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Outcome of cardiac sarcoidosis after radiofrequency ablation and placement of AICD- a propensity matched analysis

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Abstract. *Background:* Cardiac Sarcoidosis (CS) can lead to life-threatening ventricular dysrhythmias and sudden death. Immunosuppressive medications, radiofrequency ablation (RFA), and implantable cardioverter defibrillators (ICD) have been utilized to manage ventricular dysrhythmias but their benefits remain poorly defined. *Objective:* The aim of this study is to assess the durability of RFA in CS population and to determine outcome predictors after RFA. *Methods:* We compared the CS patients who had RFA±ICD against those with only ICD placement and contemporaneous patients with arrhythmogenic right ventricular dysplasia (ARVD) who had RFA. We analyzed time to a composite first event of appropriate ICD therapy, subsequent RFA, cardiac transplantation or death. We also evaluated variables predicting recurrence of ventricular dysrhythmias, including LVEF, cardiac involvement on PET scan, percent of ventricular ectopic beats, number of inducible VT foci and success of the RFA procedure. We used propensity matching and multivariable regression to adjust for baseline differences between the groups to identify outcome predictors. *Results:* Thirty ablations for VT were performed in 20 CS patients (13 had concomitant ICD placement); 12 ablations were done in eight ARVD patients and 33 CS patients with only ICD placements were included in this cohort. The median follow-up period was 48 (9-173) months. Fourteen (70%) patients reached composite end points after RFA compared to 13 (63%) following ICD placement and five (87%) in the ARVD cohort. There was a significant time difference to reach composite end points (p=0.02) in favor of ICD only cohort. The median number of ICD therapies were higher in the CS-RFA group (p=0.01). The requirement for ICD therapy increased over time following RFA, especially after 12 months. Variables predicting earlier time-to-event were EF < 40% (OR=13.2) and unsuccessful RFA procedure (OR=7.9). The presence of more than one inducible VT morphology was associated with higher likelihood of unsuccessful RFA (p=0.03). *Conclusion:* RFA can be an effective modality for the short-term treatment of ventricular dysrhythmias in cardiac sarcoidosis; however, after more than 12 months, the number of appropriate therapies escalates. Accordingly, ICD placement is recommended for all patients who undergo RFA for VT associated with CS, whether it is successful or not. Low LVEF and unsuccessful ablation were strong predictors of future events. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 70-79)*

Key words: Cardiac Sarcoidosis, AICD, RFA, Outcome, ICD therapy, Mortality

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Introduction

Sarcoidosis is an idiopathic multi-system disease, characterized by accumulation of non-necrotizing granulomata and variable fibrosis in the involved organs. Clinically overt cardiac sarcoidosis (CS) has

been reported in 2-7% of sarcoidosis patients, but autopsies suggest that as high as 27% of sarcoidosis patients have granulomatous infiltrates in the heart (1). Cardiac sarcoidosis may cause life-threatening ventricular dysrhythmias and sudden death, which may be the initial manifestation in as high as 17% of CS patients (2). Antiarrhythmic drugs, electrophysiology studies with or without radiofrequency ablation (RFA) and implantable cardioverter-defibrillators (ICD) are therapeutic options for primary and secondary prevention of ventricular dysrhythmias. However there are scant data regarding the benefits of these interventions, particularly the utility of RFA (3). The aim of this study is to review our experience with RFA to assess its success rates, durability and outcome predictors in the cardiac sarcoidosis population.

Methods

We interrogated the electrophysiology database to identify all patients who had an electrophysiology procedure between the years 1995-2010, and who had a diagnosis of cardiac sarcoidosis. To be included in this study, the patients had to have adequate follow-up (at least six months), or have met the primary endpoint prior to six months. We included patients with definite or probable cardiac sarcoidosis according to the criteria proposed in A Case Control Etiologic Study of Sarcoidosis (ACCESS) (4). In addition, we also included patients with a diagnosis of sarcoidosis (before or after the electrophysiologic procedure) who had no other ascertainable cause for their cardiac abnormality, and who had an imaging study cardiac fluorodeoxyglucose-positron emission tomography (FDG-PET) or magnetic resonance imaging (MRI) consistent with cardiac sarcoidosis (5). As a comparator, we identified all patients with a diagnosis of arrhythymogenic right ventricular dysplasia (ARVD) who had electrophysiologic procedures over the same time span. ARVD is known to mimic cardiac sarcoidosis in its clinical course (6).

