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Molecular Imaging of Cardiovascular Device Infection: Targeting the Bacteria or the Host-Pathogen Immune Response?

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Learning Objectives:

On successful completion of the activity, participants should be able to (1) understand the role of FDG PET/CT for diagnosis of cardiovascular device infection, as a functional imaging tool for assessing the overall host-pathogen immune response in infection; (2) learn about the strengths and limitations of bacterial targeting radiotracers for infection imaging, including those based on substances of bacterial maltodextrin transporters, bacterial thymidine kinase, antibiotics, antimicrobial peptides, antibacterial antibodies, bacteriophages and bacterial DNA/RNA hybrid nucleotide oligomers; and (3) discuss the pros and cons of FDG versus bacterial targeting tracers.

Running Title: FDG or bacterial targeting tracers?

Key words: FDG, PET/CT, bacteria, infection, maltodextrin transporter, cardiovascular device

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ABSTRACT

Rapid and accurate diagnosis of cardiovascular device infection remains a challenge in the clinic. Anatomical imaging tools such as echocardiography and cardiac CT/CTA are the first line modalities for clinically suspected endocarditis given their ability to detect vegetation and peri-valvular complications. Accumulating data suggest that functional imaging with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT has unique merits over anatomical imaging and could potentially diagnose early cardiac device infection before morphologic damage ensues, and identify infection source and/or bacterial emboli in the rest of the body. While an abnormal finding on FDG PET/CT was added to the 2015 guidelines of the European Society of Cardiology as a major criterion for the diagnosis of device related and prosthetic valve endocarditis, the latter has not been incorporated in the US guidelines. Beyond these clinically available imaging tools, attempts have been made to develop bacterial targeting tracers for specific infection imaging, which include tracers of bacterial maltodextrin transporter, bacterial thymidine kinase, antibiotics, antimicrobial peptides, bacterial antibodies, bacteriophages and bacterial DNA/RNA hybrid nucleotide oligomers. Most of the tracers have been studied only in experimental animals, except for radiolabeled antibiotics which have been examined in humans without success in clinical translation for infection imaging. In this article, we compare the roles of anatomical and functional based imaging for cardiac device infection, and discuss the pros and cons of FDG and bacterial targeting tracer. We recommend that FDG PET/CT, which represents host pathogen immune response to infection, should be used clinically for identifying cardiovascular device infection, while anticipating continued investigations for bacterial specific tracer in the future.

INTRODUCTION

Bacterial infection remains a worldwide health problem associated with major mortality and morbidity, yet it is treatable if diagnosed at an early stage. Patients with devices, such as electronic or prosthetic cardiac devices are prone to infection due to their older age and underlying co-morbidities (1, 2). There has been continuous increase in the implantation of cardiovascular devices such as cardiac implantable electronic device (CIED) (pacemaker, defibrillator), prosthetic valve, and left ventricular assist device (LVAD) (3). Infection is one of the major complications of device implantation, which often deteriorates fast, and is potentially life threatening, if not diagnosed and treated in a timely manner (4). On the other hand, over-diagnosis of infection often leads to unnecessary device extraction and re-implantation which is associated with increased hospital stay and mortality, imposing a substantial societal and medical burden. Thus, accurate and rapid diagnosis of cardiovascular device infection is critical for patient management and therapeutic decisions. Clinical diagnosis of cardiac device infection, particularly device related endocarditis involves a multidiscipline team including a cardiologist, an infectious disease physician, microbiology and imaging specialties (5). Imaging tools play a vital role in localizing and diagnosing cardiovascular device infection and in monitoring treatment response. These include anatomically based modalities such as transthoracic (TTE) or transesophageal echocardiography (TEE), ECG-gated cardiac CT or angiography (CTA), and functionally based modalities mainly radionuclide imaging with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT and ^{111}In- or ^{99m}Tc-labeled autologous white blood cell (WBC) single photon emission computer tomography (SPECT)/CT. These imaging modalities visualize and diagnose infection on the basis of the morphological and functional changes of the host inflammatory immune response to the infectious pathogens. In this article, we examine the

roles of these anatomically based (TEE, CT) and functionally based (PET/CT, WBC scan) imaging tools for cardiac device infection diagnosis, and discuss the pros and cons of other investigational imaging strategies, such as bacterial targeting imaging. On the basis of the overall body of articles published, we propose judicious implementation of FDG PET/CT for cardiac device infection evaluation.

