Can phase analysis of gated myocardial perfusion single-photon emission computed tomography predict adverse outcome in cardiac sarcoidosis?

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Sarcoidosis is a systemic inflammatory disorder of unknown etiology characterized by noncaseating granulomas, which most often involves the lungs, lymph nodes, eyes, skin, and central nervous system. Cardiac involvement is much more common than clinically apparent, and may cause loss of ventricular function and sudden death. The pathologic process of Cardiac sarcoidosis (CS) is characterized by granulomas and scars most commonly located in the left ventricular free wall, followed by the intraventricular septum, often with involvement of the conducting system. Autopsy studies shown cardiac involvement in about 25% of cases with systemic sarcoidosis,^{1–3} whereas clinical manifestations might be documented in only 5% of patients with CS.^{4,5} CS may occur without apparent disease activity in other organs. Up to 65% of CS patients have isolated cardiac involvement, and only 40% to 50% of patients with cardiac involvement at autopsy had clinical evident of cardiac disease during their lifetimes.⁶ Clinically, CS is manifested by ventricular arrhythmias, heart block and cardiomyopathy, with symptoms of congestive heart failure, syncope, and death. Among sarcoidosis patients, those in Japan have higher rates of cardiac involvement than do those in other countries, reaching up to 58%, and

CS is the leading cause of death in Japanese patients with sarcoidosis, accounting for up to 85% of the cases.⁷ Early diagnosis of CS is challenging because of the low rate of clinical signs, and since sudden cardiac death might be a potential initial manifestation.^{8–10} However, the sensitivity of endomyocardial biopsy in the detection of noncaseating granulomas is low, in the range of 20%–30%.¹¹

Cardiac imaging plays a key role in the diagnosis and prognostic assessment of patients with CS. Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is valuable in the detection of CS and assessment of ongoing inflammation, identifying the location for endomyocardial biopsy, and is useful in assessing response to treatment.^{12,13} Focal FDG uptake is characteristic of the inflammatory granulomatous process of CS, often coupled with perfusion defects resulting in perfusion-metabolic mismatch. Cardiac magnetic resonance with late gadolinium enhancement (LGE) detects areas of fibrosis within the myocardium, and has been shown to provide valuable diagnostic and prognostic information, but is less useful in assessing response to treatment.¹⁴ It has been proposed that FDG-PET and CMR provide complimentary information on CS, and the use of combined multimodality imaging might improve the diagnostic and prognostic assessment of CS patients.¹⁵

In the current issue of the journal of nuclear cardiology, Koyanagawa et al from Japan assessed the prognostic value of phase analysis of gated myocardial perfusion single-photon emission computed tomography (SPECT) in patients with CS. The authors conducted a retrospective outcome study in 57 patients who were diagnosed with CS based on the Japanese Circulation Society guidelines.¹⁶ All patients underwent both gated

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Tc-99m sestamibi SPECT and FDG-PET/computed tomography (CT). The study demonstrated that phase band width (BW) was inversely correlated with left ventricular ejection fraction (EF) and directly correlated with the summed rest score (SRS). No correlation was demonstrated between BW and cardiac metabolic volume and total lesion glycolysis derived by FDG-PET. Moreover, phase analysis indices including phase BW, standard deviation (SD), and entropy were independent predictors of major adverse cardiac events (MACE) over 5-year follow-up, after adjusting for age, gender, and left ventricular ejection fraction (EF), while FDG-PET indices did not predict MACE even in univariate analysis. Noteworthy, the vast majority of the patients in this study were newly diagnosed with CS, and most of them had preserved ventricular function with $EF \geq 50\%$. Interestingly, in this cohort EF was not a predictor of adverse outcome, while phase analysis indices were independent predictors of MACE. Importantly, phase analysis parameters were predictors of MACE even among patients with $EF \geq 50\%$ ($n = 51$) or those with mild myocardial injury ($SRS \leq 10$, $n = 38$).