The data were obtained from the electronic medical records, the electrophysiology database, and Social Security Death Index. Occurrences of ICD anti-tachycardia therapies were assessed by reviewing device interrogations obtained during device clinic visits or, when available, remote device transmissions. Each date of RFA was counted as a separate "case" for the purpose of the survival analysis. The cardiac sarcoidosis population was divided into two groups to analyze outcomes of interest- those who had an RFA procedure (CS-RFA group) and those with only ICD placement (CS- ICD). The primary endpoint was a composite first event that included appropriate ICD therapies for ventricular dysrhythmias, requirement for a subsequent RFA, cardiac transplantation, or death from any cause. We compared the time to reach the composite endpoints between the two CS groups and ARVD patients.

To reduce the effect of selection bias and potential confounding in this study, we used optimal pairwise propensity score (PS) matching to adjust for baseline differences between the CS groups to obtain adjusted odds ratios (aOR). The propensity score was calculated using the following covariates: age, race, gender, smoking history, echocardiographic left ventricular ejection fraction (LVEF), ventricular area affected by sarcoidosis on FDG-PET scanning, baseline use of steroids or other immunosupressives, and baseline use of anti-arrhythmic medications prior to the procedure. The absolute standardized differences were reduced to less than 10% for all the variables except age and LVEF. The effect of RFA treatment on the composite endpoint was analyzed after conducting a propensity score matching with subsequent multivariate analysis using conditional logistic regression to adjust for the effect "age" and "LVEF" which were the two covariates that remained unbalanced even after propensity matching. Propensity score matching was conducted using the package R Statistical Package, version 2.15.3.

We also evaluated other prognostic variables, including left ventricular ejection fraction (LVEF) by echocardiography, area of cardiac involvement on FDG-PET scanning, adjustment of immunosupressives or anti-arrhythmic medications after the procedures, percent of ventricular ectopic beats on 24 hour Holter monitor prior to RFA procedure, number of inducible ventricular tachycardia (VT) morphologies by programmed electrical stimulation studies, and reported success of the RFA procedure.

The RFA procedure was deemed successful when all the identified VT morphologies were non-inducible after the ablation. Partly successful procedures were those for which only some inducible

morphologies, including the clinically occurring ones, were successfully ablated. Percent of ventricular ectopic beats on Holter was obtained by dividing the total number of ectopic beats by total number of QRS complexes in 24 hours multiplied by 100.

We also analyzed the correlation between rubidium-FDG-PET (metabolism-perfusion PET) imaging with the presence of inducible VTs and their response to therapy for those patients who had FDG-PET studies. We characterized the PET findings as representing active inflammation or scars. The correlations were performed by matching the site of RFA with the PET using the standard 17 segment cardiac model (7).

The Cleveland Clinic Institutional Review Board approved the study under approval number IRB 10-442.

Results

Overall study population characteristics

Fifty-three cardiac sarcoidosis patients and eight ARVD patients had procedures during the study period. Twenty cardiac sarcoidosis patients had a total of thirty RFA procedures. In the same time period, there were eight ARVD patients who had 12 total RFA sessions and 33 CS patients who had ICD alone.

Thirteen (65%) of the CS who had RFA also received an ICD near the same time. Table 1 includes the baseline characteristics of these three groups.

The CS patients as a whole were older than the patients with ARVD; of the CS patients, those who

