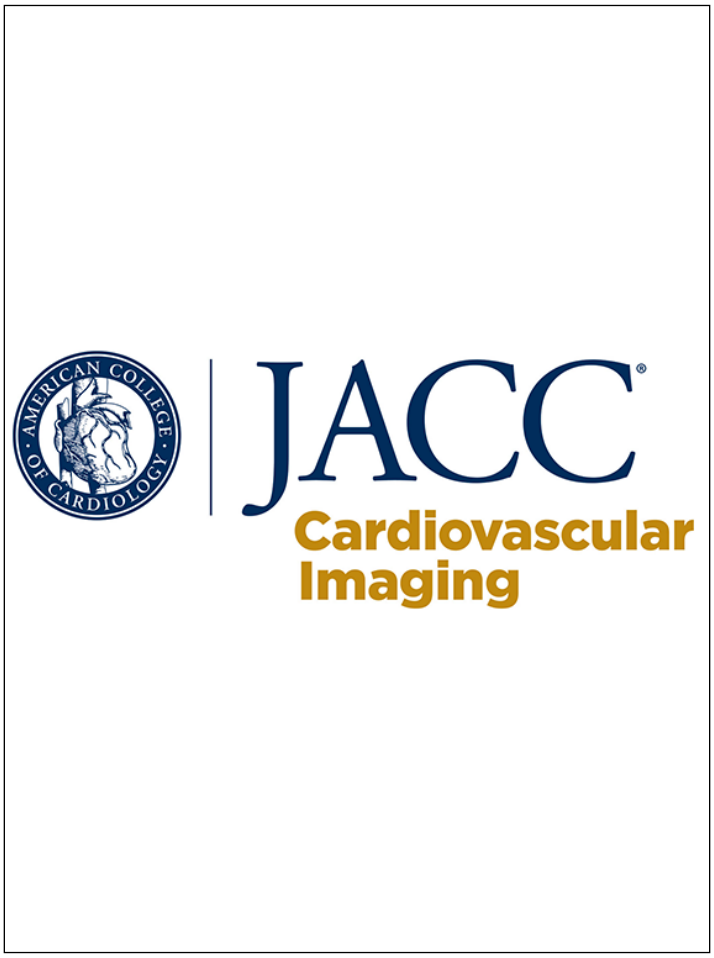

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EDITORIAL COMMENT

Radiolabeled-White Blood Cell Imaging in Cardiac Device-Related Infective Endocarditis

Worth All the Effort?*

Paola A. Erba, MD, PhD,[a,b] Riemer H.J.A. Slart, MD, PhD[b,c]

During the last years, cardiovascular medicine has faced a paradigm shift by embracing the concept of multimodal imaging and multidisciplinary team-working. Extensive imaging applications aim primarily to establish a prompt diagnosis. Further, this shift presents significant implications for treatment regarding decision-making and prognosis prediction. By this approach, the focus of attention moves away from a single organ dysfunction assessed by a single imaging modality and managed by a single specialist, to a more comprehensive approach build upon 2 pillars of the systemic involvement of a disease and patients' team-management.

For patients with infective endocarditis (IE) and cardiovascular implantable electronic device (CIED) infections, patient risk assessment is crucial. Results from the EuroEndo registry have shown that vegetation length, the presence of cerebral complications and/or abscess, and failure to undertake surgery were all independent predictors of mortality (1). Therefore, multimodality image-based predictors (imaging biomarkers) took the steps to be fully integrated into the traditional diagnostic criteria, filling in the diagnostic gap for patients with IE and CIED infections (2). In this specific setting, 2-deoxy-2-[fluorine-18]-fluoro-D-glucose positron-emission tomography/computed tomography ([^{18}F]FDG PET/CT) has emerged as a powerful tool for disease characterization (3). The technique has been mostly used in patients with prosthetic valve endocarditis, increasing the sensitivity of the diagnostic criteria from 70% to 97% (4). However, more and more commonly it is used in patients with native valve endocarditis for proper assessment of the embolic burden as well as in patients with CIED infections (5). [^{18}F]FDG uptake is not only serving as a powerful diagnostic criteria, but it entails a prognostic significance (prognostic biomarker) (6). In particular, in patients with IE, [^{18}F]FDG PET/CT provide independent information about the risk of occurrence of complications (i.e., heart failure, in-hospital and 1-year death, recurrence, new embolism, and rehospitalization) with moderate to intense uptake more strongly associated with a major cardiac event as compared with negative or low-intensity uptake. Further, in cases of both prosthetic valve endocarditis and native valve endocarditis, [^{18}F]FDG PET/CT is an independent predictor of new embolism. Similarly, in patients with CIED infections, [^{18}F]FDG PET/CT demonstration of endovascular infection without pocket involvement has been associated with unfavorable outcomes, suggesting that the infection most likely stems from an unrecognized/distant site, and is associated with poor prognosis (7). In addition, when metastatic infection is found by [^{18}F]FDG PET/CT imaging, it results in change of treatment in up to 35% of patients (8). [^{18}F]FDG PET/CT has also shown the ability to reveal the source of infection, including cases where the

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From the [a]Nuclear Medicine, Department of Translational Research and New Technology in Medicine, University of Pisa, Pisa, Italy; [b]Medical Imaging Center, Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; and the [c]Department of Biomedical Photonic Imaging, Faculty of Science and Technology, University of Twente, Enschede, the Netherlands. Dr. Erba has received royalties from Springer; and has research contracts with Sigma Tau and Gammaservizi. Dr. Slart has reported that he has no relationships relevant to the contents of this paper to disclose.

