Ventricular Tachycardia in Cardiac Sarcoidosis: Characterization of Ventricular Substrate and Outcomes of Catheter Ablation

Running title: Kumar et al.; Ventricular tachycardia in Cardiac Sarcoidosis

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Abstract:

**Background** - Cardiac sarcoid-related ventricular tachycardia (VT) is a rare disorder; the underlying substrate and response to ablation are poorly understood. We sought to examine the ventricular substrate and outcomes of catheter ablation in this population.

**Methods and Results** - Of 435 patients with non-ischemic cardiomyopathy referred for VT ablation, 21 patients (5%) had cardiac sarcoidosis. Multiple inducible VTs were observed with mechanism consistent with scar-mediated re-entry in all VTs. Voltage maps showed widespread and confluent right ventricular (RV) scarring. Left ventricular (LV) scarring was patchy with a predilection for the basal septum, anterior wall, and perivalvular regions. Epicardial RV scar overlay and exceeded the region of corresponding endocardial scar. After one or more procedures, ablation abolished at least one inducible VT in 90% and eliminated VT storm in 78% of patients, however multiple residual VTs remained inducible. Failure to abolish all inducible VTs was due to septal intramural circuits or extensive RV scarring. Multiple procedure VT-free survival was 37% at 1 year, but VT control was achievable in the majority of patients with fewer anti-arrhythmic drugs compared with pre-ablation (2.1±0.8 vs. 1.1±0.8, P<0.001).

**Conclusions** - Patients with cardiac sarcoidosis and VT exhibit ventricular substrate characterized by confluent RV scarring and patchy LV scarring capable of sustaining a large number of re-entrant circuits. Catheter ablation is effective at terminating VT storm and eliminating ≥1 inducible VT in the majority of patients, but recurrences are common. Ablation in conjunction with antiarrhythmic drugs can help palliate VT in this high-risk population.

**Key words:** cardiac sarcoidosis, catheter ablation, arrhythmia, ventricular tachycardia, ventricular tachycardia storm, radiofrequency ablation, scar mediated reentry
Introduction

Sarcoidosis is a multisystem disorder of unknown etiology characterized by non-caseating granuloma formation in pulmonary tissue and extra-pulmonary organs such as the skin, lymph nodes and the heart. Cardiac involvement is characterized by development of atrioventricular block (AVB), ventricular tachycardia (VT), congestive heart failure and/or sudden cardiac death. In autopsy studies, 20-70% of patients with recognized extracardiac sarcoid have subclinical cardiac involvement. Sustained monomorphic VT (SMVT) in cardiac sarcoidosis is a significant predictor of mortality. Cardiac sarcoid patients with an implantable cardioverter defibrillator experience ventricular arrhythmias at an incidence of 15% per year. To date, our understanding of the mechanism, electrophysiologic substrate and role of catheter ablation in sarcoid-related VT is derived from small series of patients. In this study, we report the electrophysiologic and electroanatomic substrate and outcomes of catheter ablation in a cohort of patients with cardiac sarcoid-related VT treated with catheter ablation.

Methods

Of 435 patients with non-ischemic cardiomyopathy referred for catheter ablation of sustained monomorphic VT, frequent premature ventricular contractions (PVCs), or non-sustained VT from January 1997-January 2014, 21 patients (5%) had a diagnosis of cardiac sarcoidosis. Diagnosis of cardiac sarcoidosis was based on the revised guidelines of the Japanese Society of Sarcoidosis and Other Granulomatous Disorders (Supplemental Methods). All patients gave written informed consent for the procedure; procedures were performed according to protocols approved by the Brigham and Women’s Hospital Human Subject Protection Committee.

Mapping and radiofrequency ablation

Procedures were performed as described previously (Supplemental Methods). Mapping and
ablation was performed using a 4-mm- or 3.5-mm-tip catheter (NaviStar, NaviStar ThermoCool or ThermoCool SF; Biosense Webster, Diamond Bar, California, USA). Endocardial/epicardial voltage maps were created using the CARTO electroanatomic mapping system using ventricular electrogram amplitude. Pace and entrainment mapping were performed using unipolar pacing from the distal electrode (10 mA output and 2 ms pulse width). Bipolar electrogram amplitude of <1.5 mV was defined as low voltage area consistent with scar. Dense scar was defined as voltage ≤0.5mV. Electrically unexcitable scar was defined as sites where the pacing threshold exceeded 10 mA with 2-ms pulse width. Epicardial mapping was performed using the percutaneous approach if VT was suspected to be of epicardial origin. Coronary angiography was performed before epicardial ablation to avoid coronary injury.

In all patients, complete endocardial voltage maps of the chamber of interest were obtained. For describing scar distribution, the endocardial RV was divided into: RV outflow tract (RVOT), RV free wall, septum, inferior wall, and peri-tricuspid annular (TA) and the endocardial LV regions into anterior, septal, inferior, lateral, apex and the LV outflow tract (LVOT)/aorto-mitral continuity (AMC).