Table 1. Baseline characteristics of the study population-

General Characteristics	CS-RFA (N= 20)	CS-ICD (N= 33)	ARVD (N=8)	P
Age (Mean± SD)	52± 11	46±10	36±9	0.01
Age at CS diagnosis (Mean± SD)	54± 10	49± 9		0.02
Gender (%)				
Male	12 (60%)	13 (39%)	1 (13%)	0.06
Female	8 (40%)	20 (61%)	7 (87%)	
Race (%)				
Caucasian	12 (60%)	17 (52%)	7 (87%)	0.46
African American	7 (35%)	11 (33%)	0 (0)	
Hispanic	1 (5%)	4 (12%)	1 (13%)	
Asian	0	1 (3%)	0	
Smoking History (%)				
Non-smoker	14 (70%)	18 (55%)	6 (75%)	0.63
Ex-smoker	5 (25%)	11 (33%)	2 (25%)	
Current smoker	1 (5%)	4 (12%)	0	
Initial Cardiac event (%)				
VT/VF	9 (45%)	10 (30%)	6 (75%)	0.24
SVT/ A Fib	6 (30%)	1 (3%)	1 (13%)	
Cardiomyopathy	2 (10%)	10 (31%)	1 (12%)	
Heart Block	2 (10%)	6 (18%)	0	
Syncope	1 (5%)	6 (18%)	0	
No of Procedure (N)	30	33	12	
LVEF (Mean± SD)	40± 15	38± 15	50± 14	0.59
Percent V. ectopic beat (Mean± SD)	9± 11	7± 14	10± 12	0.67
Median follow up period in months (Range)	31 (16-87)	50 (9-103)	61 (33-102)	0.33
Transplant (%)	1 (5%)	4 (12%)	2 (25%)	0.38
Death (%)	3 (15%)	3 (9%)	1 (12%)	0.96

Abbreviations: SD- standard deviation; CS- cardiac sarcoidosis, VT- ventricular tachycardia; VF- ventricular fibrillation, SVT- supraventricular tachycardia; LVEF- left ventricular ejection fraction.

had RFA were 4.5 years older than those with only ICD placement (p=0.17), suggesting that this group may have more chronic cardiac involvement. There was a trend for the CS-RFA group to have more baseline ventricular ectopic beats than the ICD- only group (9.3 ± 11.3% vs. 6.5 ± 13.9% of QRS complexes on Holter monitor, p=0.45).

There was no significant difference in use of immunosuppressive therapy, steroid use and anti-arrhythmic treatment between the CS groups at baseline. Ten (19%) of the CS patients who had either ICD placement or RFA were not recognized to have sarcoidosis at the time of their first procedure. On average, there was a 3.9 ± 2.5 year lag from the time of the EP procedure until the diagnosis of CS was made in that subset of population.

The indications for RFA during the study period were all for secondary prevention (presented with dysrhythmias)- all the RFA patients had either recurrent ventricular tachycardia (VT), ICD therapies or an episode of VT storm despite or medical therapy. Ten patients in the CS-RFA group already had an ICD prior to the RFA procedure. Three patients later required ICD placement after a median 50 (15-144) days following the RFA. In the CS-ICD group, the ICD was placed in 20 (61%) subjects for VT, in 11(33%) patients for cardiomyopathy (primary prevention) and in two (6%) patients for unexplained recurrent syncope. Four of those cardiomyopathy patients received appropriate ICD shocks within 12 months. All ARVD patients had both RFA and ICD placement.

Treatment received by the cardiac sarcoidosis cohort

Immunosuppressive therapies, most commonly corticosteroids, were already in place in 31 (58%) of CS patients at the time of the procedure, including eleven (55%) of the patients in the CS-RFA group and 20 (61%) in the CS-ICD group (p=0.77, Table-2). The baseline prednisone dose was similar in the two groups (30 ± 10 mg for CS-RFA patients and 34 ± 4 mg for the CS-ICD group, p=0.17). Three and eight patients were on methotrexate in the CS-RFA and CS- ICD group respectively.

After the procedure, 38 (72%) of the CS patients were managed with immunosupressive medications, with highly variable dosing. New immunosuppressive medications were added within 12 months of the procedure in 7 of the 20 (35%) CS-RFA patients versus 8 of the 33 (24%) in the CS-ICD (p=0.53). There was more frequent baseline use of anti-arrhythmic medications prior to the procedure in the CS-RFA group (90% vs. 61%, p=0.02). However, after the procedure, the rate of antiarrhythmic medication use was similar in both groups (Table 2). Seven (35%) patients required up-titration of their anti-arrhythmic medications within six months after the RFA procedures against eight (24%) after ICD placement.

The RFA successfully ablated all the inducible VTs in 14 (70%) of CS subjects in 18 ablation sessions; two sessions were only partly successful, and ten were unsuccessful.

