^{18}F-FDG PET/CT now endorsed by guidelines across all types of CIED infection: Evidence limited but growing

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Worldwide, the number of patients with cardiac implantable electronic devices (CIEDs), prosthetic heart valves, or circulatory support devices is increasing.[1,2] Unfortunately, despite significant advances in surgical technique, antimicrobial prophylaxis, and miniaturization, the number of device-related infections is also increasing.[1]

The incidence of CIED infection involving permanent pacemakers (PPMs) and implantable cardiac defibrillators (ICDs) ranges from 0.5 to 2.2%, and it is even higher after a revision procedure.[3–6] Infection can occur anywhere along the length of the system, from the device pocket to the intravascular and intra-cardiac portions of the pacing lead where it may also come into contact with endocardial surfaces.[7] Generator pocket infections may present with obvious abscess formation or purulent discharge,[8] and in these cases the diagnosis and indication for extraction is straightforward. However, earlier detection of pocket infections before such an advanced stage is reached, or detection of more distal infection involving intravascular to intra-cardiac lead components is sometimes more challenging as clinical signs and symptoms are often more subtle and variable.[3,9]

Detecting CIED lead infection (CIED-LI) or prosthetic valve endocarditis (PVE) by echocardiography is also challenging, as visualization is often poor due to considerable artifact. Clinical diagnostic criteria for infective endocarditis (IE) such as the Modified Duke Criteria have also been shown to have reduced accuracy for CIED-LI and PVE.[10,11] One particular shortcoming of the Modified Duke Criteria in suspected CIED-LI and PVE is that a significant proportion of patients remain categorized as ''possible endocarditis,'' which only perpetuates diagnostic uncertainty in already challenging cases.[12,13] In view of these limitations, there has been a drive to develop novel imaging strategies specific to cardiovascular device infection.[14]

In this issue of *Journal of Nuclear Cardiology*, Mahmood et al report results from a meta-analysis of 14 recent studies evaluating the diagnostic accuracy of ^{18}F-FDG PET/CT for suspected CIED infection across the full spectrum of clinical presentations.[15] This editorial considers the key findings of the manuscript in the wider context of ^{18}F-FDG imaging in the diagnosis of CIED infection and future directions.

HISTORICAL PERSPECTIVE

^{18}F-FDG PET/CT has an established role in the diagnosis of non-cardiac prosthetic infections.[16,17] It has been proposed that ^{18}F-FDG PET/CT could also help identify cardiovascular device infections and help guide clinical decisions regarding whether the device requires extraction. Particular benefit is postulated in cases where the presence of infection is not entirely clear at initial presentation.[18] However, early clinical studies demonstrated high and variable physiologic myocardial ^{18}F-FDG uptake making it difficult to distinguish pathological from physiological activity. Indeed, early studies

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reported sensitivity for the detection of IE as low as 39%.[19] More recently, studies have re-evaluated ^{18}F-FDG PET/CT for CIED infection with better patient preparation to suppress physiological myocardial uptake by dietary manipulation. Contemporary studies have optimized patient preparation through use of dietary carbohydrate restriction, thereby reducing physiological myocardial ^{18}F-FDG uptake, making it easier to identify pathological uptake.[20–25] The current meta-analysis examined a subgroup of studies that utilized appropriate dietary preparation (+/− heparin) and show that the sensitivity of ^{18}F-FDG PET/CT for detecting CIED infection was substantially increased (to 92%) using this strategy.[15] This development represents a milestone in the advancement of metabolic imaging of cardiovascular infection and has possibly contributed to increasing clinician confidence in reporting on the extent of intra-cardiac extension of infection. Low-dose unfractionated heparin has also been postulated to suppress physiological myocardial uptake, and is therefore also included in patient preparation pathways by some centers.[22,23,25]

CURRENT META-ANALYSIS

The current meta-analysis evaluated data from 492 patients across 14 studies. Despite significant heterogeneity in study design, patient preparation and imaging protocol across the studies, the meta-analysis confirms excellent diagnostic accuracy of ^{18}F-FDG PET/CT for the diagnosis of any form of CIED infection (pooled sensitivity: 85%; pooled specificity: 90%).

The diagnostic accuracy in patients with specifically generator pocket infection (CIED-GPI) was particularly high (sensitivity 96%, specificity 97%) and this is consistent with prior studies.[15,18,22,26–31] However, one caveat is that the majority of studies evaluating diagnostic accuracy in suspected CIED-GPI only include confirmed cases or those with medium-to-high pre-test probability. Paradoxically, patients at the opposite end of the spectrum (with a lower pre-test probability of infection at initial presentation) are generally considered to pose a greater diagnostic challenge and by comparison are relatively underrepresented in these studies; arguably, a novel non-invasive diagnostic tool would be most useful in this group of patients, and further studies assessing the performance of ^{18}F-FDG in this group are desirable. The utility of ^{18}F-FDG PET/CT to detect CIED-GPI in sub-muscular implants and subcutaneous ICDs located in a non-pectoral region has also not been described in large numbers.

