Editorial

Establishing an Evidence-Based Method to Diagnose Cardiac Sarcoidosis

The Complementary Use of Cardiac Magnetic Resonance Imaging and FDG-PET

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The diagnosis of cardiac sarcoidosis (CS) can be extremely challenging. Although there are several clinical criteria that have been reported and are used in clinical practice,[1–3] these criteria are fraught with problems. For example, they are insensitive to downstream cardiac events in comparison to imaging findings seen on cardiac MRI (CMR) and cardiac ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scans. In addition, all of the published criteria require the a priori diagnosis of extracardiac sarcoidosis. Further, none of the clinical criteria was experimentally derived. Last, none of the 3 major diagnostic rubrics recapitulates the process of clinical reasoning, where each additional variable informs the interpretation of the others. For example, a single focus of delayed enhancement on CMR is far more meaningful in patients with sarcoidosis if there is also complete heart block and septal thinning.

See Article by Vita et al

Therefore, clinicians caring for patients with suspected CS (as well as the patients themselves) have urgently needed a more coherent conceptual framework for the diagnosis of CS that uses both modern cardiac imaging tools available in clinical practice as well as incorporation of their clinical context. In this regard, the study by Vita et al[4] reported in this issue of *Circulation: Cardiovascular Imaging* is an important step forward in our understanding of how to approach the diagnosis of CS.

In this study, the cardiac imaging group at Brigham and Women's Hospital retrospectively evaluated the combined use of CMR and FDG-PET imaging in patients being evaluated for CS. What is unique about this cohort of 107 patients is that all had both imaging studies within a median of 8 days, and this standardization of patient care for CS enabled subsequent conclusions to drawn about the utility of each of these tests in clinical practice. This is the largest reported series of potential patients with CS imaged in this manner and is unlikely to be repeated outside of a prospective clinical trial.

The analyses performed in this trial focused on blinded reinterpretation of both the CMR and FDG-PET scans (without access to clinical data) and the assignment of a likelihood of CS from the combined imaging findings as follows:

- No CS (<10%)—no evidence of CS or an alternative diagnosis established.
- Possible CS (10% to 50%)—when imaging findings are not specific for CS. CS could not be excluded but an alternative diagnosis was more likely.
- Probable CS (50% to 90%)—when imaging findings are suggestive by not definitive for CS.
- Highly Probable CS (>90%)—when imaging findings are highly specific for CS.

Using this framework, the combination of FDG-PET and CMR image data reclassified 48 (45%) of patients compared with single-modality imaging, including 11% of patients being newly classified as highly probable and 32 out of 48 patients being reclassified to a higher likelihood overall. This result is not unexpected, because accumulating additional data points, in general, will tend to lead to increased confidence about any conclusion. Nonetheless, it more closely approximates the actual process of clinical reasoning, where test results are considered in combination, not in isolation.

After imaging reinterpretation, all available clinical data were integrated by experts in the care of patients with CS to obtain a final likelihood of CS as the reference standard. This probabilistic framework that integrates expert interpretation of all imaging, testing, and clinical data to determine a specific patient's likelihood of CS deserves consideration as a potential new gold standard for the diagnosis of CS. A more complete description of the exact process, including participants, data available, and discussion format would be useful for other institutions that may wish to reproduce this strategy. A similar approach has been widely accepted for the diagnosis of interstitial lung diseases, where a multidisciplinary discussion is widely regarded as the gold standard for diagnosis of diseases such as idiopathic pulmonary fibrosis.[5,6]

Endomyocardial biopsy has been considered as a gold standard for CS to this point. However, in this report, 21 of the 38 patients that underwent endomyocardial biopsy were judged to have highly probable (>90% likelihood) CS, but only 3 had positive biopsies. This is consistent with other small series that have consistently shown endomyocardial biopsy to be an insensitive tool. Given the insensitivity of endomyocardial biopsy for diagnosing CS, a new gold standard needs to

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be developed and validated; the multidisciplinary discussion is likely to be the optimal pathway toward that goal.

Given the absence of a truly confirmatory test for CS, any final diagnosis is tenuous. Response to immunosuppressive therapy might be useful, but the natural history of untreated CS is unknown, and it remains unproven that immunosuppression is uniformly helpful in all cases. Thus, at present, the ultimate test of a diagnostic rubric is whether it improves clinician confidence (true in this case) or improves prognostic discriminative capability (unknown to date for any of the 3 major criteria). Validation of any diagnostic criteria, or any component of a diagnostic rubric, will necessitate demonstrating at a minimum improved clinician confidence, and optimally enhanced prognostic performance. Any individual clinical characteristic (eg, ventricular tachycardia) or test (eg, FDG-PET) should be demonstrated to provide incremental confidence or prognostic capacity to be included as a validated component of a multicomponent set. In this regard, the current article forms a circular argument: clinicians think of the utility of a test, and then define the outcome (confidence in diagnosis) partly on the basis of that test, thereby corroborating the usefulness of the test. Future efforts should investigate the incremental value of each test on the overall confidence of diagnosis.

Other important contributions of this report are its concise descriptions and examples of imaging patterns for both CMR and FDG-PET that correspond to the probabilistic likelihood assignments (Figure 2 of Vita et al[4]). The nuanced description of imaging patterns is this report are commendable. Simply reporting late gadolinium enhancement or FDG as binary variables on the report without a contextual, pattern-based interpretation of the likelihood of CS for the referring clinician is inadequate. Patients are receiving potentially toxic immunosuppression and implantable cardioverter defibrillators based on unnuanced FDG and CMR interpretations, respectively. The interpretive standards advocated by this report are consistent with recent imaging society guidelines[7,8] and are a wonderful clinical guide for interpretive readers.

It should be emphasized that this report does not end the story of how best to diagnose CS. One obvious area of future study is to show that the probabilistic diagnostic approach advocated by these authors can be prospectively validated and beneficial for risk stratification. In particular, although there was no significant change in event rate based on the various classifications, the study was underpowered to evaluate this clinical outcome. But, this framework writes an important chapter in how we as imagers and caregivers for patients with CS may design the prospective clinical trials urgently needed to evaluate therapeutic decision making and outcomes in CS. Last, these data should provide strong arguments to third-party payers that the combination of CMR and FDG-PET imaging may add significant incremental benefit for many patients. Too many payers limit use of so-called advanced cardiac imaging studies, even to the point of denying use of FDG-PET for any indication for CS. These studies are complementary and not redundant, and we need to advocate to payers that both studies are of benefit in many cases.

In conclusion, as our field works to establish an evidence-based method for the diagnosis of CS, we need to acknowledge the past work and clinical criteria that have gotten us to where we are. But we also need to be ready to embrace data-driven, experimental frameworks that incorporate imaging data and clinical reasoning, can clarify the field, and add benefit to our care of patients with CS.

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Disclosures

None.

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