Three patients required epicardial ablations after endocardial ablations failed to prevent inducibility. The presence of more than one inducible VT (13 studies in 9 subjects) in the CS patients was associated with a significantly higher likelihood of unsuccessful RFA (p= 0.03). Neither LVEF less than 40% (p= 0.06), nor previous unsuccessful or partly successful RFA (p=0.57) predicted the success of subsequent RFAs.

Six CS patients had a total of ten repeat ablations performed 9 ± 2 months after the first RFA procedure when ventricular dysrhythmias recurred. Six of those ten repeat RFA procedures were completely successful on prior ablation procedure. The repeat ablations correlated anatomically with the region previously ablated in six of the ten cases. Of

Table 2. Use of Immunosuppressive and anti-arrhythmic medications before and after procedures (6-12 months post procedure) in cardiac sarcoidosis patients-

	CS-RFA (N=20)		CS- ICD (N=33)	
	Pre	Post	Pre	Post
All immunosuppressive agents (%)	11 (55%)	14 (70%)	20 (61%)	24 (73%)
Steroid use (%)	10 (50%)	12 (60%)	14 (42%)	15 (45%)
Antiarrhythmic drugs (%)	19 (95%)	19 (95%)	22 (67%)	28 (85%)

Table 3. Composite end points and ICD therapies (Shock/ATP) in cardiac sarcoidosis and ARVD patients-

	CS-RFA (%) (N=20)	CS-ICD (%) (N=33)	ARVD (%) (N=8)	P
Composite end points (N; %)	14 (70%)	21 (64%)	7 (87%)	0.19
Subjects receiving ICD therapy post -procedures (N; %)	11 (55%)	14 (42%)	5 (62%)	0.15
Median number of ICD therapies during FU per subject (Range)	19 (6-159)	10 (18-756)	12 (0-45)	0.01
Median time to first ICD therapy post procedure (months)	3	4	2.5	0.42

these ten re-do procedures, four were unsuccessful. The success rate of first ablation and redo ablation was similar (60%) in the CS- RFA group. In comparison, four out of eight patients had re-do ablation in the ARVD cohort, not significantly different from CS-RFA group (p=0.40). The success rate of the first ablation was 40% and re-do ablation 100% in ARVD patients.

Outcome analysis of the overall cohort:

The median length of follow-up was 41 (16-149) months for CS-RFA patients; 50 (9-173) months for those with ICD placement only and 51 (33-126) months in the ARVD patients. Fourteen (70%) of the CS-RFA patients reached the composite end point compared to 21 (64%) of the CS-ICD group and seven (88%) in the ARVD cohort over the follow up period (Table 3). Death occurred in 2, 3, and 1 patients in the CS-RFA, CS-ICD and AVRD groups, respectively. Cardiac transplantation was performed in 1, 4 and 2 patients, respectively.

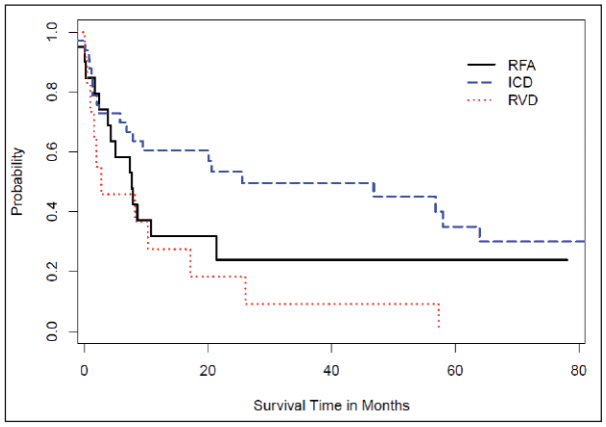

Fig. 1. Kaplan- Meier analysis of composite end points comparing the three groups (CS-RFA, CS-ICD & ARVD): p=0.02.

