Assessing severity of cardiac sarcoid: Is SUV the answer?

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The challenges involved in the diagnosis of cardiac sarcoidosis are significant; however once the diagnosis has been successfully made, the journey has only just begun. Assessing severity of cardiac sarcoidosis (CS) may be crucial in predicting the clinical course, thereby guiding initial therapy—both medical and device therapy—and is often subsequently helpful in evaluating response to such therapies.

If we could establish reliable and reproducible markers of disease severity which correlate with adverse outcomes, a validated severity index could be utilized at the time of diagnosis to help risk stratify patients, and guide therapy; either towards more aggressive immunosuppression or away from unnecessary intervention in low risk disease.

The current method of assessing severity is based mostly on expert opinion.¹ There are no practice guidelines to assist in risk stratification, and there are a number of mostly clinical parameters that are utilized.

WHAT DOESN'T WORK IN RISK STRATIFICATION?

Traditional Risk Factors

Usual cardiovascular risk calculators, such as the Framingham Risk Score and the ACC/AHA risk score,

have been found to be ineffective in predicting risk of cardiovascular events in the sarcoidosis population. In fact, both scores significantly underestimate the risk of major adverse cardiac events (MACE) by 2–5 fold, likely reflecting the additional risk conveyed by the acute or chronic inflammatory state (like that seen in rheumatoid arthritis).² Furthermore, neither age, the Japanese Ministry for Health & Welfare criteria nor the presence of extra-cardiac sarcoidosis were associated with increased adverse events in a CS cohort.³ Similarly, baseline ECG abnormalities are of limited benefit in either diagnosis or risk stratification.⁴ Traditional prognostic markers such as New York Heart Association (NYHA) functional class, left ventricular end-diastolic diameter (LVEDD), and the presence of sustained ventricular tachycardia were shown to be independent predictors of mortality in CS⁵; however, ideally the clinician would like to intervene prior to the development of heart failure, cardiomyopathy or the first instance of a potentially lethal arrhythmia.

Presence/Absence of Extra-Cardiac Sarcoidosis

It remains unclear whether a concurrent diagnosis of extra-cardiac sarcoidosis conveys mortality benefit, or is a poor prognostic sign. There have been a number of recent studies examining the increased morbidity and mortality reported in the group of CS patients found to have isolated cardiac sarcoidosis. However, there are multiple biases inherent in the analysis of this group. CS in the presence of extra-cardiac sarcoidosis is frequently diagnosed after asymptomatic screening, while those with isolated cardiac sarcoidosis have more often presented with a primary cardiac complaint.⁶

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Biomarkers

Serum ACE levels have been historically used; however, the poor sensitivity in the CS population (elevated in only 60% of patients) renders it a test of very limited utility. Furthermore, the degree of elevation has not been found to correlate with disease severity in any sarcoidosis population.⁷

Elevated serum soluble IL-2 receptor and serum lysozyme have also been identified as being of use in the diagnosis of sarcoidosis; however, there is no correlation between serum levels and disease severity.

Significant lymphopenia involving CD4-, CD8-, and CD19-positive cells is common in sarcoidosis patients and has been shown to correlate with disease severity. However, this has not been studied in the CS population.⁸

Micro-RNA, in particular miR-126 and miR-223 may have potential use in the future for diagnosis and prognostication in sarcoidosis. A correlation between the degree of abnormality in a 17-gene signature in the Jak-STAT signaling pathway and the severity of sarcoidosis has been recently reported.⁹ The gene was also found to differentiate between sarcoidosis patients and healthy controls. Another genetic polymorphism, FCGR2A and FCGR2C, has been identified as a potential tool in predicting clinical course of sarcoidosis.¹⁰

Histopathology

Endomyocardial biopsy showing non-necrotising granulomas is the gold standard of diagnosis of CS. However, due to the focal myocardial involvement, sensitivity is relatively low. Histological markers do not currently convey prognostic information beyond diagnosis in cardiac sarcoidosis.¹

Electrophysiology studies

Electrophysiology studies identifying inducible arrhythmias and 'at-risk' substrates are sometimes used to risk stratify patients with CS; however, their use has not been validated and routine use is not currently recommended.^{11,12}

CURRENT APPLICATION OF IMAGING TECHNIQUES IN ASSESSMENT OF SEVERITY

Echocardiography

Typical abnormalities found on transthoracic echocardiography include regional wall motion abnormalities not consistent with a vascular territory, particularly the basal septum. LV dilatation and systolic or diastolic dysfunction may be present, as can right

ventricular dysfunction. However, none of these parameters have been proven to correlate well with risk of future adverse events.

Echocardiography is insensitive in the detection of early stages of disease and a normal echocardiogram does not exclude the presence of significant cardiac involvement in a patient with systemic sarcoidosis.

