***** SUPPLEMENTAL MATERIAL*****

Complementary Value of Cardiac MRI and PET/CT in the Assessment of Cardiac Sarcoidosis

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Supplemental Methods:

CMR Imaging Acquisition

All CMR images were acquired on a 3.0-T system (Tim Trio, Siemens, Erlangen, Germany), with electrocardiographic gating and breath holding. The CMR protocol consisted of cine steady-state free-precession imaging (TR, 3.4 ms; TE, 1.2 ms; in-plane spatial resolution, 1.6-2mm) for assessing left ventricular (LV) function. For the calculation of LV function, the endocardial and epicardial borders of the LV myocardium were manually traced on successive short-axis cine images at end-diastole and systole. All patients underwent late gadolinium enhancement (LGE) imaging using inversion recovery gradient recall echo (TR, 4.8 ms; TE, 1.3 ms; inversion time, 200 to 300 ms) to detect focal myocardial fibrosis. LGE imaging was performed 10 to 15 min after administration of 0.15-mmol/kg dose of gadolinium diethylenetriamine pentaacetic acid (Magnevist, Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ) or gadobenate dimeglumine (Multihance, Bracco Diagnostic, Princeton, NJ). LGE images were obtained in 8 to 14 matching short-axis (8 mm thick with no gap) and 3 long-axis planes.

Nuclear Imaging Acquisition

Rest myocardial perfusion images were obtained first following the intravenous administration of ^{82}Rubidium (~50 mCi) or ^{13}N-ammonia (~20 mCi) and PET/CT (Discovery RX or DSTE Light Speed 64, GE Healthcare, Milwaukee, WI), or ^{99m}Tc-sestamibi (~20 mCi) and SPECT/CT (Symbia T6, Siemens Healthcare, Hoffman Estates, Chicago, IL). After perfusion imaging, 10-12 mCi of ^{18}F-fluorodeoxyglucose (FDG) was injected intravenously. After a 90-minute uptake period, dedicated cardiac and whole body FDG PET/CT scans were performed. Whole body images were obtained from the base of the skull to mid-thigh.

All patients were instructed to follow a high fat, very low carbohydrate diet (at least 2 meals) followed by a fast of at least 4 hours prior to the test in order to shift normal myocardial metabolism to primary fatty acid utilization and, therefore, suppress the uptake of FDG by normal myocardium.[1] The rationale, methods, and success of this patient preparation protocol have been previously described in detail[1, 2].

Rest perfusion images were classified as normal or abnormal. Perfusion defects were analyzed for each of the 17 myocardial segments and categorized as: none, mild, moderate, or severe[3].

Cases of non-specific FDG uptake were considered probably normal when there was diffuse and homogenous FDG uptake of the entire myocardium[1, 4, 5] or the lateral wall[6]. In contrast, when heterogeneous uptake or focal on diffuse uptake was present, the pattern of FDG was categorized as abnormal.

Clinical follow-up and event adjudication.

Multiple VTs in one patient were counted as one event. If a patient had multiple VTs or VT followed by death, only the first event was used for the time to event analysis. Vital status and VT were ascertained by medical record review. Subjects without ICD did not have routine electrocardiographic monitoring as this is not done in our center as part of standard of care. Mailed patient questionnaires and scripted phone interviews were used when electronic medical record was insufficient. Time to event was measured from the date of the first imaging study performed. Event adjudications were performed by 2 cardiologists. In case of discrepancy a third physician was consulted.

Ventricular tachycardia was defined as 3 or more consecutive complexes in duration emanating from the ventricles at a rate >100 bpm, which lasts more than 30seconds or requires termination due to hemodynamic compromise in less than 30 seconds[7]

Statistical Analysis

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools housed at Brigham and Women's Hospital[8]. Annualized event rates are expressed as the number of patients having events (VT or death) as a proportion of the number of patients at risk divided by the number of patient-years follow-up..

<u>Supplemental Results:</u>

Baseline Characteristics

When considering the sequence of imaging testing used in clinical care, 84 patients had CMR first, 12 patients had PET first, and 11 had combined same day testing.

CMR Findings

Notably, the concordance between CMR and perfusion defects on PET was only modest. On a per patient level, there were 65 subjects who had concordant results, while 37 had positive LGE with no perfusion defect and 5 had perfusion defect with no LGE.

Pattern of LGE on CMR

There were 3 patients who had MRI findings consistent with ARVC, while 2 patients had an MRI pattern consistent with amyloidosis. An infarct like pattern was present in 7 subjects.

Supplemental Discussion:

While not the primary focus of our paper, we observed a high event rate across our population of patients with suspected CS. However, our high event rate was consistent with a recent meta analysis which showed that patients with LGE have an annual rate of 9.5% of death or ventricular arrhythmias[9]. Our event rate is also consistent with prior studies such as, Schuller et al[10] who reported appropriate ICD therapies in 36 (32%) of 112 patients with CS who underwent ICD implantation and were followed for a mean of 29 months or Betensky et al[11] who reported ICD therapies in 17 (38%) of 45 patients with CS followed over a median of 2 years. Our higher event rate could also be due to referral bias, as our center is a quaternary care center with frequent referrals of patients with advanced heart failure and arrhythmias, as reflected by our high proportion of individuals presenting severe LV dysfunction (23%), or VT (35%). Thus, as is often the case for patients referred for an evaluation of CS, even when patients did not have CS, they often had other alternative diagnosis that adversely impacted their prognosis. Because of the high event rate present in our study, and the fact that there were very few patients with

normal CMR or PET results, our study was underpowered to detect any different in outcomes across the various sub-groups examined.

Supplemental References:

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Supplemental Table 1. Absolute number of events and annual event rate per methodology and likelihood.

Modality and Likelihood	Ventricular Tachycardia	Death	Absolute Event Rate	Annual Event Rate
Cardiac MRI				
No sarcoidosis (<10%)	1	0	1 (7%)	2.3
Possible (<50%)	7	1	8 (23%)	12.8
Probable (50-90%)	8	3	11 (32%)	13.5
Highly Probable (>90%)	4	3	7 (30%)	12.6
FDG-PET				
No sarcoidosis (<10%)	3	0	3 (17%)	6.5
Possible (<50%)	8	1	9 (31%)	13.1
Probable (50-90%)	4	3	7 (19%)	10.0
Highly Probable (>90%)	5	3	8 (35%)	14.0
Combined Images				
No sarcoidosis (<10%)	2	0	2 (19%)	5.5
Possible (<50%)	7	0	7 (27%)	12.2
Probable (50-90%)	5	3	8 (19%)	10.0
Highly Probable (>90%)	6	4	10 (34%)	14.5

Supplemental Table 2. Annual Event Rate Stratified by the presence or absence of LGE on CMR and FDG by PET.

Cardiac PET	Cardiac MRI	
	LGE (+)	LGE (-)
FDG (+)	11.8	6.1
FDG (-)	13	4.5