Prognostic assessment of patients with CS is highly important because of the risk of sudden death and deterioration of left ventricular function with progression of heart failure. Previous studies demonstrated that the presence of focal perfusion defects and FDG uptake on cardiac PET identified patients at higher risk of death or ventricular tachycardia.¹³ Another study shown that quantitative measures of perfusion-metabolism mismatch and coefficient of variation of FDG uptake provided incremental prognostic advantage in CS patients.¹⁷ A recent meta-analysis of CMR studies based on 694 patients with suspected sarcoidosis demonstrated that ventricular arrhythmias occurred only in patients with myocardial LGE, and all-cause mortality was significantly higher in patients with LGE than without LGE.¹⁸ The current study by Koyanagawa K. et al demonstrated that phase analysis of gated myocardial perfusion SPECT can predict adverse events among CS patients, including death, ventricular tachycardia and ventricular fibrillation, atrio-ventricular block, and hospitalization due to heart failure. Specifically, bandwidth $> 56^\circ$, phase standard deviation $> 14^\circ$, and entropy $> 53\%$ were independent predictors of MACE, while EF and FDG-PET measures were not. This is a pioneer study which shows the prognostic value of phase analysis by gated SPECT in patients with CS. The prognostic value of mechanical dyssynchrony by gated SPECT has been previously demonstrated in patients with coronary artery disease. In a study of 1244 patients with coronary disease, Hess et al. shown that Kaplan Meier estimates of death at 8 years were 56.8% among patients with $BW \geq 100^\circ$ and 34% among those with

$BW < 100^\circ$.¹⁹ Both mechanical dyssynchrony by gated SPECT and electrical dyssynchrony measured by QRS duration independently predicted death in clinically adjusted models, but were insignificant when EF was added to the multivariate analysis. Importantly, among subgroup of patients with $EF > 35\%$, both mechanical dyssynchrony and electrical dyssynchrony were independent predictors of death after adjustment for clinical data. Mori et al shown the prognostic value of left ventricular dyssynchrony by ^{201}Tl gated SPECT in 167 patients with chronic kidney disease and normal myocardial perfusion.²⁰ In this study, phase $BW > 12.5^\circ$ and $SD > 3.3^\circ$ were predictors of MACE, with higher event rate among patients with wide BW and high SD compared to narrow BW and low SD. It seems that phase analysis indices manifest prognostic value among various patient populations and clinical disease conditions; however, normal range of phase indices varies between different studies and with respect to the patient population studied. Nakajima et al. demonstrated that values of dyssynchrony indices vary between various software packages, and therefore software specific normal values might be required.²¹ Interestingly, LV dyssynchrony indices predicted adverse outcome in the current study by Koyanagawa et al. in CS patients with $EF \geq 50\%$, and in patients with coronary disease and $EF \geq 35\%$ in the study by Hess et al.¹⁹ These results might be important in identifying patients who might benefit from resynchronization therapy and implantable cardioverter defibrillator (ICD). According to the 2013 ACCF/AHA guidelines for the management of heart failure, ICD therapy is recommended for primary prevention of sudden cardiac death to reduce total mortality in selected patients with nonischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post myocardial infarction with EF of 35% or less and NYHA Class II or III symptoms on chronic good medical treatment, who have reasonable expectation of meaningful survival for more than 1 year (level of evidence A).²² In the current study by Koyanagawa et al., $\sim 90\%$ of 57 CS patients had normal EF. In this patient population, the EF was not a predictor of adverse events, mostly death or ventricular arrhythmias, whereas abnormal phase BW, SD, and entropy were associated with higher risk of events among the whole patient group and among those with $EF \geq 50\%$. According to the ACCF/AHA guidelines, these patients did not fulfill the criteria for ICD therapy. Mechanical dyssynchrony might provide extended criteria for ICD therapy in CS patients who are at high risk of ventricular arrhythmias and death. However, larger studies are required and threshold values of abnormal phase indices need to be defined.

Disclosure

T. Sharir and I. Hollander have no conflict of interest to disclose. G. Kovalski, Employee of General Electric Healthcare, Haifa, Israel.

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