With regard to CIED-LI, the meta-analysis reports pooled sensitivity and specificity for ^{18}F-FDG PET/CT of 76% and 83%.[15] One important limitation is that although guidelines describe three types of CIED infection (GPI, LI, and IE),[6] the authors collapsed the hierarchies of CIED-LI and IE, analyzing these cases together. The latter perhaps relates to small sample sizes and the fact that the original studies did not always differentiate between extra-cardiac and intra-cardiac CIED-LI, or between CIED-LI and IE. As a result, we do not gain additional insight from the meta-analysis as to the diagnostic accuracy of ^{18}F-FDG PET/CT in these specific sub-types, and this remains an area requiring further study—particularly as accurately defining extent of CIED infection can help determine the duration of antimicrobial treatment.[6]

The results from this meta-analysis build on data from another recent meta–analysis by Juneau et al (11 studies, 331 patients) which reported the pooled sensitivity, pooled specificity, and overall diagnostic accuracy for ^{18}F-FDG PET/CT for CIED infection to be 87%, 94%, and 94%, respectively. Notably, studies of ventricular assist device (VAD) infection were also included in this analysis.[26]

FUTURE DIRECTIONS AND AREAS FOR ADDITIONAL STUDY

Standardization

Although proposed in recent guidelines, a standardized protocol for optimal patient preparation and imaging has not yet been universally adopted—this would be desirable to reduce heterogeneity between studies and reported outcomes.[32]

Influence of Antibiotic Therapy

It is recognized that intensity of ^{18}F-FDG uptake is attenuated with antibiotic treatment for CIED infection and in the current meta-analysis only 2 studies specifically reported withholding antibiotic treatment prior to imaging. Whether the duration of pre-treatment with antibiotics in cases of suspected cardiovascular infection is a bigger problem than recent commencement of antibiotics when it comes to the diagnosis false negatives has not been explored in great detail. However, false negatives and reduced sensitivity have been described in studies reporting pre-treatment with antibiotics.[18,28,33] Although perhaps not always deliverable in a real-world setting, patients would be ideally be scanned before the administration of antibiotics to ensure greater confidence in excluding infection.

Semi-quantitative Threshold

Analysis of PET images in the studies reviewed by the current meta-analysis was variable; although most performed semi-quantitative analysis of PET images (maximum standardized uptake value, SUV_{max}, or semi-quantitative ratio, SQR), an optimal threshold for identifying infection could not be determined in the current meta-analysis as this would ideally require access to all individual patient level data. Moreover, there was marked heterogeneity in patient preparation and evaluation of ^{18}F-FDG uptake across the studies, so the reproducibility of any threshold would be questionable. As yet there is no consensus on the optimal quantitative interpretation of ^{18}F-FDG uptake in the context of suspected CIED infection. However, recent ASNC guidelines describe use of a qualitative graded visual score to report tracer uptake in a region of interest and endorse the use of dietary optimization.[32] The guidelines stop short of making recommendations on quantitative assessment of ^{18}F-FDG activity. Indeed, with continuous advancements in camera hardware and software even recommended thresholds are subject to change. In view of these considerations, it is unclear whether a single-threshold SUV_{max} or SQR is appropriate in this setting to rule in or rule out CIED infection. To date, although threshold SQRs have been identified in individual studies, these have not been validated in larger studies with identical protocols.

IMPLICATIONS ON CLINICAL PRACTICE

Infection imaging is not intended to replace existing investigations or clinical acumen—rather its position is as an additional diagnostic tool, complementing existing clinical pathways.[12] A non-invasive test with sufficient sensitivity and specificity to confirm or exclude infection in cases with a low-intermediate pre-test probability of infection at initial presentation would be valuable. Traditional management of CIED infection is reactive. We often intervene only when patients present with late indicators of infection. However, before patients present with abscess formation have an eroded device or have overt systemic infection, they often experience more subtle signs and symptoms. In these individuals, ^{18}F-FDG PET/CT may offer the potential for earlier diagnosis, allowing intervention at an earlier time point before local or systemic complications occur.[18]

The million-dollar question is how can we integrate metabolic imaging into existing clinical pathways for the diagnosis of CIED infection? The high diagnostic accuracy of ^{18}F-FDG PET/CT as a stand-alone diagnostic test in CIED-GPI has been demonstrated in small-scale observational studies. However, in cases of CIED-LI and IE ^{18}F-FDG PET/CT performs less well as a lone diagnostic tool. Comparisons can potentially be drawn from the publication by Saby et al who demonstrated the incremental value of using abnormal ^{18}F-FDG uptake around a chronically implanted prosthetic heart valve. In that setting, when used as a stand-alone diagnostic test, the sensitivity and specificity of ^{18}F-FDG to diagnose PVE were 73% and 80%, respectively. However, when the result of the PET/CT were considered, and increased ^{18}F-FDG uptake around the prosthetic heart valve was used as novel major Duke criterion, then the sensitivity of the Duke criteria increased to 97%. Importantly, with this strategy there was no significant reduction in specificity of the Duke criteria, although it could be argued that the latter was less than optimal at the outset (50% to 40%, $p = 0.5$).[13]

In 2015, the European Society of Cardiology guidelines proposed ^{18}F-FDG PET/CT as a novel major criterion for the diagnosis of suspected PVE and in cases of suspected CIED-IE where the imaging is non-diagnostic.[14] This month the Heart Rhythm Society went a step further and proposed the use of ^{18}F-FDG PET/CT in cases of suspected CIED-GPI and LI when the diagnosis cannot be confirmed by other methods (class of recommendation IIb, level of evidence C).[34] However, in both European and US guidelines, the strength of recommendation is IIb, and the level of evidence supporting this recommendation is derived from non-randomized observational studies. A higher class of recommendation is desirable, and possibly forthcoming, but will require a higher quality of evidence to be demonstrated from well-designed studies.[14,34]

Disclosure

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