Programmed ventricular stimulation was performed with up to 3 extrastimuli following a drive train 600 ms and 400 ms from 2 RV sites (Supplemental Methods). This protocol was repeated post ablation. The mechanism of VT was defined as scar-related reentry when induction and termination was demonstrable with programmed ventricular stimulation, fulfilled criteria for transient entrainment, had an exit site at a low-voltage area consistent with scar, had evidence of slowed conduction with pace maps in this region yielding a stimulus-QRS delay of >40 ms and when ablation in the putative isthmus region abolished >1 morphology of VT. Reentry circuit sites were defined by entrainment and pace mapping as reported previously.
Sustained monomorphic VT was defined as continuous VT for ≥30 s or that required an intervention for termination (cardioversion, pacing or ablation). We defined “spontaneous VT” as any inducible VT that had a 12-lead EKG morphology and rate (within 20 ms) matching a VT that had documented to have occurred spontaneously prior to ablation; only the rate cut off and intracardiac EGM data from the implanted cardioverter defibrillator (ICD) was used when the 12-lead VT morphology was not available prior to ablation. “Non-spontaneous” VTs were inducible VTs that did not have an identical rate (>20 ms difference) or 12-lead EKG morphology to the spontaneously documented VT prior to ablation.

The approach to ablation is detailed in the Supplemental Methods but has been described previously. Irrigated radiofrequency ablation (RFA) was delivered at a power of 25 to 50 Watts targeting an impedance drop of 10 to 20 ohms. Applications were repeated at target areas until they were rendered electrically unexcitable with unipolar pacing at 10 mA at 2-ms pulse width. Ablation lesions were placed only in areas of low voltage (<1.5 mV).

Intramural circuits were inferred on a combination of either: (i) suggestive 12 lead EKG morphology (septal origin); (ii) bipolar or unipolar voltage abnormality with electrogram amplitude <5.5 mV for the RV and <8.3 mV in the LV or the interventricular septum or bipolar voltage maps; (iii) when the closest sites to the circuit were identified on either side of the septum (if septal origin) or either side of the endo- or epicardial space mapped (if non-septal origin) based on entrainment, pace and/or activation mapping or by interruption of VT by ablation, and/or (iv) when intramural scarring was seen on cardiac MRI. Prior to the validation of unipolar voltage mapping, intramural substrate was inferred if the earliest activation for that chamber or epicardial space showed activation at the beginning of the QRS complex with focal spread of activation away, and if entrainment (if performed) indicated an
outer loop, exit, or bystander site, and ablation failed to abolish VT at these sites.\textsuperscript{18}

**Outcomes**

Outcomes at the end of the procedure reported included: (i) abolishment of at least one inducible VT (spontaneous or non-spontaneous); (ii) abolishment of all inducible VTs (spontaneous or non-spontaneous); and (iii) abolishment of VT storm.\textsuperscript{8} Long term outcomes reported included: (i) procedure success defined survival free of any VT during follow up after a single and after multiple procedures; (ii) arrhythmia control defined as any reduction in the number of VT episodes or number of anti-arrhythmic drugs (AADs) required for arrhythmia control during follow up; (iii) overall survival; and (iv) survival free of death or cardiac transplantation.

Survival free of VT recurrence, death or cardiac transplant in patients with “active disease” versus those with “inactive disease” was also reported. Assessment of disease activity was made by an expert treating physician in sarcoidosis using clinical symptoms, biopsy results and/or results of positron emission tomography (PET) imaging.

**Follow up**

Follow up included review of records of all hospital and outpatient clinic visits and discussion with referring cardiologists and primary care physicians. Details of implantable cardioverter defibrillator programming are provided in Supplemental Methods. The National Social Security Death Index was searched for mortality information.

**Statistical Analysis**

The Statistical Package for the Social Sciences for Windows (IBM SPSS, release 22, Armonk, New York, USA) was used for analysis. Continuous variables were expressed as mean ± standard deviation if normally distributed; median and interquartile range 25-75% (Q25-Q75) or full ranges were used if the data was clearly skewed. Where normal distribution was not present,
log transformation of the raw values was performed to meet the assumption of homogeneity of variance. Where applicable, paired sample t-test was performed using the raw values (if normally distributed) or log transformed values (if not normally distributed). Procedural success, overall survival and survival free of death or cardiac transplant were estimated by using the Kaplan-Meier procedure and log-rank $\chi^2$ test. A P value <0.05 was considered statistically significant.

**Results**

**Patient demographics**

The mean age of the cohort was 47±9 years (range 33-66 years) with 17 males (Table). At time of ablation, 12 patients were receiving immunosuppression for “active disease” (presence of granulomatous inflammation on biopsy and/or evidence of active disease of cardiac positron emission tomography scanning). Six patients were not receiving immunosuppression as the diagnosis was made after ablation, including 2 who had cardiac transplant granulomatous inflammation identified in the explanted heart, and 4 diagnosed immediately after ablation who were subsequently started on immunosuppressants for “active disease”. Three patients were felt to have “inactive disease” at time of ablation and were not receiving immunosuppression.

**Procedural data**

A total of 32 ablation procedures were performed over a mean follow up of 4.8±5.1 years (median 2, Q25-Q75: 1-9.5 years, Table). Twenty one patients underwent a single procedure, 9 patients underwent two procedures and 2 patients underwent 3 procedures. A total 99 sustained monomorphic VTs were inducible across all procedures, of which 67 VTs were felt to have occurred clinically. The majority of VTs had left bundle morphology in lead V1 (59%), followed by right bundle (32%) or indeterminate morphology (9%). All VTs had demonstrable evidence of reentry related to regions of scar (Supplemental Table).
**Electroanatomic mapping features**

Endocardial mapping was performed in all patients and epicardial mapping in 8 patients. The RV was mapped in 18 patients, LV in 15 patients and both chambers in 12/21 patients. RV scarring, present in 16/18 patients, tended to be confluent, with similar frequency in all regions of the RV (Figure 1). Extensive RV scarring with only a small region of intervening normal voltage was present in 7/18 patients. LV scarring was present in 14/15 patients. In contrast to the RV, LV scarring tended to be patchy, with a predilection for the septum, followed by the anterior wall, LVOT/AMC region, inferior wall, lateral wall and the apex (Figure 1).

