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Editorial

Quantitative precision in cardiac sarcoidosis imaging: the emerging role of myocardial-to-background ratio in FDG-PET

Cardiac sarcoidosis (CS) remains a challenging condition to diagnose. Its unpredictable clinical manifestations, ranging from silent myocardial infiltration to life-threatening arrhythmias, underscore the need for diagnostic tools that are both sensitive and specific [1]. The introduction of 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) has transformed the CS diagnostic landscape by making the detection of active inflammation in sarcoid lesions possible [2]. Yet, for all its promise, FDG-PET has stumbled on a critical limitation: its reliance on subjective visual interpretation, which is itself impacted by inter-observer variability and physiological confounders [3]. To address this gap, Ueberham et al. propose the myocardial-to-background ratio (MBR) as an innovative quantitative metric which offers a standardized approach to enhance diagnostic precision in CS.

1. The role of FDG-PET in CS diagnostics

FDG-PET has become a cornerstone in the evaluation of CS by detecting increased glucose metabolism in activated macrophages in the foci of ongoing inflammation central to the disease pathophysiology. When combined with myocardial perfusion imaging, FDG-PET allows the distinction between active inflammation and fibrosis, thus enhancing diagnostic confidence and informing clinical management [4]. This is especially valuable in CS, where endomyocardial biopsy is limited by low sensitivity due to the patchy distribution of the disease. Moreover, PET findings, such as combined perfusion defects and focal FDG uptake, have been associated with adverse outcomes, reinforcing its prognostic value [5]. However, FDG uptake is not specific to sarcoidosis and may be seen in other inflammatory or ischemic conditions. Physiologic myocardial uptake can obscure pathological findings, necessitating strict dietary preparation protocols that remain variably standardized. Additionally, the absence of FDG uptake does not exclude prior or inactive CS [4]. The absence of a robust, reproducible metric has hindered the full integration of FDG-PET into clinical decision-making frameworks.

2. Study design and key findings

Ueberham et al. conducted a study of 11 patients with biopsy-proven CS and 15 controls without cardiac involvement at their center in Germany. Using FDG-PET, they measured MBR across the American Heart Association's 17-segment left ventricular model, extended to include the right ventricular free wall to account for CS's potential biventricular involvement. The MBR was calculated as the ratio of maximum standardized uptake value in myocardium (SUVmax) to average SUV in the blood pool (SUVmean). The inclusion of histologically-confirmed cases of CS distinguishes the authors' work from prior studies, many of which relied on clinical or imaging-based diagnoses.

Among controls, the median MBR was 1.1, reflecting minimal myocardial FDG uptake. All controls exhibited MBR values below 2.1, establishing a physiological threshold. Patients with CS had a median MBR of 2.4 at diagnosis, decreasing to 1.5 post-immunosuppressive therapy. The number of myocardial segments with MBR values exceeding 2.1 was 0 in controls, 14 at diagnosis in the CS group, and reduced to 1 after therapy. These trends not only validate the MBR's sensitivity to disease activity but also highlight its responsiveness to treatment, positioning it as a potential biomarker of therapeutic efficacy. A composite score, combining mean MBR and the number of affected segments, provided an additional measure of disease burden, with higher scores seen in patients with clinical deterioration.

The study's findings also align with known patterns of CS pathology. The basal anterior and basal anteroseptal segments emerged as predilection sites for pathological FDG uptake, corroborating prior CMR studies that have identified these regions as hotspots for sarcoid granulomatous infiltration [1]. This regional specificity enhances the clinical relevance of MBR as it aligns with the disease's anatomical footprint.

However, the study's small sample size limits statistical power and generalizability, despite reflecting the rarity of biopsy-confirmed CS. The control group's systemic inflammation may introduce confounders. The reliance on surrogate endpoints rather than hard outcomes, such as mortality, tempers its prognostic claims. Finally, the study did not explore the interplay between MBR and other quantitative PET metrics, which could have provided complementary insights into CS pathology.

Towards a new diagnostic paradigm

The intellectual elegance and robustness of the MBR lies in its physiological grounding. It enhances consistency by mitigating variability from patient physiology or imaging protocols. This standardization supports its integration into clinical practice, where reducing reliance on subjective interpretation is paramount. Similar to SUVmax but with increased reproducibility, serial MBR measurements could monitor disease progression or treatment response, guiding adjustments in immunosuppressive therapy [6]. The composite MBR score, reflecting both intensity and extent of inflammation, may inform risk stratification, potentially identifying candidates for implantable cardioverter-defibrillators to prevent sudden cardiac death [7]. With the potential

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integration into artificial intelligence (AI)-driven platforms that could automate MBR calculations, this approach makes precision diagnostics accessible even in resource-limited settings. AI and machine learning could further enhance MBR's application by predicting disease trajectories [8]. Integrating MBR into multimodal diagnostic frameworks holds particular promise. Combining MBR with cardiac MRI's structural insights, electrophysiological data, and histological findings could create a comprehensive, data-driven approach to CS management. For example, MBR could quantify active inflammation, while CMR delineates fibrosis, and electrophysiological studies assess arrhythmic risk, together informing personalized treatment strategies.

The study by Ueberham et al. lays a strong foundation for future research in CS diagnostics. Larger, multi-center studies are needed to validate the 2.1 MBR cut-off across diverse populations and imaging systems. Comparative analyses with other PET metrics could further clarify MBR's unique contributions. Longitudinal studies linking MBR to clinical outcomes, such as arrhythmic events or heart failure-related hospitalizations, will strengthen its prognostic utility. MBR could also transform clinical trial design by serving as a quantifiable endpoint for evaluating therapies, reducing reliance on subjective outcomes. This could accelerate the development of novel treatments for CS, addressing a critical need in a disease with limited evidence-based therapies.

3. Conclusion

The MBR metric proposed by Ueberham et al. provides a reproducible, physiologically-based measure derived from FDG-PET imaging. It facilitates the integration of imaging data into clinical decision-making, showing promise as a diagnostic threshold, therapeutic biomarker, and prognostic tool in precision Cardiology. Further research should validate and evaluate its broader applications, with potential to enhance CS management and improve patient outcomes.

CRediT authorship contribution statement

Nitish Behary Paray: Conceptualization, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Kristian Bailey:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Raheel Ahmed:** Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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