients (specific numbers from each contributing center are included in Supplemental table 1). Patient characteristics are summarized in Table 1. The mean age at first presentation with a ventricular arrhythmia was 38±17 years. Patients were predominantly male (91[83%]) and of Caucasian descent (105 [95%]). An ICD had been implanted in 109 (99%) patients.

Antiarrhythmic drug therapy vs. single VT ablation procedure

After ≥3 VT episodes/3 shocks, 109/110 patients were treated with AAD/BB while one patient had no therapeutic interventions. Of these 109 patients, 32 (29%) underwent an adjunctive ablation procedure (including epicardial ablation in 11 patients) after the 3rd VT episode/3rd shock. Numbers of patients undergoing ablation and AAD/BB therapy are summarized in Figure 2. The remaining 77 (71%) were treated with AAD/BB alone (AAD/BB commenced in drug-naïve patients in 19 cases, AAD/BB changed in 20, a second drug added to pre-existing therapy in 11, drug dose was increased in 24, and no change in AAD in 3).

By 3 years, 35% of the patients in the ablation group were free of VT after a single ablation procedure while 28% of the patients in AAD/BB-only treated group were free of VT (p=0.46, Figure 3). When taking individual AAD into account, there were no differences in outcome amongst patients treated with VT ablation and those treated with amiodarone, sotalol, class 1 drugs, and beta blockers (Figure 4). Treatment with amiodarone or class 1 agents was associated with a trend towards improved outcome compared to sotalol therapy (amiodarone vs. sotalol p=0.20; class 1 vs. sotalol p=0.12). When taking endocardial-only and combined endocardial/epicardial ablations separately, there was a trend towards improved outcome in the combined endocardial/epicardial group (endocardial-only vs. endocardial/epicardial ablation, p=0.19; combined endocardial/epicardial group vs. AAD, p=0.15, Supplemental figure 1).

Multiple ablation procedures

Of the 77 patients treated initially with AAD/BB after 3 VT recurrences, 43 underwent ablation after more VT recurrences. Overall therefore, a total of 75 patients underwent an ablation procedure (Figure 2). These patients had between 1 and 7 procedures (for patients who underwent >1 procedure, VT ablations were performed over a period of 3.0 ± 4.2 years; range 0-17.5 years); a single procedure in 37 [49%] patients; 2 procedures in 22 [29%] patients; 3 procedures in 8 [11%] patients; 4 procedures in 3 [4%] patients; 5 procedures in 3 [4%] patients; 6 procedures in 1 [1%] patient, and 7 procedures in 1 [1%] patient. Forty of the 75 patients who underwent ablation (53%) had at least one combined endocardial/epicardial ablation procedure and 35 (47%) had exclusively endocardial ablations. Two patients had surgical VT ablation procedures. The distribution of endocardial and combined endocardial/epicardial ablation procedures for each contributing center is included in Supplemental figure 2.

Follow-up data was available in 72 of the above 75 patients. By 3 years after the last ablation procedure, 56% of patients were free of VT (Figure 5). When taking into account combined endocardial/epicardial ablations separately, 71% of patients who had at least one combined endocardial/epicardial procedure were free of VT at 3 years, compared to 47% of patients who exclusively underwent endocardial ablation procedures (p=0.05, Figure 6). Amongst patients who experienced post ablation VT recurrences, there was no significant difference in VT burden between the two groups (endocardial-only vs. endocardial/epicardial ablation; VT episodes/shocks;

median 2 [IQR 2.0; variance 11.1; skewness 2.46] vs. median 1 [IQR 2.5; variance 3.5; skewness 8.80]; p=0.86).

Complications

Procedure-related major complications occurred in 3 (4%) patients (1 right ventricular perforation, 1 myocardial infarction [14 days after epicardial ablation][22], and 1 case of subclavian deep vein thrombosis following surgical ablation). There were no procedure-related deaths.