Epicardial RV scar was present in 7 of 8 patients and was overlying and exceeded the region of corresponding endocardial scar. In contrast, epicardial LV scar did not correspond to the region of endocardial scarring in 2, and was absent altogether despite underlying endocardial scar in 2 patients. In 2 patients, it corresponded to the site of endocardial scar. One patient had no endo nor epicardial low voltage LV scar, and in another, focused epicardial mapping was performed over the RV only as all VTs were of RV origin. LV epicardial scarring, when present, was patchy and was located over the basal septum, lateral mitral annulus, the crux of the heart (posterobasal septum) and the LV summit.

**Additional information from imaging studies**

Cardiac MRI and/or PET scanning revealed scarring of the septum and RV free wall in 1 patient in whom voltage mapping of the RV was not performed. In 2 patients who did not undergo LV voltage mapping, scar in the basal inferior, basal anterior and inferior septum, mid inferior wall and apical inferior LV was noted (on MRI and PET in 1 patient respectively).

**Catheter Ablation and Acute Procedural Outcomes**

Endocardial radiofrequency ablation (RFA) was delivered in all patients; in 5 of the 8 patients
who underwent epicardial mapping, concurrent epicardial RFA was also administered (representative examples in Figures 2, also Supplemental Figures 1-4).

At the first procedure, a median of 3 VTs were inducible (range 1-8) and had a median CL of 355 ms (range 240-600 ms). At least 1 inducible VT was abolished in 19 of 21 patients (91%). All inducible VTs (spontaneous and non-spontaneous) were abolished in 9 of 21 patients (43%). All spontaneous VTs were abolished but non-spontaneous VTs remained inducible in 5 of 21 patients (24%); some spontaneous VTs were abolished but other spontaneous VTs remained inducible in 5 of 21 (24%) patients. In 2 of 21 patients (10%), the spontaneous VT remained inducible. A median of 1 VT (range 0-8) remained inducible at the end of the first procedure.

Nine patients underwent a second procedure during which a median of 4 VTs were inducible (range 1-5) and had a median CL of 310 ms (range 250-400 ms). At least one inducible VT was abolished in 7 of 9 patients (78%). All inducible VTs (spontaneous and non-spontaneous) were abolished in 2 of 9 patients (22%). All spontaneous VTs were abolished but non-spontaneous VTs remained inducible in 3 of 9 patients (33%), some spontaneous VTs were abolished but other spontaneous VTs remained inducible in 1 of 9 patients (11%). In 1 patient, programmed ventricular stimulation induction was not performed after ablation to avoid further hemodynamic stress. In 2 of 9 patients (22%), the spontaneous VT remained inducible. A median of 1 VTs (range 0-4) remained inducible at the end of the second procedure.

Two patients underwent a third procedure, both of whom had 2 VTs inducible and had a median CL of 328 ms (range 300-356 ms). At least one inducible VT was abolished in both patients (100%). All spontaneous VTs were abolished but non-spontaneous VTs remained inducible in one patient. Some spontaneous VTs were abolished but other spontaneous VTs
remained inducible in one patient. Both patients had one inducible VT left at the end of the procedure.

During any procedure (first, second or third), at least one VT was abolished in 19 of 21 patients (90%). VT storm was experienced by 9 patients; storm was a procedural indication in 7 patients on their first procedure. Ablation terminated VT storm in 5 of 7 patients (71%). In two patients, storm was a procedural indication for catheter ablation for two procedures and catheter ablation was successful in terminating VT storm on both occasions. During any procedure (first or second), VT storm was treated successfully in 7 of 9 (78%) of patients. The two patients in whom VT storm could not be acutely treated were referred for cardiac transplantation.

Failure to abolish all inducible VTs was due to septal intramural circuits (9 procedures), extensive RV scarring with multiple re-entry circuits (6 procedures), or sites of origin in close proximity to the left anterior descending coronary (3 procedures) or the ramus intermedius (1 procedure) or the parahisian region (1 procedure) prohibiting safe ablation (Supplemental Table).

The only complication was electromechanical dissociation in 1 patient necessitating urgent biventricular assist device implantation as a bridge to cardiac transplantation.

**Outcomes in follow up**

During a mean follow up of 4.8±5.1 years (median 2, Q25-Q75: 1-9.5 years), all but 3 patients had VT recurrence after a single procedure (Figure 3). Arrhythmia control, however was achieved in the remaining patients after a mean of 1.5±0.7 procedures (median 1, range 1-3 procedures). Significantly fewer AADs were required to achieve arrhythmia control at last follow up compared to pre-referral (1.1±0.8 vs. 2.1±0.8, respectively *P*<0.001). After multiple procedures, the number of VT episodes reduced from a median 3 (Q25-Q75: 2-5) episodes in the preceding month prior to the first ablation to a median of 0 (Q25-Q75: 0-1) episodes in the 6
months following the final ablation ($P<0.001$). At 1 year, the rates of freedom from any VT after a single and multiple procedures were 25% and 37%, respectively.

Four patients died during follow up (2 from progressive heart failure, 2 while awaiting transplant for recurrent VT). Survival at 1 year and at mean follow up was 91% and 85%, respectively. Five patients underwent cardiac transplant (4 due to recurrent VT, 1 due to intractable heart failure). Survival free of death or cardiac transplant 1 year and at mean follow up was 76% and 61%, respectively.

