Primary Prevention of Sudden Cardiac Death in Silent Cardiac Sarcoidosis
Role of Programmed Ventricular Stimulation

Davendra Mehta, MD, PhD; Neil Mori, BE; Seth H. Goldbarg, MD; Steven Lubitz, MD; Juan P. Wisnivesky, MD, DrPH; Alvin Teirstein, MD

Background—Cardiac involvement in sarcoidosis is often silent and may lead to sudden death. This study was designed to assess the value of programmed electric 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 MRI (CMR) were included. All patients underwent baseline evaluation, echocardiographic assessment of left ventricular function, and programmed electric 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% versus 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 1 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. (Circ Arrhythm Electrophysiol. 2011;4:43-48.)

Key Words: sudden death ■ cardiomyopathy ■ arrhythmia ■ magnetic resonance imaging ■ electrophysiology

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. In autopsy studies, cardiac involvement has been reported in 40% to 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% to 5%.3,4 Sudden death is the second most common cause of mortality in patients with sarcoidosis in the United States.

Clinical Perspective on p 48

Endomyocardial biopsy can provide a confirmative diagnosis of cardiac sarcoidosis (CS) but is associated with low sensitivity. Imaging modalities such as positron emission tomography (PET) with fluorodeoxyglucose uptake and cardiac MRI (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 CS 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 the prevention of sudden death in patients presenting with ventricular arrhythmias.7,8 However, the role of ICDs for primary prevention of sudden death in CS 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 electrophysiological testing with programmed electric 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 CS 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 CS referred to the electrophysiology 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 CS as defined by typical imaging findings on either a CMR 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 fluorodeoxyglucose (FDG) uptake images showed either increased or mismatched metabolic activity suggestive of infiltration, or matched decrease in metabolic activity indicative of scarring (Figure 1).

**Study Protocol**

Electrophysiology studies were performed using a standard stimulation protocol. None of the patients were on antiarrhythmic medica-

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**Figure 1.** A, PET scan with baseline pictures (odd rows) and FDG 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 FDG uptake, whereas areas with active disease have increased uptake (lower arrow). B, This patient had inducible ventricular tachycardia originating from the lateral wall (as apparent from morphology of the ventricular tachycardia on 12-lead ECG) near the area of scarring on PET of the ventricle. PET indicates positron emission tomography; FDG, fluorodeoxyglucose.
patients with inducible sustained ventricular arrhythmia during standard ventricular stimulation protocols were placed in the positive PES group. Sustained ventricular arrhythmias were defined as ventricular fibrillation with triple premature beats or 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 time 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 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. Nonnumeric measurements of LVEF were excluded.

It is noteworthy that, although the study by Aizer and Mehta et al10 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 CS based on imaging studies, but without symptoms of}

<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, y</td>
<td>48.7 ± 5.7</td>
<td>49.3 ± 13.3</td>
<td>0.8994</td>
</tr>
<tr>
<td>Male, n (%)</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></td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>4 (50.0)</td>
<td>34 (50.0)</td>
<td></td>
</tr>
<tr>
<td>White, n (%)</td>
<td>2 (25.0)</td>
<td>25 (36.8)</td>
<td></td>
</tr>
<tr>
<td>Other, n (%)</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, y</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, n (%)</td>
<td>5 (62.5)</td>
<td>18 (26.5)</td>
<td>0.0359</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; PES, programmed electrical stimulation.

The event rate was 75% in PES positive group (2 patients died and 4 had appropriate ICD shocks for ventricular

Table 2. Left Ventricular Ejection Fraction at 1 Year and 2 Years after Programmed Stimulation

<table>
<thead>
<tr>
<th>LVEF±SE (%)</th>
<th>Positive PES</th>
<th>Negative PES</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At time of PES (n = 61)</td>
<td>36.4±4.2</td>
<td>55.8±1.5</td>
<td>0.0119</td>
</tr>
<tr>
<td>1 year after PES (n = 38)</td>
<td>39.5±6.4</td>
<td>59.0±1.3</td>
<td>0.0151</td>
</tr>
<tr>
<td>2 years after PES (n = 23)</td>
<td>21.0±12</td>
<td>56.3±2.2</td>
<td>0.0356</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; PES, programmed electrical stimulation.