ANATOMICAL IMAGING TOOLS

Anatomically based imaging tools are frequently used in diagnosing cardiovascular device infection. Echocardiography and cardiac CT/CTA are currently the first line imaging studies for device related and prosthetic valve endocarditis diagnosis, recommended in the 2014 guideline of the American Heart Association (AHA)/American College of Cardiology (ACC) (6) and the 2015 guideline of the European Society for Cardiology (ESC) (7). Results of the recent ESC-EORP EURO-ENDO (European infectious endocarditis) registry showed that 99.8% of the patients received echocardiography with TEE being more frequently used in prosthetic valve endocarditis patients (8). Abnormal finding on echocardiography as a major criterion was found in 89.1% of the patients (8). Echocardiography particularly TEE can detect valvular vegetation, and can also assess peri-valvular complications (perforation, pseudo-aneurysm, fistulas, and valve dehiscence) with acceptable accuracy (9). TEE findings may also predict embolic events (10). However, TEE may miss up to 30% of valvular prosthetic endocarditis because of the underlying metal ring related acoustic shadowing artifact (11). Cardiac CT/CTA is a modality of choice for assessing peri-valvular complications with a high sensitivity, better than TEE (12). However, both modalities detect late morphological changes of infection, and findings are often non-specific and associated with artifacts from the device's foreign material components. TEE is limited to the intra-cardiac device components and is not able to assess other part of the device or

even the right side heart. Although CT can assess infection in the CIED pocket and leads, it is not able to evaluate the rest of the body for searching potential source of infection and/or site of infectious embolism, which are critical for clinical management. Thus, functional FDG PET/CT and radiolabeled WBC scans have been used and studied for their roles in improving the diagnosis of cardiac device infection. In addition, other strategies such as bacterial targeting tracers are under active study in experimental animals for their potential translation to the clinic.

FUNCTIONAL IMAGING TOOLS

FDG PET/CT and ^{111}In- or ^{99m}Tc-labeled WBC SPECT/CT are useful functional imaging techniques for the diagnosis of cardiac device infection. Abnormal finding on FDG PET/CT or WBC scan is added as a major imaging criterion for the diagnosis of endocarditis in the ESC guideline though not yet in US guidelines (7). Accumulating data have suggested that FDG PET/CT could have the following merits over TEE and CTA in assessing cardiovascular device infection given its functional and whole body imaging natures: 1) diagnosing infection earlier before TEE and CTA detectable morphologic damage ensues; 2) providing metabolic evidence for a confirmatory diagnosis when TEE and CTA findings are inconclusive or equivocal; 3) diagnosing infection in the extra-cardiac parts of a device such as pacemaker/defibrillator pocket and lead, or driveline of a left ventricular assist device (LVAD), which is beyond the TEE and CTA views; 4) imaging extra-cardiac portions of the body for evaluation of a primary infection source and/or infectious emboli (13, 14). **Figure 1** shows 3 examples of infections in CIED pocket, prosthetic valve and LVAD, respectively, as seen on FDG PET/CT. A systematic review showed a sensitivity of 73–100% and a specificity of 71–100% of FDG PET/CT for diagnosis of CIED pocket infection (15). A second meta-analysis showed similar results, with a pooled

sensitivity of 87% and specificity of 94%, respectively (16). For device related or prosthetic endocarditis diagnosis, it has been shown that adding FDG PET/CT positive finding as an additional major criterion to the modified Duke Criteria increased diagnosis sensitivity from 52–70% to 91–97% without compromising specificity (17, 18). FDG PET/CT may change management in up to 35% of clinically suspected endocarditis cases (19). For LVAD infections, it has been shown that in addition to being able to accurately localize the site and extent of infection along the driveline or central portion of the LVAD (20), FDG PET/CT can predict the clinical progress and outcome of patients with LVAD infection, in a superior manner to CT (**Fig. 2**) (21). WBC SPECT/CT is less sensitive for device infection but is more specific compared to FDG PET/CT (22), and a sequential FDG PET/CT and WBC scans have shown a more accurate diagnosis for cardiovascular device infection (23). However, clinical use of FDG PET/CT is low in the workup of cardiac device infection. For example, the European endocarditis registry data showed that FDG PET/CT was only performed in 16.6% of patients, with a better sensitivity in prosthetic valve endocarditis (62.5%), than native (28.0%) and device related endocarditis (16.3%) (8). The use of FDG PET/CT for cardiac device infection imaging in the US is probably even lower, as it has not been endorsed in the US guidelines, and at the present time, it is not reimbursed for infection and/or inflammation imaging. While most of the studies using FDG PET/CT for cardiac device infection are retrospective in nature, current clinical practice and expert consensus support the judicious use of FDG PET/CT in the workup of cardiovascular device infection (24, 25).

Table 1 compares anatomical (TEE and CT/CTA) and functional (FDG PET/CT, WBC scan) imaging modalities for evaluation of cardiovascular device infection.