At 1 year, patients with “inactive disease” who were not receiving immunosuppression (n=3) had a significantly better survival free of the combined endpoint of VT recurrence, death or transplant versus those who had “active disease” and/or were receiving concurrent immunosuppression (n=18; 67% vs. 6%, $P=0.03$ by log rank).

**Discussion**

This study characterizes the ventricular substrate, electrophysiologic mechanism and long-term outcomes of patients with cardiac sarcoidosis who developed VT treated with catheter ablation. Cardiac sarcoidosis is a rare disorder, accounting of only 5% of non-ischemic cardiomyopathy patients undergoing catheter ablation for ventricular arrhythmia over a 17-year period.

We found that the substrate for VT in this population is characterized by re-entry around confluent regions of endo- and epicardial RV scarring with no predilection for any particular RV region. In contrast to confluent RV scarring, LV scarring tended to be patchy with a predilection for the septum, anterior wall and peri-valvular regions. RV epicardial scarring frequently overlay and exceeded the corresponding region of endocardial scar, however this relationship was not consistently observed over the epicardial LV. This substrate was capable of sustaining a large number of re-entrant VT circuits. Catheter ablation was effective at terminating at $\geq 1$
spontaneous (clinical or inducible) VT in the majority of patients (90%). Importantly, catheter ablation eliminated VT storm in the majority (78%) of patients.

Although VT recurrence after ablation was common, arrhythmia control was achieved in the majority of patients with repeat ablation and required fewer AADs compared to pre-ablation. Elimination of all inducible VTs was difficult to achieve either due to diffuse and heterogeneous RV involvement, intramural scarring or close proximity to critical epicardial structures such as the coronary arteries prohibiting ablation. The inability to abolish all inducible VTs, as well as the high risk of recurrence, death, or cardiac transplant underscores the need for better treatment options in this high-risk group. Furthermore, given the tendency for advanced heart failure (specifically, RV dysfunction that was noted in approximately three-quarters of patients), and one case of electromechanical dissociation post-ablation, peri- and post-procedural circulatory support should be strongly considered.

**Prior studies**

Ventricular arrhythmias in cardiac sarcoidosis portend an increased risk of mortality. Prior pathological studies have shown myocardial involvement in the LV free wall and papillary muscles, the basal ventricular septum, and the RV free wall in decreasing order of frequency. In the present population who developed clinical arrhythmia, detailed endo- and epicardial voltage mapping showed that this population almost universally exhibit confluent RV scarring with patchy LV involvement with a predilection for the septum, anterior wall and the outflow tracts. In contrast to prior studies with fewer patients with RV involvement, all of our patients had spontaneously occurring VTs, suggesting that RV involvement may be particularly arrhythmogenic.

Triggered activity and abnormal automaticity have been observed with cardiac
sarcomeiosis patients with reduction in arrhythmic burden after initiation of immunosuppression. Cardiac sarcoidosis is characterized by myocardial inflammation and interstitial fibrosis that can lead to conduction slowing and macro re-entrant arrhythmias, our findings are consistent with such a mechanism. One prior multi-center study of 8 patients reported VT circuits to be predominantly located around the tricuspid valve; however the authors reported that the entire VT circuit was not mapped in most patients. VT circuits were also mapped in the RVOT and the mitral annulus, findings that are consistent with the locations noted in our study. Another study reported that VT circuits had a predilection for the RV apex. We found that VT circuits were intimately related to the location of scarring, which tended to be widespread around confluent regions anywhere in the RV and patchy in the LV. We did not find a predilection for the peri-tricuspid region or the RV apex as reported previously. This may represent more advanced disease substrate in our cohort. As reported by prior studies, multiple inducible VTs were observed in our study, consistent with the diffuse nature of myocardial involvement.

Outcomes of catheter ablation in this group of patients have previously been reported in smaller case series (<10 patients) with shorter follow up compared to the present study. Decreased or complete elimination of all VTs was observed in all patients in one study. Our group likely represents a higher risk cohort with lower LVEF (36±14% vs. 42±14%) and more extensive VT substrate than that reported by Jefic et al. In that study, the disease may have been more localized (peri-tricuspid valve), and thus more amenable to successful catheter ablation.

Limitations

Being a tertiary referral center, our patients may represent those with the most severe disease. The current experience is based on a relatively modest sample size; nevertheless, it is one of the largest series in this rare disorder and encompasses over 17 years of experience with catheter
ablation in these patients. Comparing outcomes of “active” versus “inactive” disease was limited by statistical power due low numbers in each group (18 and 3 patients, respectively). We were unable to systematically assess the effect of disease staging and immunosuppression on outcomes after catheter ablation, as the diagnosis was made after ablation in 6 of 21 patients and immunosuppression started thereafter. Further studies are needed to establish a systematic strategy of disease staging that may guide immunosuppression, the timing of catheter ablation, and perhaps provide an indicator of the likelihood of procedural success.

Conclusions

Patients with cardiac sarcoidosis and spontaneous VT exhibit ventricular substrate characterized by diffuse and heterogeneous RV scarring and patchy LV scarring capable of sustaining a large number of re-entrant circuits. Catheter ablation is effective at terminating ≥1 inducible VT in the majority of patients, but extensive scarring and intramural circuits prohibits abolishment of all inducible VTs. VT recurrence after ablation is common, but ablation is particularly effective at treating VT storm, and may provide palliation of recurrent uncontrollable arrhythmias. Despite a combination of medical therapy and ablation, a significant proportion of patients experience death or need for cardiac transplant, underscoring the need for better treatment options in this high-risk group.

