Added value gated PET with phase analysis for the detection of scar burden and prognostication in cardiac sarcoidosis?

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Sarcoidosis is known as a systemic autoimmune disease with non-caseating granuloma that can manifest in any organs with preference for perihilar-mediastinal lymph nodes and the lungs.^{1,2} Interestingly, a substantial variability in the prevalence of sarcoidosis ranging between 3 and 10 per 100,000 for Caucasians (highest in Scandinavians), from 35 to 80 per 100,000 African American has been noted.^{1,2} Further, there is an increasing awareness that the life span of patients with sarcoidosis is increasingly stringent on the cardiac involvement. Notably, the prevalence of cardiac involvement in sarcoidosis in autopsy studies has been appreciated between 20% and 27% in the United States population and even up to 58% in Japan.^{1,3} While cardiac sarcoidosis may not become apparent as a subclinical bystander to systemic disease activity, it can induce acute-inflammatory myocardial disease activity that potentially may result into mild fibrotic alterations and/or even scar tissue.³ Clinically, cardiac sarcoidosis may manifest with complete heart block, ventricular arrhythmias (tachycardia and/or fibrillation), sudden cardiac death, and congestive heart failure.^{4,5} Given the potential adverse outcome of clinically manifest cardiac

sarcoidosis, its early and accurate detection is of utmost importance. With the advent of advanced imaging modalities such as cardiac positron emission tomography (PET), magnetic resonance (MR) imaging or as integrated PET/MR,⁶⁻⁹ cardiac sarcoidosis can be detected and characterized non-invasively that implies critical prognostication and a timely installation of immune-suppressive treatment options.² As regards perfusion and FDG-PET imaging, the typical location of resting perfusion deficits (basal segments; commonly affecting the septum or lateral wall of the left ventricle) with corresponding abnormal focal FDG-uptake, so called “mismatch”, is widely diagnostic for active-inflammatory cardiac sarcoidosis.^{2,10} Importantly, such focal regions of “mismatch” between perfusion and inflammation may be related to regional leukocyte infiltration with associated inflammation, edema, and/or fibrosis. Surprisingly, such regions may have maintained or normal left ventricular wall motion that contrast classical regional hypo-to-akinesis in infarcted tissue after acute coronary syndromes.^{2,11} The reason for this discordant observations remain uncertain but may be related to relatively low spatial resolution of SPECT or PET perfusion imaging, edema induced compression of the coronary arteriolar vessels, low grade of interstitial fibrosis and/or patchy pattern of scar tissue (if present). In addition, compensatory increases in regional contractility within the affected wall segments may also account for the observed normal transmural wall motion on gated PET perfusion images.¹² In this respect, adding phase analysis on gated single photon emission computed tomography, assessing the heterogeneity of perfusion deficits, and the dyssynchrony of the left ventricular wall motion in cardiac sarcoidosis, may be of further help.^{11,13}

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In this issue of the Journal of Nuclear Cardiology, Elwazir et al.¹⁴ could indeed demonstrate that adding phase analysis to gated PET-derived volume and wall motion resulted in an improved detection of sarcoidosis-related regional scar tissue superior to perfusion assessment with ¹³N-ammonia images alones. As it was observed, the sensitivity and specificity of ¹³N-ammonia perfusion images was about 45% and 89%, respectively. Adding, PET-derived left ventricular volumes and function in a logistic regression model enhanced the sensitivity to 57% with a drop in specificity to 80%. Importantly, subsequent evaluation with phase analysis with maximal segmental onset of myocardial contraction > 61 resulted in an improvement of the AUC from .72 to .75. This resulted in a relabeling of 16.3% of patients as scar with a net reclassification index of 8.2%.

Overall, 176 patients underwent delayed enhancement (DE) cardiac magnetic resonance (CMR) and also ¹³N-ammonia rest perfusion combined with ¹⁸F-fluorodeoxyglucose (FDG) cardiac PET/CT for evaluation of patients with suspicion for cardiac sarcoidosis. Scar was defined as DE on CMR without concordant ¹⁸F-FDG uptake on ¹⁸F-FDG uptake. The latter definition to define scar tissue by DE-CMR without corresponding ¹⁸F-FDG uptake may be suboptimal as DE on CMR images could also represent, at least in part, edema in particular in the absence of regional wall motion abnormality. The additional application of non-contrast T2-weighted CMR sequences would certainly have been helpful to reliably identify myocardial edema in these patients with cardiac sarcoidosis. Conversely, there is an ongoing debate whether T2-weighted CMR sequences may accurately differentiate between myocardial edema and scar tissue with DE on T1-weighted CMR images when of preexisting sarcoidosis-induced cardiac structural alterations are present.^{7,15}

Interestingly, in the group with apparent scar tissue the global left ventricular ejection fraction (LVEF), as determined with cine CMR, was in the normal range with a mean value of 56% and a standard deviation of 14%. It would have been of interest to subgroup the group with “defined” scar tissue into those with regional wall motion abnormality and in those without. It is quite possible that fibrotic changes or minor scar tissue islets were compensated by increase in regional circumferential contractility so that on gated PET it appeared as normal regional transmural wall motion. In this respect, it may be of interest to apply tagging CMR for the assessment circumferential, radial, and/or longitudinal strain in order to evaluate the accuracy of this approach in the detection of regional contractile abnormalities when gated PET appears to be normal in regions with DE on CMR images. Someone could argue that tagging CMR could indeed be helpful to

differentiate between edema and minor scar burden in these regions with cardiac DE that, however, needs to be investigated. In the current study, Elwazir et al.¹⁴ elegantly demonstrate that adding phase analysis to gated PET-derived volume and wall motion may indeed increase the detection of regional scar tissue with an AUC of about .75 that led to a relabeling of 16% of patients with sarcoidosis related scar burden. Given that the residual scar burden after active-inflammatory cardiac sarcoidosis is a major and independent long-term predictor in clinical outcome in these patients,⁵ the additional application of phase analysis with gated ¹³N-ammonia PET may hold promise for a further improvement in prognostication of cardiac sarcoidosis patients that deserves further investigations in large-scale clinical trials.

Disclosure

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