BACTERIAL TARGETING TRACERS

In an effort to specifically image bacterial infection, attempts have been made to develop tracers that directly target bacterial pathogens in a suspected infection site, which include bacterial metabolic substances (for example, carbohydrates and nucleosides), antibiotics, antimicrobial peptides, bacterial antibodies, bacteriophages and bacterial DNA/RNA hybrid nucleotide oligomers. Among these classes of tracers, radiolabeled antibiotics, particularly, ^{99m}Tc-ciprofloxacin has been extensively studied in clinical trials, without success for clinical translation. Others, such as maltodextrin-based tracers, are still mainly in experimental stages of investigation with variable clinical promise.

Bacterial Metabolic Substances

Carbohydrates

Different from glucose (and its ^{18}F labeled analogue of FDG) which can be utilized by both mammalian cells and microbes, certain types of polysaccharides such as maltodextrins can only be taken up and used by bacteria via maltodextrin transporter (26). Maltodextrin transporter belongs to a family of ATP-binding cassette transporters, which is only expressed in bacteria but not in mammalian cells (26), making it an attractive target for specific bacterial infection imaging. Bacterial maltodextrin transporter can transport maltodextrins with glucose units from 2 (maltose) up to 7 (maltoheptaose) (27). The non-reducing end of a maltodextrin is required for initial binding to the transporter, while the reducing end is required for intra-bacterial transport (28). Labeling can be performed at the reducing end as bacterial maltodextrin transporters could generally tolerate structure modifications/substitutions at the reducing end (29). Meanwhile, both the non-reducing and reducing ends of maltodextrins are susceptible to degradation by plasma α-

glucosidase and α-amylase, respectively (29), which could result in low tracer stability in the blood with a short imaging window. This should be considered when designing a maltodextrin based tracer for imaging. Certain type of maltodextrin, for example, maltotriose is found natively resistant to the α-amylase, whereas others, like maltopentaose is degraded by the enzyme very quickly (29).

Different types of florescence- and ^{18}F-labeled maltodextrin tracers have been synthesized and tested in animals for their potential clinical translation for bacterial specific infection imaging, which include florescence-maltohexaose (30), ^{18}F-maltohexaose (31), ^{18}F-maltose (32), ^{18}F-maltotriose (33), ^{18}F-sorbitol (34), and^{18}F-Trehalose (35).

Work in this field was initiated by Ning et al who first synthesized florescence- and ^{18}F-labeled maltohexaose for optical and PET imaging of bacterial infection, respectively (30, 31). Both tracers could visualize bacterial infection in rat thigh, with very low activity in the contralateral thigh with lipopolysaccharides (LPS)-induced inflammation, indicating potential distinguish between bacterial infection and sterile inflammation. A subsequent study of cardiac pocket infection in a rat model showed that both tracers accumulated in the cardiac pocket infection sites, but not in sterile inflammation sites induced by turpentine oil. In contrast, FDG uptake was observed in both the infection and inflammation sites (36) (**Fig. 3**). ^{18}F-maltohexaose uptake could also be detected in a biofilm model indicating its potential use for biofilm infection (36). The florescence tracer was found mainly in the liver with very low counts in the kidneys indicating its primary hepatobiliary excretion (36). While the ^{18}F-maltohexaose showed significant excretion in the urine at the early time points (36), the stability of the florescence- and ^{18}F-maltohexaose tracers in the blood was not reported. It should be pointed out that in addition to different plasma amylases activities, human and rats may also show different

pharmacokinetics of the tracers. At present, there are no clinical human studies reported with these 2 tracers.

A new tracer, ^{18}F-labeled maltotriose, was recently shown to have a superior pharmacokinetic feature for infection imaging with urinary clearance (33). Mouse PET imaging showed that ^{18}F-maltotriose accumulated in bacteria-induced muscle infection but not in LPS-induced inflammation, indicating its specificity for bacterial infection. Although maltotriose has previously been shown natively resistant to α-amylase (29), ^{18}F-maltotriose stability in the blood was not reported, and human study is also lacking.

In addition to the above mentioned tracers, other maltodextrin based tracers have also been developed and tested in animal models, but with certain limitations. For example, ^{18}F-maltose could also accumulate in inflammation site, raising concerns of non-specificity (32). The radio-pharmacokinetics of the ^{18}F-maltose tracer was suboptimal with predominant hepatic excretion. Another tracer, ^{18}F-sorbitol can only target Gram-negative enterobacteriaceae specific infection, as sorbitol can only be metabolized by Gram-negative enterobacteriaceae (34). In addition, ^{18}F-Trehalose could be a specific tracer for mycobacteria-specific imaging (35).

In summary, while maltodextrin based tracers are promising for bacterial infection imaging, such as ^{18}F-maltohexaose and ^{18}F-maltotriose, published studies thus far are limited to experimental animal models and translational clinical data are lacking. More studies are needed to address issues such as tracer stability in the blood and more importantly, pharmacokinetics of the tracers, before applying them in human subjects.

