Published in final edited form as:

J Cardiovasc Electrophysiol. 2019 October ; 30(10): 1949–1951. doi:10.1111/jce.14055.

Risk stratification in cardiac sarcoidosis: The tricky business of predicting the future

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“Prediction is very difficult, especially if it’s about the future.”

-Nils Bohr, Nobel laureate in Physics

In an ideal world, primary prevention defibrillators would be placed only in patients who will suffer from life-threatening ventricular arrhythmias in the future. Since electrophysiologists cannot predict the future, we must settle for risk stratification—identifying patients who are at high enough risk of a life-threatening ventricular arrhythmia that the risk of complication from a device and the inconvenience of having one are outweighed by the potential that it will be needed. Features that identify the highest risk in cardiac sarcoidosis (CS) patients include significantly reduced left ventricular (LV) or right ventricular (RV) function, delayed gadolinium enhancement on cardiac magnetic resonance (CMR), and perfusion defect on fluorodeoxyglucose–positron emission tomography (FDG-PET) scan.^{1,2} Recent data from Finland also support implantable cardioverter-defibrillator (ICD) implantation in CS patients with high degree AV block regardless of LV ejection fraction (LVEF). Sarcoidosis patients presenting with AV block and preserved LV function had a 24% 5-year risk of ventricular arrhythmia or sudden cardiac death (SCD).³

In the current study, Zipse et al⁴ seek to use electrophysiology study (EPS) to risk-stratify 120 patients with biopsy-proven extracardiac sarcoidosis and preserved LV and RV function. All patients had either probable CS (abnormal CMR or FDG-PET) or possible CS (normal advanced imaging but abnormal electrocardiogram (ECG), signal-averaged ECG, Holter monitor, or clinical symptoms). Programmed ventricular stimulation was performed at two RV sites at two drive train cycle lengths with double and triple extrastimuli with and without isoproterenol. Ninety-one patients also underwent RV voltage mapping. Seven patients (5.8%) had a positive EPS and underwent ICD placement, six with probable CS, and one with possible CS. Three patients (43%) with positive EPS subsequently had ICD therapies for ventricular arrhythmias. Outcome of freedom from ventricular arrhythmias and SCD was statistically worse in patients with positive EPS compared with negative EPS ($P = .009$), driven entirely by patients with probable CS.

The authors define “possible CS” as biopsy-proven extracardiac sarcoidosis and one or more of the following: report of palpitations, syncope or presyncope, abnormal 12 lead ECG,

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Disclosures: None.

abnormal echocardiogram, abnormal signal-averaged ECG (SAECG), or abnormal outpatient telemetry. These patients had normal advanced cardiac imaging, but there remained a concern for early or undetected CS based on history, exam, or other studies. On the basis of the 2014 HRS Consensus Statement, patients with symptoms (palpitations, presyncope, or syncope), abnormal ECG, or abnormal echocardiogram should be screened with advanced cardiac imaging (CMR and/ or FDG-PET.) If advanced imaging is negative, these patients do not meet criteria for probable CS. The HRS Consensus Statement does not define possible CS. In the current study, in patients with possible CS, the event rate for positive EPS was 0/1 (0%) and for negative EPS was 1/50 (2%). It is not possible to draw conclusions based on the single positive EPS. Patients characterized as “possible CS” may have had early or mild cardiac involvement or may not have had cardiac involvement at all. Patients with “possible CS” may even have had another cardiac pathology such as nonischemic cardiomyopathy or arrhythmogenic RV cardiomyopathy to explain their symptoms and abnormal diagnostic studies.

1 | PRIOR STUDIES OF PROGRAMMED VENTRICULAR STIMULATION

Aizer et al⁵ performed programmed ventricular stimulation in 32 patients with CS and followed patients for a mean of 32 ± 30 months. Twelve patients who had spontaneous or inducible sustained ventricular arrhythmias received ICDs. Five of six patients (83%) with spontaneous sustained ventricular arrhythmias and four of six patients (67%) with inducible sustained ventricular arrhythmias received appropriate ICD therapies. Two of 20 patients (10%) with neither spontaneous nor inducible sustained ventricular arrhythmias experienced sustained ventricular arrhythmias or sudden death. These results suggest that while positive EPS for sustained ventricular arrhythmias clearly identifies patients at high risk of spontaneous ventricular arrhythmias or SCD, a negative EPS may not confer long-term low risk. EPS may simply not be able to identify all high-risk patients, or due to disease progression, patients initially at low risk may develop an increased risk of arrhythmic events.