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References:


Table: Demographic data

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### Right ventricular dysfunction

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<td>Moderate or severe</td>
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#### Number of failed anti-arrhythmic drugs prior to referral, mean ± SD

| Mean ± SD                        | 2.1±0.8 |

#### NYHA class ≥ 2 at time of ablation

| NYHA class ≥ 2 at time of ablation | 11 |

#### Number of VT episodes experienced in 1 month prior to referral, mean ± SD, (median, Q25-Q75)

| Mean ± SD, (median, Q25-Q75)       | 4.3±3.1 (3, 2-5) |

#### ICD

| ICD                             | 20 |

#### CRT-D

| CRT-D                           | 4  |

#### Number of procedures performed

| 1 procedure                     | 21 |
| 2 procedures                    | 9  |
| 3 procedures                    | 2  |

#### Procedural indication

| SMVT                            | 30 |
| VT storm                         | 11 |

#### Incessant NSVT

| Incessant NSVT                  | 2  |

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*cardiac biopsy alone (6), cardiac + lymph node biopsy (1), whole heart histopathologic examination post cardiac transplant (2)

†mediastinal lymph nodes (11), liver biopsy (1)

‡median of 17 (Q25-Q75 15-96) months after first symptomatic presentation.

§median of 9.5 (range 7-9.5) months after first symptomatic presentation.

¶both patients also had inducible VT matching non-sustained VT morphology during EP study

Abbreviations (alphabetical order): AVB- atrioventricular block, CRT-D: cardiac resynchronization therapy defibrillator, ICD-implantable cardioverter defibrillator, Q25-Q75- interquartile range, NSVT- non-sustained VT, RFA- radiofrequency ablation, SD- standard deviation, SMVT- sustained monomorphic VT, VF- ventricular fibrillation.
Figure Legends:

Figure 1: Scar distribution in the patient cohort.

Figure 2: Left panel: 32-year female who presented with 2nd degree AVB, LBBB (QRS >120 ms) and LV dysfunction (EF 25-30%) and was diagnosed with cardiac sarcoidosis. A cardiac resynchronization therapy/defibrillator was implanted and she developed SMVT 1 month later. She had 2 inducible VTs (LV and RV origin) related to scar-mediated re-entry around the endocardial periaortic/basal septal LV and the peri-tricuspid region of the RV respectively. Ablation in the basal septal LV resulted in complete heart block. Right panel: 39 year old male with cardiac sarcoid-related VT storm with two clinical RV VTs, one from the region of the inferobasal RV (VT1) and another from the RVOT (VT2) that were related to re-entry around extensive, confluent scarring in the endocardial RV (red regions, bipolar voltage <0.5 mV; purple regions representing normal bipolar voltage >1.5mV). Substrate modification was performed (red dots).

Figure 3: Outcomes following catheter ablation. Percentages are calculated based on all 21 patients.
RV scarring present in 16/18 patients mapped
- RVOT 12/18
- Septum 12/18
- Inferior 12/18
- Peri-TA 11/18
- Free wall 10/18

LV scarring present in 14/15 patients mapped
- Septum 11/15
- Ant wall 7/15
- LVOT/AMC 5/15
- Inferior 3/15
- Lateral 2/15
- Apical 1/15
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**SUPPLEMENTAL MATERIAL**

**Supplemental Methods**

**Diagnosis of cardiac sarcoidosis**

Diagnosis of cardiac sarcoid was based on the revised guidelines of the Japanese Society of Sarcoidosis and Other Granulomatous Disorders using either: (i) histological diagnosis of cardiac sarcoid in addition to histologic or clinical diagnosis of extracardiac sarcoid or (ii) histologic or clinical diagnosis of extracardiac sarcoid plus a combination of major or minor criteria for cardiac involvement.¹

**Mapping and radiofrequency ablation**

Procedures were performed under either conscious sedation or general anesthesia as described previously.² Using femoral venous access multipolar electrode catheters were positioned in the right ventricular (RV) apex and the His bundle region. Arterial access was obtained for hemodynamic monitoring and to facilitate retrograde aortic access to the left ventricle when necessary. When available, intracardiac echocardiography was used for image integration into an electroanatomic mapping system (CARTO, Biosense Webster, Diamond Bar, CA), to confirm catheter-tissue contact and assess for complications.

Mapping and ablation was performed using a 4-mm- or 3.5-mm-tip catheter (NaviStar, NaviStar ThermoCool or ThermoCool SF; Biosense Webster). Access to the left ventricle was obtained retrogradely across the aortic valve or by transseptal puncture. Endocardial and where clinically relevant, epicardial voltage maps were obtained using the CARTO electroanatomic mapping system using ventricular
electrogram amplitude with electrograms which pass filtered at 20 to 30 Hz and low pass filtered at 400 Hz. Bipolar electrograms were band-pass filtered from 30 to 500 Hz and digitally recorded along with a 12-lead surface ECG using the Cardiolab electrophysiology system (General Electric Healthcare, Buckinghamshire, UK). In the electroanatomic mapping system bipolar electrograms were high pass filtered at 20 to 30 Hz and low pass filtered at 400 Hz. Pace and entrainment mapping were performed using unipolar pacing from the distal electrode with an initial current strength of 10 mA and a pulse width of 2 ms.³