Survival following VT ablation and antiarrhythmic drug therapy

Patients were followed-up for 6.1±4.5 years after the 3rd VT episode/3rd shock. During the follow-up period, 10 patients (9%) underwent cardiac transplantation. Mortality from any cause occurred in 9 patients (8%), three of whom had previously undergone transplantation. Details of the cause of death were available in 7 of these 9 patients (heart failure [n=3]; VT storm [n=1]; VF [n=1]; stroke [n=1]; sepsis [n=1]). As demonstrated in Figure 7, there was no significant difference in survival between patients who were treated with AAD/BB alone to those who underwent adjunctive VT ablation (p=0.61).

Early versus late ablation

We compared outcomes of the first-time combined endocardial/epicardial VT ablation in patients who had <10 VT episodes/shocks prior to ablation (median 5 [IQR 3; variance 4.5; skewness 0.87], experienced over median of 3.3 years [IQR 3.8 variance 47.2; skewness 1.35]) to patients who had their first ablation after >10 VT

episodes/shocks (median 15, [IQR 16; variance 180.8; skewness 1.05], experienced over a median of 7.7 years [IQR 8.4; variance 28.9; skewness 0.43]). As shown in Supplemental figure 3, ablation performed in patients with <10 VT episodes/shocks was associated with improved VT-free survival (p=0.04). Of note, there were no differences in AAD/BB therapy between the >10 and <10 VT episodes/shocks groups (Supplemental table 2).

Amongst patients undergoing endocardial ablation alone on the other hand, we did not observe differences in outcome in patients with <10 VT episodes/shocks (median 4 [IQR 2; variance 3.4; skewness 1.38], experienced over a median of 2.5 years [IQR 5.2; variance 32.3; skewness 1.83]) and patients with >10 VT episodes/shocks (median 16 [IQR 5; variance 68.4; skewness 1.43], experienced over a median of 3.1 years [IQR 5.5; variance 21.3; skewness 0.91]). The results are shown in Supplemental figure 4. Details of AAD/BB therapy between the >10 and <10 VT episodes/shocks groups are included in Supplemental table 3.

Discussion

In this multicentre study of ARVC patients, we found that after ≥3 VT episodes, adding a single ablation procedure (endocardial-only ablation in the majority) to antiarrhythmic drug therapy was not associated with better VT-free survival when compared to continuing or escalating antiarrhythmic drug therapy. Overall, multiple procedures were necessary to maintain freedom from VT. Consistent with previous reports, combined endocardial/epicardial ablation demonstrated superior VT-free survival when compared to endocardial-only ablation. We also found that early VT

intervention with combined endocardial/epicardial ablation maybe associated with improved VT-free survival. Finally, VT ablation did not have a significant impact on mortality or the need for cardiac transplantation.

To our knowledge, this is the first report comparing outcomes in ARVC patients undergoing VT ablation to patients treated with AAD/BB alone. While ARVC patients had a high risk of recurrent VT despite antiarrhythmic drug therapy or ablation, it is important to consider that a number of factors may have contributed to non-optimal ablation strategies, which in turn may have influenced outcome. Firstly, only a third of patients had epicardial ablation with their first procedure and only 53% of ablation patients ever had an epicardial ablation. As discussed below, a combined endocardial/epicardial approach is associated with improved VT-free survival. Secondly, a significant proportion of patients in our cohort underwent late interventions. As outlined above, earlier interventions may be associated with more favourable outcomes. These considerations underscore the importance of optimization of the ablation strategy to improve VT-free survival. Future studies specifically comparing combined early endocardial/epicardial ablation to AAD/BB therapy are necessary to fully define the impact of VT ablation in ARVC.

The outcome of VT ablation in ARVC has been investigated in multiple previous studies. The reported freedom from VT following ablation in these studies is between 45% to 85%, with variable procedure methods and follow-up periods.[11, 13-15, 23, 24] The outcomes in the present study are comparable, with success rates of 63% at one year. Furthermore, consistent with previous studies, we demonstrate that combined

endocardial/epicardial ablation is associated with superior VT-free survival as compared to endocardial ablation alone.[11, 14, 23] It is important to note however, that a number of more recent reports have suggested that in selected patients, endocardial-only ablation is associated with comparable long-term outcomes to the combined endocardial-epicardial approach.[15, 25] Furthermore, endocardial ablation has been reported to be effective for elimination of epicardial VT substrates in ARVC patients.[26] These findings suggest that with evolving VT ablation techniques, the efficacy of endocardial-only ablation may be improving.