Nucleoside

Fialuridine-5-iodouracil (FIAU) is an analogue of a nucleoside substrate for bacterial thymidine kinase (TK) but is not phosphorylated by the human kinase (37). It has been shown that ^{124}I labeled FIAU (^{124}I-FIAU) was able to visualize infection in mice induced by a wild-type strain of *E. coli*, but not with a TK deficient mutant strain, indicating its bacterial TK specificity (37). However, not all bacteria have an FIAU-binding TK. For example, *P. aeruginosa* and *Nocardia* species do not take up FIAU because of lack of the kinase (38). This limits the use of ^{124}I-FIAU for imaging a broad bacterial infection. A preclinical human study with ^{124}I-FIAU for assessing prosthetic joint infection showed that the tracer lacks specificity, likely related to host mitochondrial TK metabolism (39), leading to a high background activity particularly muscle uptake, which limits its use clinically.

Antibiotics

Antibiotics have been radiolabeled for their potential use of bacterial infection imaging given their specific binding and uptake in bacteria. Among the different groups of radiolabeled antibiotics that have been tested for almost 2 decades (40), ^{99m}Tc-labeled ciprofloxacin is the most extensively studied tracer and has been assessed in large clinical trials for its use in bacterial infection imaging. Ciprofloxacin is an analogue of quinolone, a broad-spectrum antibiotic that inhibits bacterial DNA synthesis by binding to bacterial DNA gyrase. An early clinical study showed that compared to radiolabeled WBC scan, ^{99m}Tc-ciprofloxacin was the preferred imaging tracer for infection, but it had a fairly high false-negative rate (41). A later large multicenter clinical trial showed that ^{99m}Tc-ciprofloxacin had a compromised specificity likely due to its accumulation in noninfectious inflammation sites (42). Ciprofloxacin was also labeled with ^{18}F for PET imaging (43) and a study showed that although increased activity was

detected in infected tissue, it was subsequently washed out, likely representing increased regional blood flow and vascular permeability instead of specific ciprofloxacin binding to bacteria (43). In addition, emerging bacterial resistance to ciprofloxacin was also a concern which could lead to a false-negative imaging (44). Besides ciprofloxacin, many other groups of antibiotics have also been labeled and tested (40). Unfortunately, no single radiolabeled antibiotic tracer has been shown to be highly specific for bacterial infections. Thus, although radiolabeled antibiotics, particularly, ^{99m}Tc- or ^{18}F-labelled ciprofloxacin have been extensively studied at both experimental animals and human subjects, they are not used clinically due to their non-specificity and low sensitivity. In addition, there is no report regarding radiolabeled antibiotics for imaging cardiovascular device infection in either animal models or human subjects.

Antimicrobial Peptides

To overcome the non-specificity and bacterial resistance of radiolabeled antibiotics, some antimicrobial peptides have been radiolabeled for their potential use of specific bacterial infection imaging. For example, a synthetic peptide ubiquicidin 29–41 (UBI29–41) was radiolabeled and studied for its use of bacterial infection imaging. Animal studies showed that ^{99m}Tc-UBI29–41 accumulated in bacterial infection site but not in sterile inflammation site (45). However, small clinical trials showed a variable specificity of 80 to 100% (46, 47). Binding of UBI to bacteria is initiated and mediated by its positive charges, which interact with negatively charged phospholipids in the bacterial walls (48). This raises concerns regarding UBI-bacterial binding strength and mechanistic specificity. In addition, ubiquicidin also binds to fungus, and thus ^{99m}Tc-UBI29–41may not be able to differentiate bacterial infection from fungal infection (49). ^{68}Ga-label UBI29–41 was also developed for PET imaging and showed similar findings

(50). Similar to radiolabeled antibiotics, radiolabeled antibacterial peptides are less likely to be clinically translatable.

Bacterial Antibodies

Radiolabeled antibodies are one of the first approaches applied for bacterial infection imaging. Early animal studies using radiolabeled (^{111}In and ^{99m}Tc) human immunoglobulin (HIG) showed that although much higher activity was seen in infection site, less activity was observed in inflammation site, likely due to increased vascular permeability, and non-specific Fc fragment binding to immune cells recruited to the site of infection (51). To overcome the non-specific binding related to Fc region, radiolabeled antibody fragment lacking the Fc region such as Fab' fragment was designed, without success (51). As an alternative, antigen-specific monoclonal antibodies were tested (52), but monoclonal antibodies would only target a specific strain or species of bacteria with the same antigen and thus limited its use for broad bacterial infection detection. In addition to the non-specificity, radiolabeled antibodies are well known for its slow blood pool clearance and poor imaging quality, making it less likely for rapid diagnosis of infection, which is critical for immediate clinical management. Thus, although different approaches have been attempted, none of the antibody-based tracers has shown desirable radio-pharmacokinetic features for diagnosis of infection.