Areas of scar were identified based on bipolar electrogram amplitude of <1.5 mV.⁴ Dense scar was defined as voltage ≤0.5mV. Electrically unexcitable scar was defined as sites where the pacing threshold exceeded 10 mA with 2-ms pulse width.³ Intramural substrate was sought by assessing unipolar voltage maps with electrogram amplitude <5.5 mV for the RV free wall⁵ and <8.3 mV in the left ventricle (LV) or the interventricular septum identifying potential intramural scar.⁶

In all patients, complete endocardial maps of the chamber of interest were obtained based on the morphology of clinical VT to identify scar regions. Those regions showing low amplitude electrograms were mapped with greater point density to delineate the extent and border zones of scar areas. To describe scar distribution for the purpose of this study, the endocardial RV and LV were compartmentalized into pre-defined anatomic regions. The endocardial RV regions were: RV outflow tract (RVOT), RV free wall, septum, inferior wall, and peri-tricuspid annular (TA). The endocardial LV regions were: anterior, septal, inferior, lateral, apex and the LV outflow tract (LVOT)/aorto-mitral continuity (AMC).

The mechanism of VT was defined as scar-related reentry when induction
and termination was demonstrable with programmed ventricular stimulation, fulfilled criteria for transient entrainment, had an exit site at a low-voltage area consistent with scar, had evidence of slowed conduction with pace maps in this region yielding a stimulus-QRS delay of > 40 ms and when ablation in the putative isthmus region abolished >1 morphology of VT. Reentry circuit sites were defined by entrainment and pace mapping as reported previously.\(^7\)

Programmed ventricular stimulation for initiation of VT was performed with up to 3 extrastimuli scanned to refractoriness or a minimum coupling interval of 180 ms, applied following a basic drive of 600 ms and then 400 ms from 2 RV sites; burst pacing was also employed if the above failed to induce VT.

The approach to ablation was as follows, as described previously.\(^8\) After identification of scar regions, the catheter was positioned at a site where pace mapping resembled the clinical or inducible VT and/or where stimulus-QRS delay was >40 ms indicative of slowed conduction. VT was then initiated with programmed stimulation and entrainment maneuvers attempted immediately. If there was evidence of entrainment with concealed fusion with a stimulus-QRS interval of <70% of the VT cycle length (CL) with a post-pacing interval and VT CL difference of ≤30 ms with the presence of an isolated mid-diastolic potential or presystolic potential, this suggested a putative isthmus site and ablation was commenced immediately. If pacing did not suggest an isthmus, mapping continued in VT if it was hemodynamically tolerated.

If the induced VT was hemodynamically unstable, it was terminated with RF ablation, rapid pacing, or cardioversion.\(^3\) Further mapping was then performed during sinus or paced rhythm using high-density substrate mapping of the
endocardium and/or epicardium. Presumptive channels and exits within the low voltage region were identified if the paced QRS morphology was similar to the VT QRS morphology with long stimulus-to-QRS delays (>40 ms)\(^9\) indicating slowed conduction; these sites were tagged and targeted for ablation. These findings have been shown to be related to the reentry circuit exit and sites where ablation abolishes VT.\(^10\) Sites with long duration fractionated potentials and isolated late potentials during sinus or paced rhythm were tagged and targeted for ablation if they yielded long stimulus-QRS delays with matching QRS morphologies to that of the clinical or inducible VTs. Ablation was targeted at presumptive channels and exits within the low-voltage area. When these sites were adjacent to a valve annulus or region of electrically unexcitable scar, ablation lesions were extended to the unexcitable area with the intention of transecting reentry circuit paths.\(^8\) If no low-voltage area was identified, ablation was attempted at the likely exit region identified as sites with presystolic electrograms during VT or where pace mapping resembled the VT QRS. Irrigated RF energy was delivered at a power of 25 to 50 Watts targeting an impedance drop of 10 to 20 ohms. Applications were repeated at target areas until they were rendered electrically unexcitable with unipolar pacing at 10 mA at 2-ms pulse width.\(^3\) Ablation lesions were placed only in areas of low voltage (<1.5 mV).

Epicardial mapping was performed using the percutaneous approach if VT was suspected to be of epicardial origin.\(^11\) Coronary angiography was performed before epicardial ablation at sites where there was the possibility of an adjacent artery supplying viable ventricular myocardium. After ablation, VT inducibility was
assessed using programmed electric stimulation at two drive trains of 600ms and 400 ms, with up to three extrastimuli from two RV sites.

If any monomorphic VT was inducible after the initial set of RF lesions, the mapping and ablation process was repeated with further ablation within the putative isthmus unless entrainment of the new VT demonstrated that the region was not involved in the VT circuit. The procedure ended when either no monomorphic VT was inducible, when VT was inducible but no endo or epicardial target site critical to reentry could be found (as assessed from entrainment and interruption of VT by ablation), or if the target site critical to reentry was in close proximity to critical epicardial structures as a coronary artery or the phrenic nerve, prohibiting safe ablation.