The efficacy of different antiarrhythmic drugs in ARVC remains incompletely defined. Marcus and colleagues reported that empirical therapy with amiodarone is associated with superior efficacy compared to sotalol.[27] In contrast, amongst patients undergoing serial testing with programmed stimulation, sotalol has been reported to be more effective than amiodarone in supressing ventricular arrhythmias.[28] Relatively little is known about the efficacy of class 1 antiarrhythmics in ARVC. The addition of flecainide to sotalol/beta blockers has been reported to enhance VT-free survival.[29] In the present study we demonstrate that in patients with a high VT burden, amiodarone and class 1 antiarrhythmic drugs are associated with a trend towards improved VT-free survival when compared to sotalol. Of note, the use of amiodarone in our cohort was relatively limited, which could potentially have influenced overall outcome. However, future prospective studies with larger patient numbers are necessary to more clearly define the relative efficacy of class 1 agents, amiodarone and sotalol.

Limitations

This study has the inherent limitations of a non-randomized, retrospective observational study. There are also a number of potential sources of bias. Selection of antiarrhythmic drugs and ablation (and ablation techniques) were left to the treating physicians, with some variation among centers. The efficacy of ablation has likely improved over time, which may also have a confounding effect. Acute ablation outcomes were not fully defined. Specifically, while all clinical VTs were targeted in all patients, data on the proportion of patients with elimination of all clinical VTs was not available. Therefore, the relative efficacy of endocardial-only and combined endocardial/epicardial VT ablations in the acute setting was not defined. Finally, non-uniform ICD programming between participating centers is a potential confounding factor that could influence device detection and therapy for recurrent arrhythmias.

Conclusion

Amongst ARVC patients with a high VT burden, mortality and survival free from transplantation is not significantly different between drug- and ablation-treated patients. These patients have a high risk of recurrent VT despite drug therapy and/or endocardial ablation. However, optimization of the ablation strategy, including epicardial ablation can be expected to improve outcomes.

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Figure legends

Figure 1. Representative data from a substrate based VT ablation in a patient with ARVC. A. 3D endocardial and epicardial bipolar voltage maps (RAO projection) demonstrating a predominantly inferior right ventricular endocardial scar and a more extensive epicardial scar extending to the free wall and outflow tract. Ablation lesions (*red circles*) were delivered in the mid and inferior right ventricle. B. An example of late potentials recorded from ablation sites (arrows indicate late potentials, dashed line indicates end of QRS). C. The *left* panel demonstrates the 12-lead ECG of the first clinical VT. (VT-1) which had a left bundle branch block morphology and superior axis. The pacemap at the ablation site in the inferior right ventricle matched the VT-1. The *right* panel demonstrates the 12-lead ECG for the second clinical VT (VT-2). The pacemap at the ablation site in the mid right ventricular free wall matched the VT-2. Abbreviations: BiV, bipolar voltage.

Figure 2. Flow diagram demonstrating numbers of patients initially undergoing VT ablation and AAD/BB-only therapy and subsequently all patients who underwent VT ablation. Abbreviations: AAD/BB, antiarrhythmic drugs/beta blockers; ARVC, arrhythmogenic right ventricular cardiomyopathy

Figure 3: Outcome of therapy after 3 VT episodes/shocks. Kaplan Meier curve comparing VT-free survival between patients treated with AAD/BB-only after the 3rd VT episode/shock (*dotted line*) and those treated with an adjunctive VT ablation (single ablation procedure after 3rd VT episode/shock, *solid line*). There was no significant difference between the two initial approaches (p=0.46)