Bacteriophages and Bacterial DNA/RNA Hybrid Nucleotide Oligomers

Other tracers that have been tested for bacterial specific infection imaging include ^{99m}Tc-labeled bacteriophages (53), which are viruses that specifically infect bacteria but not mammalian cells, and radiolabeled bacterial DNA/RNA hybrid nucleotide oligomers that

specifically target the bacterial DNA or RNA in the pathogens (54, 55). These could be attractive tracers for specific bacterial imaging at least in theory; however, studies are in their early stages.

CONSIDERATIONS OF FDG AND BACTERIAL TARGETING TRACERS FOR INFECTION IMAGING

Given the tremendous clinical impact, it is imperative to develop an imaging tool for rapid and accurate diagnosis of cardiovascular device infection with a high sensitivity and specificity. FDG PET/CT has unique merits over anatomical imaging techniques for earlier and more sensitive diagnosis of cardiovascular device infection. In addition, FDG PET/CT can identify extra cardiac infection source or infectious emboli, which are critical for patient management. Thus, FDG PET/CT has been recommended by the ESC for the diagnosis of cardiac device related and prosthetic valve endocarditis (7). Although FDG is criticized by its non-specific accumulation in inflammation site (56, 57), differentiation between infection and inflammation can be reasonably achieved by recognizing the FDG uptake pattern: FDG uptake in an infection site is generally heterogeneous with focal increased activity, while distribution of FDG in an inflammatory area is more homogeneous and mild in intensity (58, 59). In addition, clinical information such as device material (metal or bio-prosthesis), and surgical technique (use of adhesion glue or anticalfication material) is also very useful for the differentiation. For example, just like surgical adhesive glue application to a mechanical prosthesis (60), anticalcification treatment to a bioprosthetic tissue with alpha-amino oleic acid can cause a characteristic pattern of FDG uptake: low shortly after surgery while intense homogeneous at 6 months, persisting up to 1 year and even longer (61). A recent study showed that diagnostic accuracy of FDG PET/CT for prosthetic endocarditis can be significantly improved after

adjusting clinical cofounders (62). If differentiation of infection and inflammation can be reasonably made on the basis of FDG uptake pattern and surgical information, then the non-specific FDG uptake may actually represent a unique feature of FDG for infection diagnosis: its high sensitivity for infection with a low rate of missing an infection (low false negative rate).

FDG signal in an infection site represents the overall host-pathogen immune response and thus the underlying severity of infection. In addition, FDG uptake and distribution pattern in the liver, spleen and bone marrow seen on whole body scan provide information regarding activation status of the reticuloendothelial system, representing body's systemic response to the infection. Thus, findings on FDG PET/CT represent severity of the infection and body's overall immune response, which are more critical for patient management decision-making than the accuracy for diagnosis per se (63). FDG PET/CT finding thus may be in fact more reliable in guiding patient management and predicting outcome. A negative FDG PET/CT finding, which represents either no infection (true negative) or mild infection (but false negative based on standard diagnosis), may warrant conservative antibiotics treatment without device extraction. A positive FDG PET/CT finding (when inflammation is excluded based on uptake pattern and surgical history) confirms infection and necessitates complete device extraction. In other words, FDG PET/CT may have the potential to quantify the severity of infection and accordingly guide patient management beyond its capacity of cardiac device infection diagnosis. This hypothesis is supported by several prior studies though with small number of patients (64, 65).

On the other hand, bacterial targeting tracers only detect the specific bacteria itself without providing information regarding the severity of the infection and the body's immune response to the bacterial infection. Although the primary goal of developing bacterial imaging tracers is to provide a specific diagnosis of infection, unexpectedly, many of these assumed

bacterial specific tracers also show non-specific accumulation in inflammation sites with undesirable radio-pharmacokinetic features for infection imaging. There are also additional limitations associated with each group of the tracers.

Antibiotics and antimicrobial peptides kill or inhibit bacteria at a low concentration. Thus, antibiotics and antimicrobial peptides based tracers lack signal amplification with low intra-bacterial accumulation, which limits their signal sensitivity. Although their binding to bacteria is specific, these tracers also show activity in inflammation sites due to increased vascular permeability and decreased washout (43). Pre antibiotic treatment could also significantly decrease the bacterial viability and loading, further decreasing the sensitivity (41). Finally, bacterial antibiotic resistance can potentially lead to a false negative finding (44). Thus, these tracers have not and are not expected to make their final inauguration in the clinic for specific bacterial infection imaging.

Antibody-based tracers are mainly studied in oncology imaging. Radiolabeled antibodies suffer from low target accumulation, non-specific binding (related to Fc segment), high blood pool retention due to slow excretion, and poor imaging quality. The same issues exist in radiolabeled bacterial antibodies for infection imaging (51, 52).