There have been recent studies examining the application of strain imaging in early detection of regional wall motion abnormalities. A recent study in CS patients found an inverse relationship between global longitudinal strain (GLS) magnitude and the more sensitive measure of late gadolinium enhancement (LGE) burden on cardiac MRI (CMR), raising GLS as a possibly useful measure of disease severity.¹³

Cardiac Magnetic Resonance Imaging (CMR)

Typical findings are of sub-epicardial and mid-wall myocardial enhancement, particularly in the basal and lateral segments. There can also be subendocardial or transmural changes, and this may also be present in the right ventricular free wall. CMR can also aid in detection of regional wall motion abnormalities and areas of thinned myocardium. RV LGE (in addition to LV disease) has been found to carry higher risk, possibly due to involvement of a larger overall amount of myocardium or a more arrhythmogenic substrate.¹⁴ LGE in a non-ischaeamic distribution has been shown to be a better predictor of adverse outcomes than ejection fraction.

LGE has been found to correlate with significantly more ventricular arrhythmias in the CS population,¹⁵ as well as all adverse events.¹⁶ When added to positive cardiac fluorodeoxyglucose positron emission tomography (FDG-PET), the presence of LGE identifies the group at highest risk of MACE among the CS population.¹⁷

In current literature, LGE is largely used as a binary measure. Therefore, the utility of CMR as a quantitative measure of disease severity is limited.

Future studies examining the use of T1 and T2 mapping suggest a possible benefit in the identification of oedema or inflammation, compared with the fibrosis detected by LGE. The role of such mapping in assessing severity is still unknown.

SPECT Imaging

Gallium-67 scintigraphy, while still included in the HRS Consensus Statement for diagnosis of cardiac sarcoidosis, has been almost entirely replaced by PET scan in the modern era.¹⁸ ²⁰¹Tl-SPECT, ^{99m}Tc MIBI

SPECT, and ^{82}Rb PET, showing perfusion defects have also fallen in usage in favor of the improved sensitivity and better image quality of PET and CMR. The perfusion tracers are still often used together with FDG-PET to evaluate metabolism-perfusion mismatch.

FDG PET

PET has multiple advantages over other imaging modalities in the investigation of CS. PET is more sensitive in identifying areas of active inflammation and can therefore be used to monitor response to therapy. Many patients in the CS cohort have cardiac devices in situ, and therefore MRI can be contra-indicated. There is also no requirement for potentially nephrotoxic contrast.¹⁸ PET and MRI often provide complementary information, and when combined currently provide the most accurate risk stratification available.¹⁴

CURRENT EVIDENCE IN FDG PET

The article by Flores et al,¹⁹ published in today's issue, aims to add to the current body of evidence suggesting benefit in the use of FDG PET in risk stratification of patients with CS. Their study used a number of different quantitative and semi-quantitative measures of FDG uptake in the PET scans of 67 CS patients, and aims to relate the severity of FDG uptake with clinical outcomes. While a number of studies have examined the prognostic role of PET in CS, this trial is one of the first to firmly assess quantitative standardized uptake values (SUV) measures for both global and segmental location, in an effort to begin the journey towards formalized reference ranges for severity that could reliably risk stratify and therefore help guide therapy.

67 PET scans were analyzed and max SUV, mean SUV, localisation of FDG uptake by segment and LV ejection fraction (LVEF) were all recorded. There are yet no concrete subdivisions of severity by FDG in CS; therefore, each odds ratio was calculated per 1 point

increment in mean and max SUV, with average max SUV in diseased segments being 5.4. Both SUV max and mean were shown to have a statistically significant correlation with total cardiac events. Additionally, location of FDG uptake was analyzed. 91% of scans were found to have evidence of disease in basal segments, with an elevated mean SUV in the basal segments found to be independently significant in correlating with cardiac events.

An obvious criticism of Flores' study is the retrospective nature of the trial. Looking forward, further trials should aim to first validate and ultimately utilize PET severity criteria to help guide prospective therapy and assess outcomes. Additionally, clinicians were not blinded to PET result and therefore severity of inflammation on PET was likely considered when determining course of therapy, with possibly more intensive immunosuppression or prophylactic device insertion performed in those patients with a higher degree of inflammation.

While efforts were made to record evidence of arrhythmias such as ventricular tachycardia, complete heart block or atrial fibrillation, as well as new device placement, a thorough cataloguing of all device checks (either new or old) was not able to be performed, leaving any subclinical arrhythmia unrecorded. Considering the large proportion of patients with either implanted defibrillator or pacemaker devices in situ at the commencement of the trial (55% and 59% respectively) this is a significant omission. In addition, any events resulting in presentation to alternative centers were not recorded. These missing data culminated in an overall lower average event rate than other trials in comparable CS cohorts.