Kaplan-Meier estimation for the composite endpoint (Figure 1) revealed a significant difference between the groups (p= 0.02), favoring earlier time-to-event in the CS-RFA group. The most common reason for attaining the endpoint was appropriate ICD therapy, which occurred in 11 patients (79%) for the CS-RFA group, 14 patients (67%) for the CS-ICD group, and five patients (71%) for the ARVD group. However, time to event analysis did not show any significant differences between the three groups when only ICD therapies were considered as an endpoint (Figure 2A). Similar analysis excluding those patients with ICD placement for primary prevention (11 cardiomyopathy patients in the CS-ICD group) yielded similar result (Figure 2B; p=0.68). The median number of ICD therapies during the entire follow-up period was 19, 10 and 12 per subject respectively for CS-RFA, CS-ICD and ARVD group (p= 0.01, Table 3). The median time to an appropriate ICD therapy in those who had events was two months in CS-RFA group, four months for CS-ICD patients and two months in the ARVD group. The frequency of ICD therapies in the first year of follow-up was similar in all three groups, but after the first year they were more frequent in the CS-RFA group (Figure-3).

After propensity matching and multivariate adjustments, the aOR for attaining the composite end point was 2.3 (95% CI 0.33-16) following RFA in cardiac sarcoidosis patients compared to ICD therapy alone. Likewise, the aOR for ICD therapy was 2.2 (95%CI 0.36-13.4) after RFA.

Analysis of outcome predictors in the CS-RFA group

For the CS-RFA group, we analyzed which baseline or procedural variables might predict the requirement for future ICD therapies after RFA. The strongest predictor in multivariable analysis was

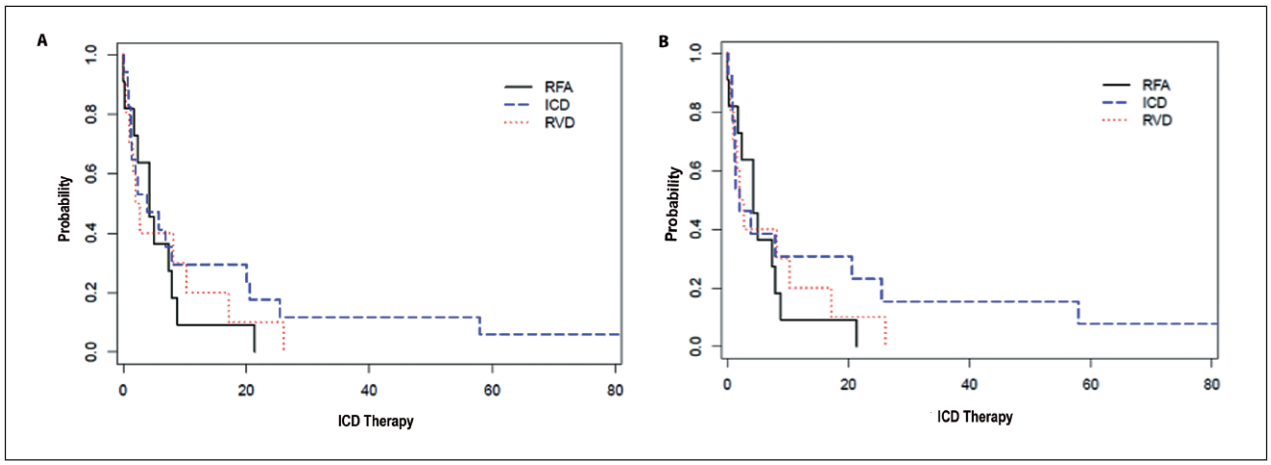

Fig. 2. A. Time to event analysis of ICD therapies (shock & ATP) comparing the three groups (CS-RFA, CS-ICD & ARVD): p=0.65; B. Similar estimation of ICD therapies (shock & ATP) comparing the three groups- patients with dilated cardiomyopathy, who had an ICD inserted for primary preventions are excluded (p=0.68).

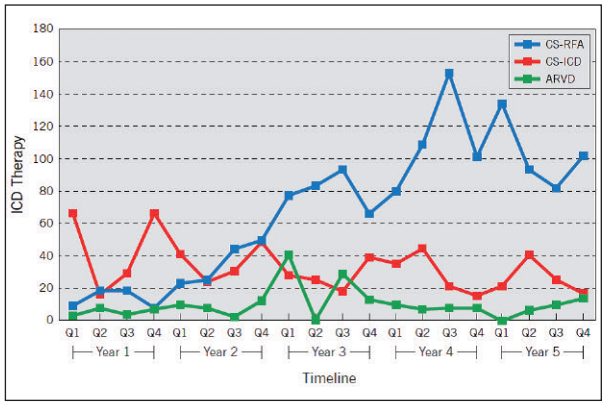

Fig. 3. Distribution of appropriate ICD therapies in the three groups (CS-RFA, CS-ICD and ARVD) over 5 year follow-up period, each year is divided into four quarters to describe the number of ICD therapies in each quarter of the year.