Bacterial thymidine kinase targeting FIAU can also be phosphorylated by mammalian cell mitochondrial kinase raising concern of non-specificity and it is less likely clinically translatable (38, 39). Tracers based on bacteriophages and bacterial DNA/RNA hybrid nucleotide oligomers are in their early stages of development, and are conceptually attractive (53, 55).

Unlike the above mentioned types of tracers, uptake of the maltodextrin tracers is actively mediated by the bacterial maltodextrin transporter, similar to FDG which is mediated by the

glucose transporter. Maltodextrin tracers can reach high intra-bacterial activity as there is continuous internalization through the transporters, facilitating a highly sensitive detection (29). Meanwhile there is efficient and rapid renal excretion of some of the maltodextrin tracers such as ^{18}F-maltotriose (33). However, not all maltodextrin transporter targeting tracers show efficient excretion and ideal radio-pharmacokinetic features. For example, ^{18}F-maltose is mainly excreted by hepatobiliary pathway with minimal renal excretion, making it an undesired tracer for infection imaging (32). Among the current reported maltodextrin transporter targeting tracers, ^{18}F-maltotriose holds the most promise for clinical translation based on animal study (33). However, different from FDG which is trapped inside the cell as FDG-6-P, the metabolism of ^{18}F-maltotriose inside the bacteria is unknown. It remains unclear whether or not ^{18}F is trapped inside the bacteria or whether it will efflux or diffuse out of the cell after ^{18}F-maltotriose degradation. In addition, its stability in the blood is unknown either. More studies are needed to explore its potential for clinical translation. **Table 2** summarizes and compares the main findings of FDG and other bacterial targeting tracers.

TECHNICAL CHALLEGNES FOR BACTERIAL TARGETING PET TRACERS

In addition to the inherent limitations of the bacterial targeting tracers, other challenges for direct PET imaging of infection with these tracers include the complex clinical setting of infection (including empirical antibiotic treatment, biofilm formation), and the technical capability of the current PET camera for detecting small size or for lesion with low counts. Empirical antibiotics therapy is generally started for any suspected cardiac device infection case before a definite diagnosis is made. The treatment may greatly decrease bacterial signal, much more significantly than host immune response signal as revealed by FDG. In addition, cardiac

device infection is frequently associated with biofilm formation which limits permeation of tracers such as antibiotics and antibodies (66). Although preliminary animal work showed that ^{18}F-maltotriose could potentially penetrate the biofilm (33), detailed work is lacking. Most of the current PET camera may not be able to detect a small lesion with a low counts give the limited spatial resolution. In addition, these tracers are unable to access intracellular bacteria when bacteria are phagocytosed by immune cells. Cardiac and respiratory motions during data acquisition would impose further technical challenge. These issues need to be addressed when translating these bacterial targeting tracers to the clinic (67).

CONCLUSION:

Direct bacterial targeted tracers were assumed to be more specific than FDG for imaging bacterial infection. However, it turns out that most of the bacteria-targeted tracers also show non-specific accumulation at inflammation sites. Moreover, most of the bacterial tracers suffer from low sensitivity due to no intra-bacterial signal amplification, prior antibiotics treatment and impermeability of biofilm. One exception could be maltodextrin-based tracers such as ^{18}F-maltotriose which shows specificity for bacteria with high sensitivity due to signal amplification from continuous intra-bacterial accumulation by the maltodextrin transporter. However, current data are limited to early experimental studies in animals and it is unclear whether or not it can be successfully translated into the clinic. On the other hand, FDG PET/CT is very sensitive for early diagnosis of infection, and FDG findings represent overall infection severity and body's immune response to the infection, which is more reliable for patient management decision making. Accumulating clinical data support the use of FDG PET/CT for imaging cardiovascular device infections.