Mehta et al⁶ evaluated the role of programmed ventricular stimulation in 76 patients with biopsy-proven systemic sarcoidosis, without cardiac symptoms, but with evidence of CS on FDG-PET or CMR. Eight patients (11%) were inducible for sustained ventricular arrhythmias and received an ICD while none of the noninducible patients received an ICD. Over a median follow-up of 5 years, 6 of 8 patients with positive EPS had ventricular arrhythmia or died, four with ICD shocks or death, compared with one death from respiratory failure in the noninducible group ($P < .0001$). Unlike the patients evaluated by Zipse et al,⁴ the patients in this study did not all have preserved LV and RV function. Mean LVEF in patients inducible at EPS was $36.4\% \pm 4.2\%$ vs $55.8\% \pm 1.5\%$ in the noninducible group ($P < .05$). The patients in this study all had tissue diagnosis of sarcoidosis and advanced imaging confirming CS. While there can be false-positive results on imaging studies, the patients in the Mehta et al⁶ all met HRS diagnostic criteria supporting a diagnosis of CS.¹

2 | ARRHYTHMIA MECHANISM

Of 435 patients with nonischemic cardiomyopathy referred for VT ablation, 21 patients (5%) had CS.⁷ Multiple inducible VTs were observed with scar-mediated re-entry in all VTs. Triggered activity and abnormal automaticity related to myocardial inflammation in myocarditis have also been described.^{8,9} In patients with advanced disease, scar-mediated re-entry is the most common mechanism for VT in CS, but inflammation-causing triggered activity and abnormal automaticity may be a more common mechanism in early or mild CS with preserved LV function and no delayed enhancement on CMR. A standard ventricular extrastimuli protocol may be more likely to induce reentrant VT in a scarred heart with advanced CS than other arrhythmias mechanisms in a heart with minimal or no scar.

3 | RV MAPPING

Surprisingly, only 4% of the patients with probable CS and 2% of the patients with possible CS had evidence of abnormal bipolar or unipolar RV voltage. Voltage-guided biopsy is advocated as a method to increase the diagnostic yield of endomyocardial biopsy compared with blind biopsy of septal myocardium.¹ For example, in 40 biopsy specimens taken from 11 patients undergoing evaluation of myocarditis and CS, 19 had electrogram voltage less than 5 mV, all of which resulted in histopathologic abnormality.¹⁰ Normal myocardium, signified by a normal signal with voltage greater than 5 mV, had no significant diagnostic yield. The low rates of abnormal bipolar and unipolar RV voltage in probable and possible CS patients with preserved RV and LV function suggest that voltage-guided biopsy is unlikely to be useful to make a definitive diagnosis of sarcoidosis in this cohort.

4 | CONCLUSIONS

Despite the limitations of a retrospective study performed at a single referral center, the data presented by Zipse et al⁴ add an important contribution to our current understanding of risk stratification in CS. The data confirm prior findings that positive EPS in CS identifies patients at high risk for ventricular arrhythmia and SCD, and show this to be true even in the setting of normal LV and RV function. A negative EPS suggests a low risk of arrhythmic events, however, because disease activity in CS can fluctuate and progress, a normal EPS at one point in time may not accurately predict future long-term risk. While we may not be able to predict the future, with advances in advanced cardiac imaging and enlightening studies like the current one, electrophysiologists and sarcoidosis patients can work together to make rational, data-based decisions regarding primary prevention ICD implantation, considering elements that increase the risk of ventricular arrhythmias in CS, including LV or RV dysfunction, LGE on MRI, perfusion defect on FDG-PET scan, high degree AV block, and, as highlighted here, inducible ventricular arrhythmias with programmed stimulation.

Acknowledgments

Dr. Kron is supported by the VCU Wright Center for Clinical and Translational Research.

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