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TABLE 1 Advantages and Disadvantages of Both Nuclear Imaging Techniques Diagnosing Cardiac Device-Related Infective Endocarditis

Pros	Cons
[^{18}F]FDG PET/CT	
Spatial resolution	Suboptimal suppression of FDG in the myocardium
Short acquisition time	Recent surgery results in inflammatory activity on PET
Septic embolic detection	False positive findings, e.g., thrombi, polyp
CIED infection detection	Possible false-negative test in patients with small vegetations or prolonged antibiotic therapy
	Brain not possible to evaluate due to physiological uptake
WBC scintigraphy SPECT/CT	
Higher specificity	Time-consuming
Septic embolic detection possible, but not a standard	Possible false-negative result in patients with small vegetations or prolonged antibiotic therapy
	Procedure involves handling blood products
	Cases of false-negative study seen with antibiotic use

CIED = cardiovascular implantable electronic device; CT = computed tomography; [^{18}F]FDG = 2-deoxy-2-[fluorine-18]-fluoro-D-glucose; PET = positron-emission tomography; WBC = white blood cell; SPECT/CT: single-photon emission CT.

sustaining portal of entry was a neoplasia (colonic cancer) which could result in prevention of recurrence (9). [^{18}F]FDG PET/CT has several advantages: it is fast, easy to perform, is readily available, and it provides high-resolution imaging in association with CT angiography in a single scan (Table 1). However, [^{18}F]FDG PET/CT requires proper imaging evaluation by experienced operators. The application of specific interpretation criteria will reduce potential pitfalls (2). Combination of PET/CT and CT angiography findings represents an accurate strategy to overcome these limitations (10) as well as the clinical integration of imaging results within the endocarditis team (5). An alternative to increasing imaging specificity is the use of another imaging method, radiolabeled white blood cell (WBC) scintigraphy. WBC imaging has resulted in improved identification of endocardial involvement and extracardiac complications of IE (11,12) and in the detection of infectious device involvement with additional diagnostic value, particularly in the subset of possible CIED infections (13–15). Because of the capability to explore the whole device, WBC imaging has the ability to help differentiate superficial surgical site infection from true generator pocket infection, as well as superficial from deep pocket infection. This is particularly relevant when patients present with either systemic infection or blood-positive culture in the absence of the typical signs of involvement at the generator pocket. However, a longer scan-time, a more complex procedure for the radiopharmaceutical preparation, lower spatial resolution of single-photon emission CT (SPECT)/CT system as compared with PET/CT, and limited availability among clinical centers worldwide are generally considered limitations to the appropriate implementation of this imaging modality (Table 1).

The prospective, single-center study presented by Holcman and colleagues in this issue (16) represents a reinforcement of the value of imaging for better disease understanding, offering insights into the underlying mechanisms and potential therapeutic strategies. This study, which includes 103 consecutive patients suspected of CIED infections observed for a mean time of 17.48 ± 11.9 months, demonstrated that the presence of technetium-99m-WBC SPECT/CT uptake was associated with an increased rate of in-hospital mortality, and was the strongest factor associated with complications. Technetium-99m -WBC SPECT/CT findings guide treatment, and more often result in complete hardware removal. These results further expand the evidence to support active use of multimodality imaging in the diagnostic algorithm of patients with suspected CIED infection to optimize their management and potentially reduce management costs, as recently suggested by the European Heart Rhythm Association international consensus document on how to prevent, diagnose, and treat CIED infections (17). Thus, WBC findings might also be considered similar to [^{18}F]FDG as a prognostic imaging-derived biomarker.

In the era of revived interest in SPECT imaging where movement to digital imaging detectors (18) and advancements in informatics, software, and analytics show significant improvement in image quality, image reconstruction, automate quantification, and reproducible measurements, there is the potential now to leverage research activities in the field of SPECT imaging of the metabolic profile of disease. This has already been part of clinical routine in cancer

management driven by medical need for new or improved imaging targets, imaging probes, better labelling options, and (multimodal) imaging technologies. Multimodality imaging is a promising new area in this respect, but integration of image data across different modalities represents the first step in a wider integration of the imaged-derived parameters with clinical, microbiologic, and biochemical parameters. This will open the opportunity for a new multidomain approach in disease characterization. Where capability of instrumentation continues to evolve, we can foresee a great expansion of the field of nuclear cardiology with a concomitant increase in volume and diversity of procedures, including a new opportunity for radiopharmaceuticals currently considered a niche in clinical application. Taking into account the aforementioned scientific drivers, technological breakthroughs, as well as the rapid changing in available technology, transparent assessment of each single modality strength and limitation is timely and even necessary. It is critical to develop evidence to establish and refine the successful implementation of the methods which are worth the effort.

ADDRESS FOR CORRESPONDENCE: Dr. Paola A. Erba, Nuclear Medicine, Department of Oncology, University of Pisa Medical School, via Roma 67, Pisa, 56126, Italy. E-mail: paola.erba@unipi.it.

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