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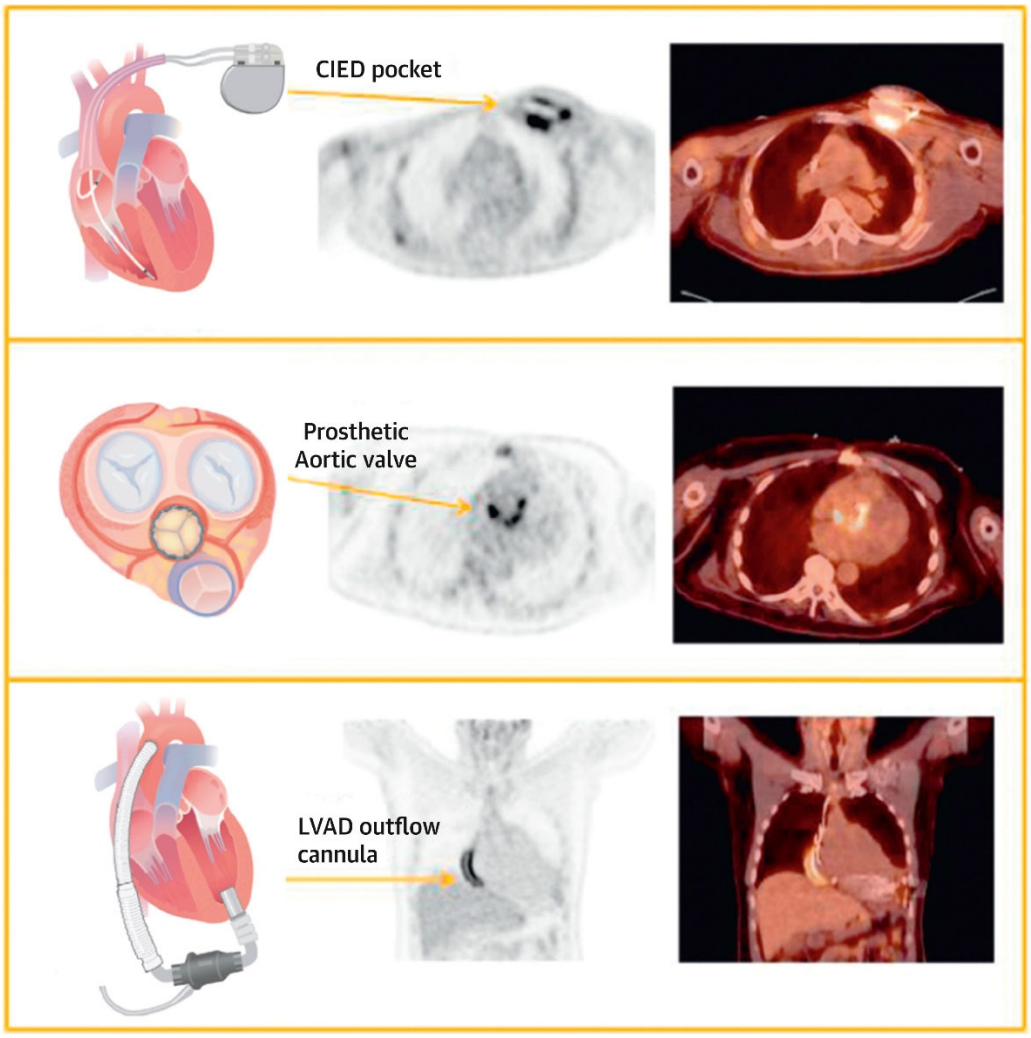
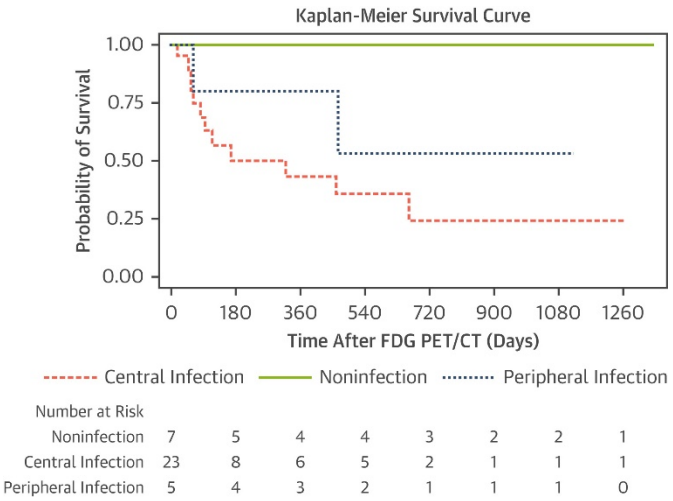
Figure 1. Examples of Cardiac Devices Infections on FDG PET/CT