Statistical Analysis

Differences in distribution of baseline characteristics including age, sex, race, and corticosteroid use between patients in the positive PES group and negative PES group were evaluated using the χ² 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 2 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 black. Two thirds of the patients had received corticosteroids. There was no statistically significant difference in age, sex, 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). Atrioventricular conduction times were not significantly different in the 2 groups (AH interval: 95±14.6 versus 85.5±28.3, HV: 58.2±11.1 versus 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 with 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 PES negative group after 1 and 2 years. Using LVEF of 40% as a cutoff, 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

It is noteworthy that, although the study by Aizer and Mehta et al10 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 CS based on imaging studies, but without symptoms of
advanced cardiac involvement,12 patients with even small
more common cause of death than arrhythmia in patients with
development of lethal arrhythmias. Although heart failure is a
and myocardial inflammation and scarring precedes the
Sudden cardiac death or tachyarrhythmia may be the initial
clinical presentation of CS. The true incidence of sudden
death in CS is unknown, but may be up to 35%.1

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 to 8.1 years). Four of the 6 had
received appropriate ICD therapy for ventricular tachycardia;
one patient who had appropriate shocks also has received
inappropriate ICD shocks for atrial tachyarrhythmias. The 2
defects occurred in patients with inducible sustained ventricu-
lar tachycardia. One occurred 2 months after ICD implanta-
tion; the cause of death could not be determined. The
second died 18 months after ICD implantation from a
ventricular arrhythmia storm that failed to respond antiar-
rrhythmic therapy. Four of the 6 patients in the PES positive
who had arrhythmic events (ICD shocks or death) had
LVEF of <40% at the time of PES. There was one death in
the PES negative group from respiratory failure 5 1/2 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 to 6.3 years);
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 PES negative group (P<0.0001).

Discussion
Sudden cardiac death or tachyarrhythmia may be the initial
clinical presentation of CS. The true incidence of sudden
death in CS 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 conduc-
tion 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. Although 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 a heightened risk for
reentrant ventricular arrhythmia.

Identification of patients with sarcoidosis who are at risk
for sudden death has been difficult because of the low
sensitivity of diagnostic testing. Endomyocardial biopsy often
misses focal areas of myocardial involvement. Traditional
noninvasive measures such as electrocardiography and echo-
cardiography lack specificity and have not been validated in
clinical studies. Advanced cardiac imaging has been used
more recently to detect myocardial involvement in sarcoid-
osis. PET has good positive concordance in cases of estab-
lished CS 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 Japanese
Ministry of Health and Welfare clinical criteria in diagnosing
cardiac involvement in 81 patients with extracardiac sarcoid-

Figure 2. Kaplan–Meier estimation of event free survival. Vertical
markers indicate the time when follow-up was terminated in
each patient. PES indicates programmed electric stimulation.

PET and CMR will lead to the diagnosis of CS in an
increasing number of patients. However, improved sensitivity
is offset by a loss of specificity, as delayed hyperenhance-
ment 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 ven-
tricular arrhythmia or significantly reduced left ventricular
function otherwise qualifying for a primary prevention ICD
are likely to benefit. However, the diagnosis of CS 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 propor-
tion of patients with CS and LVEF of <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
electrophysiological 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 CS. 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. Although 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 CS, 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%). Over their mean follow-up of 21 months, Patel et al reported that 19% of CMR positive patients had cardiac death. Six of the 76 patients (8%) in the present study with evidence of CS on imaging had events over a mean follow-up of 5 years, and all had a positive EP. The relatively smaller event rate in the present study compared with that reported by Patel et al (8% versus 19%) could be related to a larger number of patients with preserved left ventricular function. A larger prospective multicenter trial is needed to confirm the present study’s 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 because 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 noninvasive 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 after diagnosis. Larger prospective studies are needed to determine how ICD therapy could be optimally prescribed in this population.

Note Added in Proof

This article is dedicated to Dr Alvin S. Teirstein, who passed away on January 31, 2011. Dr Teirstein was Professor of Medicine at Mount Sinai Medical Center in New York. He was a pioneer and authority in sarcoid research, and we are grateful to him for his guidance to our work on cardiac sarcoidosis.

Disclosures

None.

References


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**CLINICAL PERSPECTIVE**

Cardiac involvement in sarcoidosis is uncommon but can cause ventricular tachycardia (VT) and sudden cardiac death. PET scanning and cardiac magnetic resonance imaging can detect myocardial involvement before cardiac symptoms, but the means to predict arrhythmia risk are not well defined. This study examined the use of programmed electrical stimulation in patients with evidence of cardiac sarcoidosis on imaging, but without prior cardiac symptoms. Of 76 patients who underwent programmed electrical stimulation, 8 had inducible VT and received an implantable defibrillator. Left ventricular ejection fraction was lower in the inducible group. Over a median follow-up of 5 years, 6 of the 8 with inducible VT died or had spontaneous VT requiring defibrillator therapy. One of the 68 patients without inducible VT died. Our study suggests that programmed ventricular stimulation may assist in assessing arrhythmia risk in this population.
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