Despite the above criticisms, the authors should be praised for maintaining a cohort of 67 patients over a 3-year follow-up period in such a rare condition. This study was able to forge a path towards several statistically significant conclusions of great potential clinical relevance.

Other Papers Using FDG Quantification

Article	Patient group	PET parameter used	Median follow-up	Results
Blankstein et al ¹⁴	125 pts with suspected CS	- Binary FDG uptake - Binary focal perfusion defects	17 months	HR 2.7 ($p < 0.01$) of death or sustained VT in PET positive
McArdle et al ²⁰	20 pts with CS + AV block or CS + VT vs clinically silent CS controls	- Mean SUV - Max SUV	N/A	Mean and max SUV higher in VT group vs AV block ($P = .016$ and $P = .005$) and vs controls
Muser et al ²¹	20 pts with CS + VT over 92 serial scans	- Max SUV - Mean SUV - Lesion metabolic activity (LMA)	35 months	-Poor response (LMA decrease by $< 25\%$) associated with 20-fold increase in MACE ($P = 0.007$) -Inverse linear relationship between change in LMA and change in LVEF ($P = .003$)
Ahmadian et al ²²	17 pts with CS over 43 serial scans pre- and post-treatment	- Number of FDG-positive segments - Max SUV - Cardiac metabolic volume - Cardiac metabolic activity - Volume above SUV thresholds of 2.7 and 4.1 g/mL	9.6 months	-Reduction in CMA and CMV more frequently identified full response to treatment -Partial responders had higher max SUV post-treatment ($p < 0.001$) and higher volume above 2.7 g/mL threshold ($p < 0.001$)
Ahmadian et al ²³	38 pts with CS vs. negative controls	- Cardiac metabolic activity (CMA)	N/A	-CMA greater in visually positive studies vs visually negative and controls ($P = .02$) -CMA greater in LVEF $< 50\%$ ($P = .03$) and preceding a MACE ($P = .006$) -CMA reduced with steroids in 5 of 6 pts

continued

Article	Patient group	PET parameter used	Median follow-up	Results
Lee et al ²⁴	16 pts with CS over 54 serial scans pre and post-treatment	<ul style="list-style-type: none"> - Max SUV - Mean SUV - Cardiac metabolic volume (CMV) - Global metabolic volume 	8.7 months	<ul style="list-style-type: none"> -All 4 parameters significantly decreased in pts classified as stable/improved. -Significant only for max SUV ($P = .03$) and mean SUV ($P = .04$) -All pts who deteriorated had no change to PET scan
Osborne et al ²⁵	23 pts with CS over 92 serial scans	<ul style="list-style-type: none"> - Max SUV - Volume above SUV 2.7 g/mL and 4.1 g/mL 	2 years	<ul style="list-style-type: none"> -Inverse linear relationship between max SUV vs LVEF ($P = .008$), also between volume above 2.7 g/mL and 4.1 g/mL vs LVEF ($P = .028, = .022$)
Sperry et al ²⁶	203 pts with suspected CS	<ul style="list-style-type: none"> - Binary perfusion/metabolism - Summed score of resting perfusion defects in segments with FDG +ve 	1.8 years	<ul style="list-style-type: none"> -Higher summed score associated with increased MACE ($P = .029$)
Ishiyama et al ²⁷	16 pts with suspected CS pre and post-treatment	<ul style="list-style-type: none"> - Max SUV across all organs - Max SUV (cardiac) 	6 months	<ul style="list-style-type: none"> -Only lower max SUV in all organs associated with lower steroid dose at 6 months ($P = .04$)

WHERE TO FROM HERE?

More streamlined diagnostic pathways and severity scoring, both at time of diagnosis and for assessing response to therapy in cardiac sarcoidosis are needed. Multiple new technologies across the spectrum of imaging modalities are currently being trialed, as are multi-modal imaging platforms. The use of T1 and T2 mapping for early detection of inflammation on MRI, late enhancement on cardiac CT²⁸ and integrated PET/MRI scanners are techniques that have shown promise and are now being investigated in larger trials. A recent pilot study utilizing a sarcoid-specific radiotracer (68-

Ga-DOTA-NaI-octreotide) found it to be superior to standard FDG-PET in diagnosing CS.²⁹

As seen in the above literature review, different groups are utilizing various measures of FDG uptake, often with successful prediction of future clinical events, or response to therapy. Larger trials are needed, recording a number of different quantitative measures, to accurately establish which measures are of greatest utility in the staging of CS. Ideally, a combination of multi-modality imaging factors could be used to generate a severity score, which potentially will accurately predict MACE in CS, and hence offer the clinician a

valuable tool to guide therapy; SUV may prove to be this tool.

Disclosure

None of the authors have any disclosures.

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