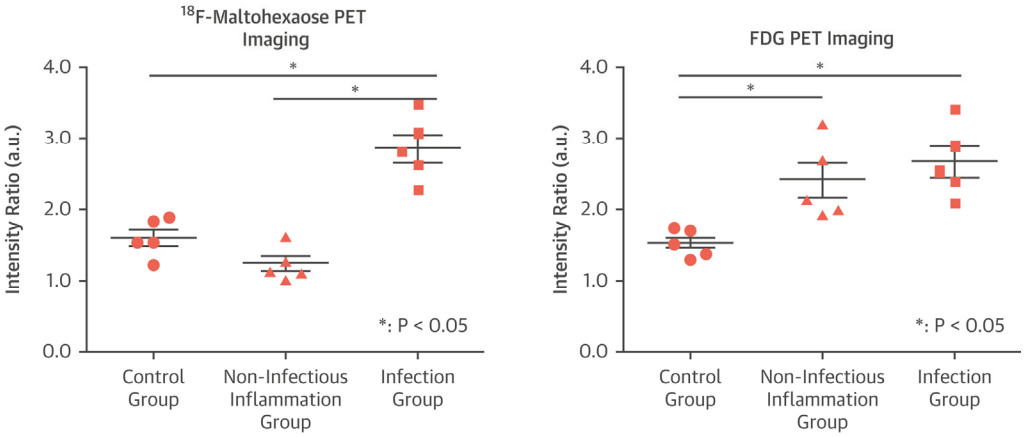
(Upper row): An illustration of cardiac implantable electronic device (CIED) (right). There is intense FDG uptake beneath the left upper chest wall CIED pocket (middle of PET, and left of fused PET/CT), compatible with deep pocket infection. (Middle row): An illustration of cardiac prosthetic valve. There is intense FDG uptake along the prosthetic aortic valve (middle of PET, and left of fused PET/CT), compatible with prosthetic valve endocarditis. (Lower row): An illustration of left ventricular assist device (LVAD) (right). There is intense FDG uptake along the outflow cannula of the LVAD in the mediastinum (middle of PET, and left of fused PET/CT), compatible with central LVAD infection. Reproduced with permission from Chen et al. (ref. 14).

Figure 2. Kaplan-Meier Survival Curves in Left Ventricular Assist Device Patients



Patients are grouped according to non-infection of the left ventricular assist device (LVAD) (green line), peripheral infection (blue dashed line), and central infection (pink dashed line), on the basis of the diagnosis on FDG PET/CT diagnosis. There was a significantly higher mortality in the FDG-avid central versus peripheral infection group. None of the uninfected patients died ($p < 0.03$, log-rank test). Reproduced with permission from Kim et al. (ref. 21).

Figure 3. ^{18}F-Maltohexaose PET and FDG PET in Mouse Infection Models



On ^{18}F-maltohexaose PET scan, the infection mice showed a significant increase in tracer intensity compared with the control and the noninfectious inflammation mice. In contrast, with FDG PET imaging, both the infection and noninfectious inflammation groups had similar significant increases in intensity compared with the control group, demonstrating a lack of specificity. Reproduced with permission from Takemiya et al. (ref. 36).

Fig. 1

Table 1. Comparison of anatomical and functional imaging modalities for imaging cardiovascular device infection

Modality	Pros	Cons
TEE/TTE	First-line imaging for IE Detects vegetation and perivalvular complications Assesses valvular function Predicts embolic risk No radiation	Shadowing artifact/missing lesions Unable to differentiate infectious from noninfected vegetation Unable to evaluation right side heart and chest wall CIED pocket and leads
Cardiac CT	First-line imaging for IE Detects large vegetation Better than TEE for perivalvular complications evaluation Detects chest wall CIED infection	Metallic artifact, non-specific findings Less sensitive for small vegetation Not for extra-thoracic evaluation Radiation exposure
FDG PET/CT	High imaging sensitivity Earlier diagnosis Assess extracardiac infection Signal of host immune response	False positive in inflammation Less sensitive for small vegetation Radiation exposure
WBC scan	High specificity Assess extracardiac infection	Moderate sensitivity Labor intensive Radiation exposure

TEE/TTE: Transesophageal/transthoracic echocardiography; IE: infective endocarditis; CIED: Cardiac Implantable electronic Device

Table 2. Comparison of FDG and bacterial targeting tracers

	Target	Studies at Animal	Studies at Human	Main findings
^{18}F-FDG	Glut	Y	Y	Early and sensitive diagnosis of infection in cardiac and extracardiac portions May guide management based on severity
MDT targeting tracers				
^{18}F-maltotriose	MDT	Y	N	Tested in rat cardiac device infection model Differentiates infection from inflammation
^{18}F-maltohexaose	MDT	Y	N	Tested in mice muscle infection model Differentiates infection from inflammation
^{18}F-maltose	MDT	Y	N	Suboptimal radiopharmaceutics in mice
^{18}F-Trehalose	MDT	Y	N	limited to mycobacteria
^{18}F-sorbitol	MDT	Y	N	limited to Gram negative bacteria
^{124}I-FIAU	TK	Y	Y	Non-specific uptake in inflammation, Not clinically translated
Antibiotics				
^{99m}Tc-ciprofloxacin	DNA gyrase	Y	Y	Low sensitivity, non-specific uptake Not clinically translated
Antimicrobial peptides				
^{99m}Tc-UBI29–41	innate immune	Y	Y	Low sensitivity, non-specific uptake Not clinically translated
Antibodies	antigen	Y	Y	Slow blood pool clearance Non-specific uptake, poor imaging quality Not clinically translated

Glut: Glucose transporter; MDT: Maltodextrin transporter; TK: thymidine kinase