Intramural circuits were inferred on a combination of either: (i) suggestive 12 lead EKG morphology (septal origin);\(^1\) (ii) bipolar or unipolar voltage abnormality with electrogram amplitude <5.5 mV for the RV\(^5\) and <8.3 mV in the LV or the interventricular septum\(^6\) or bipolar voltage maps; (iii) when the closest sites to the circuit were identified on either side of the septum (if septal origin) or either side of the endo- or epicardial space mapped (if non-septal origin) based on entrainment, pace and/or activation mapping or by interruption of VT by ablation, and/or (iv) when intramural scarring was seen on cardiac MRI.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\) Prior to the validation of unipolar voltage mapping,\(^5\)\(^,\)\(^6\)\(^,\)\(^1\) intramural substrate was inferred if the earliest activation for that chamber or epicardial space showed activation at the beginning of the QRS complex with focal spread of activation away, and if entrainment (if performed) indicated an outer loop, exit, or bystander site, and ablation failed to abolish VT at these sites.\(^1\)\(^4\)
**Implantable Cardioverter-Defibrillator Programming**

Programming of implantable cardioverter defibrillator (ICDs) was left to the discretion of the treating electrophysiologist. In general, two zones were programmed. The first zone had a minimum rate cut off >140 bpm (usually >165 beats per minute [bpm]) delivered a minimum of 2 rounds of 3 bursts of anti-tachycardia pacing (ATP) followed by maximum of four 35 joule (J) shocks. The second zone had a minimum rate cut off of >188 bpm delivering ATP during charging followed by maximum of six 35J shocks. In general, programming was kept consistent before and after an ablation procedure, where possible.

**Supplemental Results**

**Implantable-Cardioverter Defibrillators**

ICDs were present in 20/21 patients (including CRT-D in 4 patients). One patient did not have an ICD due to inactive disease, a small scar on cardiac MRI and acute/long term success with catheter ablation. This patient remains free of VT after 2 years of follow up and is being monitored closely with repeat PET-CT for disease activity/scar progression.
Supplemental References


### Supplemental Table

Morphology of VTs seen, scar distribution, putative circuits and reasons for inability to abolish all inducible VTs in the cohort studied.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>VT morphology</th>
<th>Scar distribution</th>
<th>Putative VT circuits</th>
<th>Reason for inability to abolish all inducible VTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RB SA, LB SA</td>
<td>LV basal septal</td>
<td>LV inferobasal septum</td>
<td>Intramural basal septal circuit</td>
</tr>
<tr>
<td>2</td>
<td>LB SA, LB IA, RB SA</td>
<td>RV: basal and inferior septum, free wall LV: septum</td>
<td>Basal septal (RV and LV side), inferoseptal, RV free wall</td>
<td>Intramural basal septal circuit</td>
</tr>
<tr>
<td>3</td>
<td>LB IA, LB SA</td>
<td>RVOT, inferolateral TA</td>
<td>RVOT</td>
<td>Intramural circuit</td>
</tr>
<tr>
<td>4</td>
<td>RB IA, LB SA, LB IA</td>
<td>RVOT: septum and free wall LV: basal septum</td>
<td>RB tachycardias: Earliest activation 2 cm leftward and posterior from the AV annulus; RF had no effect on tachycardia; RF at septal RVOT had no effect. LB tachycardias: appear to originate from the IVS with no exit of the septal RV; CS and AIV showed late activation</td>
<td>Intramural circuit likely, epicardial mapping showed earliest site of activation underneath LAD</td>
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<tr>
<td>5</td>
<td>LB SA, LB IA</td>
<td>RVOT, RV infundibulum LV: basal septum</td>
<td>RV infundibulum LV basal septum</td>
<td>Intramural basal septal circuit</td>
</tr>
<tr>
<td>6</td>
<td>Multiple LB SA, RB SA VTs</td>
<td>RV: inferoseptum (small) LV: inferoseptum (small)</td>
<td>Intramural inferoseptal RV/LV</td>
<td>Intramural inferoseptal circuits</td>
</tr>
<tr>
<td>7</td>
<td>LB SA, LB IA</td>
<td>RV: majority, except small area septum/mid inferior</td>
<td>LBSA: Lateral aspect of inferoapical RV; LB IA: TV annulus/free wall</td>
<td>Not assessed to avoid hemodynamic stress</td>
</tr>
<tr>
<td>8</td>
<td>LB IA multiple LB SA</td>
<td>RV: basal septal Majority RV except small area in basal RV</td>
<td>Basal septal RV multiple VTs sharing a common exit in the apical septal RV</td>
<td>Acute success Extensive RV scarring with multiple circuits</td>
</tr>
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<td>9</td>
<td></td>
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<tr>
<td>10</td>
<td>RB IA, LB IA</td>
<td>LV: mid lateral; basal septal Basal free wall LV; basal septal LV</td>
<td>Acute success</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>RB SA, LB IA</td>
<td>LV: inferior wall from MA apically for 3-4 cm; basal LV septum (small); anterior wall (small) LV: inferior wall</td>
<td>Acute success</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>RB SA, LB SA</td>
<td>RV: septum, inferior, basal, anterior wall (large); epicardial same areas but larger Multiple circuits involving the inferior and anterior RV, endocardially and epicardially</td>
<td>Extensive scarring</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>LB SA, LB IA</td>
<td>RV: RVOT, RV septum, inferior, free walls LV: LVOT, anterior, basal inferior, septum Epicardial: lateral/superior MA overlying LAD diagonal branches Anteroseptal RVOT; LV septal, inferobasal; Epicardial: lateral, superior MA</td>
<td>Close proximity to LAD</td>
<td></td>
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<tr>
<td>14</td>
<td>LB IA, RB IA</td>
<td>RV: leftward aspect RVOT, inferior aspect TA extending to septum RVOT, inferobasal RV</td>
<td>Acute success</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>RB SA, RB IA</td>
<td>LV: small region basal septal superior and apical to His bundle LV basal septal</td>
<td>Acute success</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>LB IA, LB SA</td>
<td>RV: basal, lateral, inferior (large); septal, posterior, free wall RVOT RV: lateral TA, inferobasal RV, anteroseptal and posteroseptal RVOT, free wall RVOT</td>
<td>Acute success</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>LB(iso) SA, LB (iso) IA, LB IA, LB SA, RB SA</td>
<td>RV: basal (around TA), free wall, RVOT septal and free wall; Epi: RV free wall/septum, inferior/anterior/basal RV Inferior/inferoseptal RV, RVOT; basal inferior and lateral RV near TV; epi: basal inferior and anterior RV</td>
<td>Extensive scarring</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>LB IA, LB SA, RB IA</td>
<td>RV: entire RVOT (septal and free walls), anterior RV along base, TV, free wall, septum, Anterior RV near TV, RVOT (septal and free walls) LV: periaortie, inferoseptum/parahisian, inferior wall</td>
<td>Extensive scarring; parahisian scar</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>LB SA, RB SA, RB IA</td>
<td>RV: basal posteroseptal, basal inferoseptal; peritricuspid, inferolateral RV, posterior RVOT; Epi: crux of heart adjacent to endocardial posterobasal septum LV: basal septum, septum, inferoseptal, AMC, periaortic, perimital intramural circuits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>RB SA, LB IA</td>
<td>LV: basal septal under AV RV: basal septal Basal septal (intramural) Acute success</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>RB IA</td>
<td>RV: septal RVOT (small) LV: lateral wall; epi: LV summit underneath large ramus LV summit underneath LAD and large ramus Proximity to ramus</td>
<td></td>
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</tbody>
</table>