Figure 4: Outcome of therapy after 3 VT episodes/shocks. Kaplan Meier curve comparing VT-free survival between individual AAD/BB after the 3rd VT episode/shock (amiodarone *dash-dotted grey;* sotalol *dash-dotted black;* class 1 drugs *solid grey*; beta blockers *dashed black*) and those treated with an adjunctive VT ablation (*solid black*). There were no significant differences in outcome between individual AAD/BB and ablation. Amiodarone, class 1 drugs and ablation were associated with a trend towards improved outcome when compared to sotalol (amiodarone vs. sotalol p=0.20; class 1 vs. sotalol p=0.12; ablation vs. sotalol p=0.21).

Figure 5: Outcome after last ablation procedure (following 2±1 ablation procedures). Kaplan Meier curve demonstrating VT-free survival for all patients treated with ablation procedures

Figure 6: Outcome after last ablation procedure (following 2±1 ablation procedures). Kaplan Meier curve comparing VT-free survival between patients treated with combined epicardial/endocardial ablation procedures (endo + epi ablation, *dotted line*), patients treated with endocardial-only ablation (endo ablation, *solid line*). Of the 40 patients in the combined endocardial/epicardial group and 35 patients in the endocardial-only ablation group, follow-up data was available in 38 and 34 patients, respectively. Combined endo + epi ablation was associated with a superior outcome compared to endocardial-only (p=0.05).

Figure 7: Kaplan Meier curve comparing overall survival free of death or cardiac transplantation in ARVC patients treated with AAD/BB alone (*dotted line*) to patients who additionally underwent VT ablation (*solid line,* p=0.61). Survival is plotted from the time that patients experienced their third VT episode.

Table 1. Baseline characteristics

	Ablation N=32[#]	AAD/BB N=77[#]	P value
Age (at first VT)	36±13	39±18	0.35
Male (%)	28 (88%)	63 (81%)	0.37
Caucasian (%)	31 (97%)	74 (96%)	0.80
LVEF (%)	55±13	52±14	0.39
Global/regional dysfunction and structural alterations*			
Major (%)	18 (56%)	48 (62%)	0.72
Minor (%)	5 (16%)	9 (12%)	
Tissue characterization of wall*			
Major (%)	2 (7%)	4 (5%)	0.79
Minor (%)	0 (0%)	1 (1%)	
Repolarization abnormalities*			
Major (%)	18 (56%)	49 (64%)	0.06
Minor (%)	4 (13%)	19 (40%)	
Depolarization/conduction abnormalities*			
Major (%)	10 (31%)	29 (38%)	0.14
Minor (%)	6 (19%)	22 (29%)	
Family history*			
Major (%)	15 (47%)	46 (60%)	0.34
Minor (%)	0 (0%)	1 (1%)	
Genotype positive (%)	15/21[¶] (71%)	38/52[¶] (73%)	
PKP2	9	22	
DSC2	1	2	
DSG2	2	3	
DSP	1	5	
JUP		1	
PLN		1	
TMEM43	2	4	
Drugs at 3rd VT episode			
Beta blockers	6 (19%)	17 (22%)	0.72
Sotalol	13 (40%)	25 (33%)	0.49
Amiodarone	7 (22%)	8 (10%)	0.10
Class I	1 (3%)	11 (14%)	0.09
None	5 (16%)	16 (21%)	0.55
Drugs after 3rd VT episode			
Beta blockers	4 (13%)	12 (16%)	0.69
Sotalol	15 (47%)	35 (45%)	0.85
Amiodarone	3 (9%)	20 (26%)	0.05
Class I	2 (6%)	10 (13%)	0.29
None	8 (25%)	0 (0%)	0.0001

[#]One of the 110 ARVC patients in the study was not treated with either AAD/BB or VT ablation
*Abnormalities as defined by 2010 ARVC taskforce criteria.[17] [¶] No. patients who underwent genotyping. Abbreviations: LVEF. left ventricular ejection fraction; VT. ventricular tachycardia