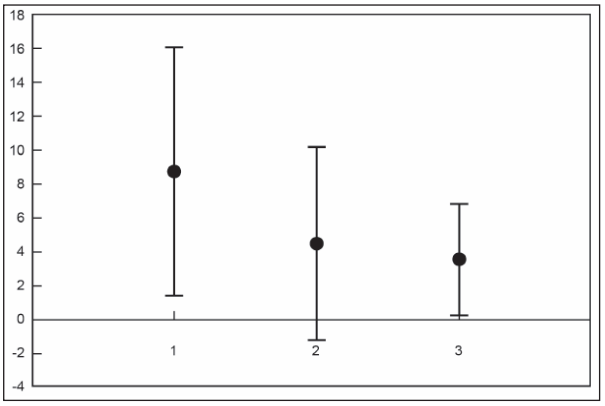

Fig. 4. Percentage of ventricular ectopic beats before and after RFA in cardiac sarcoid patients by Holter monitor (Mean± 2SD), no significant difference noted on follow-up Holter analysis although there was a downward trend (p=0.1): 1.- Pre-RFA, 2- Post RFA 1-6 months, 3- Post RFA 12-18 months.

LVEF ≤ 40% (odds ratio 13.2, 95% CI 2.1-82.5, p=0.003), followed by having an unsuccessful or partly successful RFA procedure (odds ratio 7.9, 95% CI 1.3- 47). In follow-up, those patients who had an escalation of either immunosuppressive therapy or anti-arrhythmic medications following the RFA procedure also had a higher a higher future events (OR-2.3; p=0.05). In contrast, the extent of cardiac involvement on PET scan and degree of pre-procedure ectopy (percent ectopic beats) were not associated with a higher risk of ICD therapies (Table 4). We did not examine whether the use of specific medications influenced the need for subsequent therapies, since all the patients were treated with anti-arrhythmic medications and the immunosuppressive regimen in this cohort was highly variable.

On follow-up Holter monitor within a month, the mean frequency of ventricular ectopic beats fell from 9 ± 12% to 4 ± 7% after the RFA procedure. However, there was no significant change after longer term follow-up (mean difference of 3 ± 3%, p=0.1, Figure-4). Since the number of appropriate ICD therapies increased over time but the percent of

Table 4. Variables predicting future ICD therapy (shock/ATP) following RFA procedure in cardiac sarcoidosis patients-

Variable	OR	95% CI	P
Percent of heart involved in PET scan			0.10
Percent of Ventricular ectopic in Holter monitor			0.12
LVEF <40%	13	2.1- 82.5	0.01
Unsuccessful RFA ablation	7.9	1.3- 47	0.02
Escalation of therapies post procedure	2.3	1.5- 10	0.05

ventricular ectopic beats was persistently reduced after the RFA procedure, Holter monitoring may not be a sensitive tool to follow patients for prediction of ventricular dysrhythmias after RFA.

Correlation of FDG-PET and RFA procedure in Cardiac Sarcoidosis:

Nine of our patients had a follow-up perfusion-metabolism PET scan (Rb-FDG-PET) done between 6-12 months following their RFA. Among nine segments that were previously ablated in the nine patients, six (67%) exhibited metabolism perfusion mismatch suggestive of ongoing inflammation, whereas three (33%) had evidence of scar at the sites of ablation. Eight of these nine patients had been treated with immunosuppressive medications, including prednisone (n=7) with a median daily dose of 25 (20-60) mg, methotrexate (n=4), and leflunomide (n=1) after RFA. Two of those six patients with persistent high uptake on PET scan and one patient with scar required redo ablation. Average LVEF of the patients with most segments exhibiting active inflammation on FDG-PET was 50±11%, versus 37±10% for patients with most segments exhibiting scar (p=0.13). In three patients, all of whom had persistent active inflammation at the RFA site on follow-up Rb-FDG-PET, a pre-procedure scan within six months before RFA was also available for review. For all three subjects, the site of inducible VT corresponded to the location of active inflammation rather than scar.