Abbreviations: AMC- aorto-mitral continuity, IA- inferior axis, iso- isoelectric, LAD- left anterior descending coronary artery, LB- left bundle, LV- left ventricular, MA- mitral annular, PDA_ posterior descending coronary artery, PLV- posterior left ventricular branch, RB- right bundle, RV- right ventricular, RVOT- right ventricular outflow tract, SA- superior axis, TA- tricuspid annulus, VT- ventricular tachycardia.
Supplemental Figure Legends

**Figure 1:** 56 year old man with cardiac sarcoid-related VT in whom 6 hemodynamically unstable RV-origin VTs were inducible (A). Pace mapping (B) was performed within regions of low voltage (red, <0.5 mV) in the RV endocardium and epicardium (C; epicardium labeled) identified putative isthmii of slow conduction with stimulus-to-QRS delays of 80-100 ms (B). Endo- and epicardial regions harbored long duration fractionated signals and late potentials (D, arrows) around regions of dense, electrically unexcitable scar (gray dots, C). Extensive substrate modification was performed (red dots). Purple areas represent normal bipolar voltage (>1.5 mV).

**Figure 2:** 65-year-old man with cardiac sarcoidosis, LVEF 30% and multiple episodes of VT and PVCs. Over 2 procedures, multiple VT morphologies were spontaneously present or inducible (A). Patchy endocardial scarring was evident in the RVOT, basal postero-septal RV (underneath TV), inferolateral RV and epicardial crux of heart adjacent to the endocardial basal postero-septal scar between the posterior descending and posterior left ventricular branch coronary arteries (B). Patchy endocardial scarring was present in the aortomitril continuity and the peri-aortic region (B). PVC/NSVT1 appeared to be exiting in a region of low voltage in epicardial surface of the crux of the heart (B, bottom left images, white arrow) with site of origin lying a distance of >4 mm from the posterior descending and the posterior let ventricular branch h (ablation catheter at site of successful ablation shown in the bottom right coronary angiography image); RF ablation rendered this PVC/NSVT non-inducible. VT 2 was ablated in the region of low voltage in the endocardial basal posteroseptal RV beneath the TV (B, top left image). VT 3 was ablated in a region of
low voltage in the RVOT. VT 4 and 5 were ablated small regions of low voltage in the aorto-mitral continuity and peri-aortic region respectively.

**Figure 3:**

57-year-old man with cardiac sarcoidosis, LVEF 39% and frequent, symptomatic PVCs. There was evidence of patchy scarring in the septal RVOT and lateral LV. Activation mapping showed late endocardial sites in the septal RVOT and lateral papillary muscle. Great cardiac vein activation was also late. Epicardial activation was the earliest, occurring 40 ms pre-QRS at the LV summit. This site lay right over the ramus branch, prohibiting ablation (C).

**Figure 4:**

49-year-old man with cardiac sarcoidosis who had 6 inducible VTs of RV and LV origin (A). The mechanism was re-entry around extensive endocardial scar in the RVOT (septal and free walls), anterior RV along base, tricuspid valve, free wall, septum, and parahisian region; in the LV, scar was present in the periaortic, aorto-mitral continuity and basal septal region. Epicardial mapping revealed extensive RV free wall scar (B). In the RVOT, sites with no recorded bipolar signal would capture and reveal pace maps of clinical VT (C, pace map resembles VT 4). Extensive substrate modification was performed (red dots). Red regions represent bipolar voltage <0.5 mV; purple regions represent normal bipolar voltage >1.5mV).
Supplemental Figures

Figure 1:
Figure 2:
Figure 3:

(A) I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

(B) I
II
III
V1
V2
ABLd
ABLp
ABLU1
ABLU2
ABLU1w
His d
His m
His p
RV a
RV d

(C) LAO
RAO

41 ms
Figure 4: