Primary Prevention of Sudden Cardiac Death in Silent Cardiac Sarcoidosis:

Role of Programmed Ventricular Stimulation

Running title: Mehta et al.; Sudden Death in Subclinical Cardiac Sarcoidosis

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Journal Subject Codes: [5] Arrhythmias, clinical electrophysiology, drugs; [106] Electrophysiology
Abstract:

Background - Cardiac involvement in sarcoidosis is often silent and may lead to sudden death. This study was designed to assess the value of programmed electrical stimulation of the ventricle (PES) for risk stratification in patients with sarcoidosis and evidence of preclinical cardiac involvement on imaging studies.

Methods and Results - Patients with biopsy proven systemic sarcoidosis but without cardiac symptoms who had evidence of cardiac sarcoidosis on positron emission tomography (PET) or cardiac magnetic resonance imaging (CMR) were included. All patients underwent baseline evaluation, echocardiographic assessment of left ventricular function, and programmed electrical stimulation of the ventricle. Patients were followed for survival and arrhythmic events. Seventy-six patients underwent PES of the ventricle. Eight (11%) were inducible for sustained ventricular arrhythmias and received an implantable defibrillator. None of the noninducible patients received a defibrillator. Left ventricular ejection fraction was lower in patients with inducible ventricular arrhythmia (36.4±4.2% vs 55.8±1.5%, p<0.05). Over a median follow-up of 5 years, 6 of 8 patients in the group with inducible ventricular arrhythmias had ventricular arrhythmia or died, compared with one death in the negative group (P<0.0001).

Conclusions - In patients with biopsy-proven sarcoidosis and evidence of cardiac involvement on PET or CMR alone, positive PES may help to identify patients at risk for ventricular arrhythmia. More importantly, patients in this cohort with a negative PES appear to have a benign course within the first several years following diagnosis. PES may help to guide the use of implantable cardioverter defibrillators in this population.

Key words: Sudden Death, Cardiomyopathy, Arrhythmia, Magnetic Resonance Imaging, Electrophysiology
Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. In autopsy studies cardiac involvement has been reported in 40-50% of patients [1-2]. Cardiac manifestations are silent in the majority of patients; however, heart block, ventricular arrhythmias and congestive heart failure may be manifest in 2-5% [3-4]. Sudden death is the second most common cause of mortality in patients with sarcoidosis in the United States.

Endomyocardial biopsy can provide a confirmative diagnosis of cardiac sarcoidosis (CS) but is associated with low sensitivity. Imaging modalities such as positron emission tomography with fluoro-deoxyglucose uptake (PET) and cardiac magnetic resonance imaging (CMR), which may reveal early granulomatous disease, are being increasingly used for diagnosis of preclinical cardiac involvement. The specificity of PET and CMR imaging for diagnosis of cardiac sarcoidosis is better than clinical criteria alone, although their role in long-term prognosis is still not clear [5-6]. Implantable cardioverter defibrillator (ICD) therapy has been shown to be effective in prevention of sudden death in patients presenting with ventricular arrhythmias [7-8]. However, the role of ICDs for primary prevention of sudden death in cardiac sarcoid is not known.

We evaluated the risk of malignant ventricular arrhythmias and survival of patients with systemic sarcoidosis but without clinical manifestations of cardiac involvement. All patients demonstrated evidence of cardiac involvement on PET or CMR and underwent electrophysiologic testing with programmed electrical stimulation of the ventricle (PES) for risk stratification. We hypothesized that PES would predict the future risk of malignant ventricular
arrhythmias and sudden death in patients who had evidence of cardiac sarcoid based on imaging studies, but who did not have arrhythmic symptoms.

Methods

Patient Population

Seventy-six patients were included in this analysis. The institutional review board of the medical center approved the study. Consecutive patients with an established diagnosis of cardiac sarcoidosis referred to the EP service for risk stratification between June 1998 and June 2008 who consented to have PES were included. Patients with history of prior ICD implantation or ventricular arrhythmia were excluded. All patients had extracardiac tissue biopsy proven systemic sarcoidosis and evidence of cardiac sarcoidosis as defined by typical imaging findings on either a cardiac CMR [9] or PET. CMR findings diagnostic of CS included localized intramyocardial increased signal intensity on T2 weighted sequence indicative of edema and delayed contrast enhancement suggestive of infiltration and scarring. PET was considered positive when perfusion images showed no evidence of ischemia and fluoro-deoxyglucose uptake images showed either increased or mismatched metabolic activity suggestive of infiltration, or matched decrease in metabolic activity indicative of scarring [5](Figure 1).
Study Protocol

Electrophysiology studies were performed using a standard stimulation protocol. None of the patients were on antiarrhythmic medications at the time of PES. Therapy with beta blockers and calcium channel blockers was not discontinued. Ventricular stimulation was performed using up to 3 premature beats at 2 drive cycle lengths at both right ventricular apical and outflow tract pacing sites. Premature beats were delivered until refractoriness or to a minimum coupling interval of 200 msec. If no sustained ventricular arrhythmias were induced, burst ventricular pacing was performed from cycle lengths of 300-220 ms. If baseline stimulation failed to induce any arrhythmia, programmed stimulation was repeated during infusion with isoproterenol. The rate of infusion was titrated to increase sinus rate by 20%. Patients with inducible sustained ventricular arrhythmia during standard ventricular stimulation protocols were placed in the positive PES group. Sustained ventricular arrhythmias were defined by >30 seconds of sustained monomorphic ventricular tachycardia (Figure 1), tachycardia requiring termination prior to 30 sec due to hemodynamic instability, sustained polymorphic ventricular tachycardia. Ventricular fibrillation with triple premature beats of less than 220 ms was considered a non-specific response and thus grouped in the non-inducible category.

Demographic information and medication history were obtained by review of electronic medical records. An electrocardiogram (EKG) recorded at the time of PES was interpreted. The 12-lead EKG was defined as abnormal if any of the following were present: QRS duration > 120ms; atrial fibrillation or flutter; > 50% atrial or ventricular pacing; evidence of right ventricular hypertrophy in the absence of pulmonary arterial hypertension. The presence of prednisone,
methylprednisolone, and/or hydrocortisone on the patient’s medication list after the date of the PES was considered positive corticosteroid usage, regardless of dosage or duration. Mortality was ascertained by review of medical records and the Social Security Death Index. Event free survival was calculated as the length of time from PES date to the date of first documented ventricular arrhythmia, death, or the end of the follow-up period, whichever came first. Follow-up period ended in July 2010. For each patient, all left ventricular ejection fraction (LVEF) measurements with a numerical value recorded on the institutional cardiovascular database were ascertained and dated from time of PES. In most cases, an LVEF was taken on the same date as the PES. The majority of additional LVEF measurements were available through echocardiography, PET, and CMR. When available, secondary LVEF measurements closest to 1 year after PES (up to 15 months), and closest to 2 years after PES (up to 27 months), were recorded. Non-numerical measurements of LVEF were excluded.

[Note: Although the study by Aizer and Mehta et al [10] was completed at this institution, the patients in the present study are unique and reflect a more homogenous cohort, all of whom had evidence of cardiac sarcoid based on imaging studies, but without symptoms of arrhythmias. None of the patients from that data set were included in the present study.]

**STATISTICAL ANALYSIS**

Differences in distribution of baseline characteristics including age, gender, race, and corticosteroid use between patients in the positive PES group and negative PES group were evaluated using the chi-square or Wilcoxon test, as appropriate. Sensitivities and specificities
were calculated according to standard methods [11]. The Kaplan-Meier method was used to estimate event-free survival among patients in each group. The LVEF at 0, 1, and 2 years of the PES study across the two study groups were compared using the Wilcoxon test.

Results

Baseline clinical characteristics are listed in Table 1. A majority of the patients in the study were female and African-American. Two thirds of the patients had received corticosteroids. There was no statistically significant difference in age, gender, race, corticosteroid use, or length of follow-up between the positive and negative PES groups (p>0.2 in all cases).

Eight of the 76 patients (10.5%) were inducible for sustained ventricular arrhythmia during PES and placed in the positive PES group. All 8 patients subsequently received ICD implantation. The remaining 68 patients were placed in the negative PES group and none received ICD implantation during the follow-up period. None of the patients in the EP negative group had evidence of significant AV conduction disease (HV>70 ms). Atrio-ventricular conduction times were not significantly different in the two groups (AH interval: 95±14.6 vs 85.5±28.3, HV: 58.2±11.1 vs 49.9±13.4 in PES positive and negative groups respectively). None of the patients in PES negative group had findings to warrant a pacemaker implantation. One patient in the EP positive group had evidence of prolonged HV of 85 ms, and was implanted with a dual chamber defibrillator.
Compared to the negative PES group, mean LVEF was found to be significantly lower in the positive PES group at the time of the PES, a difference also seen 1 and 2 years after the procedure (p<0.05)(Table 2). Compared with measurements at time of PES, there was no significant reduction in LVEF in the negative PES group after 1 and 2 years. Using left ventricular ejection fraction of 40% as a cut off, 18 (26.5%) of 68 patients in the PES negative group had reduced ejection fraction as compared with 5 (62.5%) of the 8 in the PES positive group (Table 1).

**EVENT RATE**

The event rate was 75% in PES positive group (2 patients died and 4 had appropriate ICD shocks for ventricular tachycardia) and 1.5% in the PES negative group (<0.0001). Six of the 8 patients in the positive PES group were alive at the end of the follow-up period with a median follow-up time of 5.6 years (range 4.5-8.1 years). Four of the 6 had received appropriate ICD therapy for ventricular tachycardia; one patient who had appropriate shocks has also received inappropriate ICD shocks for atrial tachyarrhythmias. The 2 deaths occurred in patients with inducible sustained ventricular tachycardia. One occurred 2 months after ICD implantation; the cause of death could not be determined. The second died 18 months after ICD implantation from ventricular arrhythmia storm that failed to respond antiarrhythmic therapy. Four of the six patients in the PES positive group who had arrhythmic events (ICD shocks or death) had LVEF of less than 40% at the time of PES. There was one death in the PES negative group from respiratory failure five and half years after PES. The other 67 patients in the negative PES group were alive at the end of the follow-up period with a median (range) follow-up time of 5 years.
(range 4.5-6.3); none had symptomatic ventricular arrhythmia or required ICD at the conclusion of the study period. Event free survival in the 2 groups is shown in Figure 2. Kaplan-Meier survival estimation showed that survival was significantly higher in the negative PES group (p<0.0001).

Discussion

Sudden cardiac death or tachyarrhythmia may be the initial clinical presentation of cardiac sarcoidosis. The true incidence of sudden death in cardiac sarcoidosis is unknown, but may be up to 35% [1]. Autopsy studies in the United States suggest that up to 50% of patients with systemic sarcoidosis may have cardiac involvement, although the incidence of documented arrhythmia or conduction disturbance in this group is much lower [1-2]. Because sudden cardiac death is a common cause of mortality in this population, it is likely that subclinical cardiac involvement and myocardial inflammation and scarring precedes the development of lethal arrhythmias. While heart failure is a more common cause of death than arrhythmia in patients with advanced cardiac involvement [12], patients with even small areas of myocardial scarring are at an heightened risk for reentrant ventricular arrhythmia.

Identification of patients with sarcoidosis who are at risk for sudden death has been difficult due to the low sensitivity of diagnostic testing. Endomyocardial biopsy often misses focal areas of myocardial involvement. Traditional noninvasive measures such as electrocardiography and echocardiography lack specificity and have not been validated in clinical studies. Advanced cardiac imaging has been used more recently to detect myocardial involvement in sarcoidosis. Positron emission tomography has good positive concordance in
cases of established cardiac sarcoidosis and better sensitivity than other scintigraphic techniques [5, 13]. More recently, Patel et al. showed that CMR was more than twice as sensitive as the standard JMHW clinical criteria in diagnosing cardiac involvement in 81 patients with extracardiac sarcoidosis [6]. In their study, patients with evidence of myocardial damage on CMR had an 11.5-fold higher risk of cardiac death than patients with no evidence of damage.

Electrophysiologic testing including programmed ventricular stimulation has been shown to be useful in risk stratification of patients with coronary artery disease and other forms of cardiomyopathy [8, 14-16]. PES has been reported to have some benefit in risk stratification of patients with cardiac sarcoidosis [10,17]. In a prospective study of 32 patients with sarcoidosis completed at this institution, 15 of whom received an ICD, Aizer et al demonstrated that induction of ventricular tachycardia during PES was associated with subsequent arrhythmic event, with a relative hazard of 4.5 in their cohort overall, and a higher hazard rate of 7.0 in patients without prior arrhythmia [10]. Nine of 12 patients with inducible sustained ventricular tachycardia received appropriate ICD therapy over an average follow-up of 84 months. Of note, the mean ejection fraction in their study was below 35%, indicating that many of the patients might have qualified for primary prevention ICDs under present guidelines [7].

With advanced imaging techniques, patients with established systemic sarcoidosis will be increasingly screened for asymptomatic cardiac involvement. The greater sensitivity of PET and CMR will lead to the diagnosis of cardiac sarcoidosis in an increasing number of patients. However, improved sensitivity is offset by a loss of specificity, as delayed hyperenhancement on CMR may be seen in a number of conditions, including ischemic heart disease, as noted by Patel et al [6]. Should all patients with systemic sarcoidosis and evidence of cardiac involvement on imaging studies receive an ICD? Patients with high-risk features including asymptomatic
ventricular arrhythmia or significantly reduced left ventricular function otherwise qualifying for a primary prevention ICD are likely to benefit. However, the diagnosis of cardiac sarcoidosis by imaging studies alone may overestimate the at-risk group, or be confounded by secondary cardiac diagnoses including coronary artery disease.

Based on present clinical indications a significant proportion of patients with CS and left ventricular ejection fraction of less than 35% would qualify for ICD implantation. There are no data to guide management of patients with minimal or mild left ventricular dysfunction who lack evidence of ventricular arrhythmia or conduction system disease. We demonstrate the additional benefit of electrophysiologic testing in systemic sarcoidosis patients with evidence of CS by PET or CMR. Findings of the present study are applicable to a significant and largely undiagnosed proportion of patients with previously unrecognized cardiac sarcoidosis. Absence of inducible ventricular arrhythmias in these patients was associated with good long-term prognosis. It may be that these patients have microgranulomas, but that fibrosis or scarring in the myocardium is insufficient to lead to reentrant ventricular arrhythmias. While reduced LVEF was associated with a positive PES on our study, the degree of reduction at initial PES was mild to moderate in the positive group. Those patients with a reduced ejection fraction and a negative PES, who accounted for 37% of patients, were not at higher risk of events over the follow-up period.

The patients in our study appear to be representative of the population of sarcoidosis patients with preclinical cardiac involvement. Similar to the population in the study by Patel et al examining CMR for diagnosis of cardiac sarcoidosis, mean ejection fraction was mildly diminished (mean EF=53.8%); in our study, it was lower in the group with positive PES (mean EF=36.4%)[6]. Over their mean follow-up of 21 months, Patel et al reported that 19% of CMR positive patients suffered cardiac death. Six of the 76 patients (8%) in the present study with
evidence of cardiac sarcoidosis on imaging had events over a mean follow-up of 3.1 years, all of whom had a positive EP. The relatively smaller event rate in the present study as compared to that reported by Patel et al (8 vs 19%) could be related to a larger number of patients with preserved left ventricular function. A larger prospective multi-center trial is needed to confirm our findings.

The present study is limited by the relatively low event rate in this cohort, which is not unexpected given that the increased sensitivity of noninvasive imaging probably captures patients earlier in their disease course. In addition, it is difficult to predict asymptomatic ventricular arrhythmias in patients in the negative PES group, as these patients did not undergo any monitoring. A necessary but limiting assumption of our analysis is that malignant ventricular arrhythmias in this group would lead to sudden death or, if survived, medical attention and implantation of a defibrillator. Furthermore, disease activity in sarcoidosis fluctuates, so that PES at a given point in time may not accurately predict long-term risk of ventricular arrhythmias and sudden cardiac death. Patients without events initially may later acquire an increased risk for arrhythmia over a longer follow-up period. Nonetheless, early recognition of inflammatory activity might prompt therapy with corticosteroids and could prevent long term and potentially proarrhythmic scarring. Finally, although PES carries only minimal risk, a non-invasive means of predicting risk would be preferable.

**Conclusions:**

In patients with biopsy-proven sarcoidosis and evidence of cardiac involvement on imaging studies who have no clinical manifestations of CS, a positive PES may help to identify
those at risk for ventricular arrhythmia who thus would benefit from a primary prevention ICD. More importantly, patients in this cohort with a negative PES appear to have a benign course within the first several years following diagnosis. Larger prospective studies are needed to determine how ICD therapy should be optimally prescribed in this population.

**Conflict of Interest Disclosures:** None

**References:**


Table 1. Clinical variables and duration of follow-up in patients with and without positive programmed electrical stimulation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Positive PES* (n=8)</th>
<th>Negative PES* (n=68)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age +/- SD (yrs)</td>
<td>48.7 +/- 5.7</td>
<td>49.3 +/-13.3</td>
<td>0.8994</td>
</tr>
<tr>
<td>Male</td>
<td>5 (62.5%)</td>
<td>28 (41.2%)</td>
<td>0.2497</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.6177</td>
</tr>
<tr>
<td>African-American</td>
<td>4 (50.0%)</td>
<td>34 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>2 (25.0%)</td>
<td>25 (36.8%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (25.0%)</td>
<td>9 (13.2%)</td>
<td></td>
</tr>
<tr>
<td>Corticosteroid use (%)</td>
<td>71.4</td>
<td>61.0</td>
<td>0.5913</td>
</tr>
<tr>
<td>Median length of follow-up (yrs)</td>
<td>5.6</td>
<td>5.0</td>
<td>0.26</td>
</tr>
<tr>
<td>Patients with LVEF† &lt; 40% at time of PES* (%)</td>
<td>5 (62.5%)</td>
<td>18 (26.5%)</td>
<td>0.0359</td>
</tr>
</tbody>
</table>

*p: programmed electrical stimulation
†left ventricular ejection fraction

Table 2. Left ventricular ejection fraction at one year and two years after programmed stimulation.

<table>
<thead>
<tr>
<th>LVEF* +/- SE (%)</th>
<th>Positive PES† (n=61)</th>
<th>Negative PES† (n=38)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At time of PES†</td>
<td>36.4 +/- 4.2</td>
<td>55.8 +/- 1.5</td>
<td>0.0119</td>
</tr>
<tr>
<td>One year after PES†</td>
<td>39.5 +/- 6.4</td>
<td>59.0 +/- 1.3</td>
<td>0.0151</td>
</tr>
<tr>
<td>Two years after PES†</td>
<td>21.0 +/- 12</td>
<td>56.3 +/- 2.2</td>
<td>0.0356</td>
</tr>
</tbody>
</table>

*left ventricular ejection fraction
†programmed electrical stimulation
Figure Legend

**Figure 1:** A: PET (positron emission tomography) scan with baseline pictures (odd rows) and FDG (fluoro-deoxyglucose) uptake (even rows) showing areas of fibrosis (upper arrow) and areas of increased uptake in the lateral wall of the left ventricle. Areas of fibrosis do not change on FDR uptake, while areas with active disease have increased uptake (lower arrow). This patient had inducible ventricular tachycardia originating from the lateral wall (as apparent from morphology of the ventricular tachycardia on 12-lead EKG (B)) near the area of scarring on PET of the ventricle.

**Figure 2:** Kaplan-Meier Estimation of Event Free Survival. Vertical markers indicate the time when follow up was terminated in each patient. (PES = programmed electrical stimulation).
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