Discussion

Our experience suggests that RFA is an effective therapy for bothersome ventricular dysrhythmias in cardiac sarcoidosis patients, with long-term outcomes that are similar to patients who present with less aggressive disease and are therefore managed with ICD alone, and to those with ARVD. However, we also show that individuals who are treated with RFA have a higher chance of developing recurrent dysrhythmias more than a year following the RFA, regardless of its success. Therefore, RFA alone for a clinically occurring VT cannot be viewed as adequate management for ventricular dysrhythmias in cardiac sarcoidosis. We also identified several markers of risk for future events following RFA, including LVEF<40%, unsuccessful or partly successful RFA procedure, presence of more than one inducible foci during the procedure and escalation of immunosuppressive or anti-arrhythmic therapy after the procedure.

Sudden death may be the first sign of CS, potentially accounting for a high proportion of deaths due to cardiac sarcoidosis (8). Nevertheless, the optimal treatment approach in cardiac sarcoidosis remains controversial. A Delphi study of cardiac sarcoidosis specialists amply highlighted the disagreement in approach (9).

ICD placement is currently a Class IIA recommendation in CS; some small trials have suggested a survival benefit from ICD (10,11). These studies also showed that the CS patients who received ICDs are at high risk of ventricular tachycardia and that the population has a high rate of ICD therapy following device placement (10,12). Unfortunately, there appears to be a high risk of inappropriate therapies (defined as ICD therapy delivered for reasons other than nonventricular tachyarrhythmias) in this population as well (13). Since occurrence of VT/VF is the main interest of our paper, all ICD therapies listed in our study were appropriate.

In contrast, the clinical course following RFA

in CS is less well defined. Tokuda et al demonstrated worse outcomes in CS patients after RFA than for other non-ischemic cardiomyopathies (14). Seventy percent of our cardiac sarcoid patients reached composite end points and 55% received appropriate ICD therapy following RFA after a median follow-up period of 41 months. Koplan and colleagues noted ICD therapies as high as 75% within six months of RFA in eight cardiac sarcoid patients (15). The present study had a concomitant ICD placement in only 65% of the CS-RFA patients. Therefore, it is probable that we underestimated the true proportion of patients with significant dysrhythmias. However, the correlation between the need for appropriate therapy and mortality due to dysrhythmias has not been clearly demonstrated, so the survival benefit of demonstrating changes in the number of therapies is unclear at present.

The success of RFA for sarcoidosis has been thought to depend on the duration and disease activity (16). In that regard, our CS-RFA patient population was older than the previous two studies describing the efficacy of RFA in CS patients (15,17). Nevertheless 67% patients had a successful or partly successful RFA in our study, which is comparable to other cohorts (15,17). Also, in our institution, RFA is generally limited to those patients with persistent VT despite medical and/or anti-arrhythmic therapy.

The rate of attaining the composite endpoint was similar in the CS-RFA group and the CS-ICD group, but there was a significant trend for earlier events in the CS-RFA group. A requirement for repeat RFA is the most likely explanation for this apparent finding, since there were no significant differences in the rate of appropriate ICD therapies between the two groups. Nonetheless, the current data provide support for a strategy of placing an ICD alone and managing with immunosuppressive and anti-arrhythmic medications as a viable approach, rather than early use of RFA for all patients with dysrhythmias.

Our study revealed that 45% of patients who had RFA had no requirement for ICD therapies within a median follow up period of 41 months. Even among those with completely successful RFAs, the number of appropriate therapies increased after a year following the procedure, possibly due to progressive myocardial damage. These outcomes are similar to those in a multicenter registry, where all nine patients who had RFA achieved excellent initial control but four of the nine required repeat procedures over a mean follow-up of 19 months (17). In contrast, in a single center study, six of the eight patients had recurrence of ventricular dysrhythmias within six months of RFA (15). Prior reports have demonstrated that the rate of ICD therapies depends on duration of follow-up, and whether the ICD is placed for primary or secondary prevention (13,18). Since our population was followed for longer time periods, and all the RFA procedures were performed for secondary prevention, higher rates of ICD therapies are not unexpected.

Nineteen percent of our patients had delayed diagnosis of sarcoidosis, on average 3.8±2.5 years after presentation with cardiac difficulties. As a result, many of our patients in the CS cohort were not taking any immunosuppressants at the time of their procedure. Variable proportions of the patients were treated with anti-arrhythmic agents or immunosuppressants due to differences in patient tolerance or clinician preference. In general, patients for whom ICD was placed for primary prevention were not started on anti-arrhythymic medications. Our clinical practice contrasts with prior experiences, where antiarrhythmic and immunosuppressive medications were prescribed for a high proportion of the patients (15,17). Since corticosteroids have been suggested to be efficacious for treatment of CS (19,20), our outcomes may not be entirely reflective of those where more aggressive medical therapy is routinely used. Nonetheless, we did not find a statistically significant effect of post-procedure adjustment of immunosupressives on the primary outcome. Because our usual clinical practice is to employ RFA as a last resort after other modalities have failed, it is likely that our population was enriched for individuals with a high propensity for VT or a relatively refractory electrical substrate.

Our experience with Rb-FDG-PET suggests that most of the bothersome dysrhythmias in sarcoidosis arise in areas of active inflammation, rather than in scarred segments, in contrast to ischemic heart disease. Other authors have also noted that increased segmental FDG uptake is associated with a higher likelihood of VT (21,22). In our cohort, a persistent high FDG uptake at the same location as the prior RFA was seen in a significant number of patients, despite aggressive immunosuppressive

treatment in most cases. This finding may be due to failure of immunosuppressive therapy, further stimulation of granulomatous inflammation by RFA-induced injury, or inadequate time between the RFA and the follow-up PET. This observation correlates well with the previously described mechanism of ventricular tachyarrhythmia associated with cardiac sarcoidosis i.e. granuloma serving as a re-entrant substrate for VT (23). In our experience, cardiac FDG-PET improvement is much slower than that in the rest of the body.

We confirmed that LVEF<40% is the single strongest risk factor for ICD therapy, whether in those with ICD only or in conjunction with RFA. In other series, the average LVEF threshold for inducing VT and appropriate ICD therapy varied 37 to less than 55% (11,17,23-25). Existing guidelines advises theo use of clinical judgment regarding ICD placement as well, because LVEF determination may be inaccurate and lacks "gold standard" in those with LVEF >35% (26).

The current study has several limitations. While we attempted to correct baseline differences between the groups, using propensity matching and multivariable regression analysis, the small sample sizes limited the robustness of our statistical approach. The study is also limited by the significant variability in medical management for CS, as well as the absence of a pre-determined explicit set of criteria for proceeding with RFA. Finally, not all our patients in the CS-RFA group had concomitant ICD, which possibly led to underestimation of ICD therapy and composite end points.

In conclusion, this study has several clinical implications. It confirms that RFA can be an effective modality for short-term treatment of dysrhythmias in cardiac sarcoidosis, but that it does not provide assurance regarding long-term freedom from dysrhythmias. Therefore, ICD placement is recommended for all patients who require RFA for VT associated with CS, whether it is successful or not. We confirmed that significant risk factors for poor outcome included ejection fraction <40% and absence of fully successful ablation of inducible foci. In contradistinction to ischemic cardiomyopathy, most dysrhythmias appear to arise in areas of active inflammation, rather than scar; the inflammation tended to persist on follow-up PET scan despite aggressive medical therapy. This suggests that areas of active inflammation in otherwise viable cardiac muscle may be more likely to provide the slow conduction substrate for reentry. In contrast, the characteristics of sarcoidosis-generated scarring may have fewer propensities for such slow conduction, perhaps due to the density of such scarring that lessens the survival of myocardial fibers within the scar. If this were the explanation, aggressive immunosuppressive therapy, perhaps with combination anti-inflammatory medications, may have better long term outcome than catheter ablation of the VT substrate. Further studies are necessary to more precisely define the role of RFA in the management of cardiac sarcoidosis.

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