Single Photon Emission Tomography in the Diagnostic Assessment of Cardiac and Vascular Infectious Diseases

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Abstract

Background: Cardiac and vascular infection is a arising cause of mortality and morbidity in the adult population. Diagnosis based on culture and anatomic imaging is frequently inconclusive. Radiolabeled leucocyte scintigraphy plays a useful role in the diagnosis and management of these serious infectious conditions.

Objective: In this paper, we present an update on the diagnostic performance of single-photon emission tomographic (SPECT) techniques using different radionuclides in the management of patients with cardiac and vascular infections.

Methods: We performed a thorough search of recent literature on the topic. We present a discussion on the clinical utility of different SPECT tracers in cardiac and vascular infections including infective endocarditis, cardiac implantable electronic device (CIED) infections, left ventricular assist device infection, and vascular graft infection.

Results: Radionuclide techniques using SPECT tracers is a useful imaging modality in the diagnosis of cardiac infection. Among the different SPECT tracers for infection imaging, radiolabeled leucocytes scintigraphy is currently the most useful tool in the diagnosis and management of patients with suspected cardiac and vascular infection. Radiolabeled leucocytes scintigraphy has a high specificity, a result of the ability of the leucocytes to accumulate as sites of pyogenic infection but not at sites of sterile inflammation such as seen in the early post-operative period or in response to the presence of a prosthetic cardiac or vascular material. Limited experience with radiotracers for in vivo labelling of leucocytes such as ^{99m}Tc-sulesomab and ^{99m}Tc-besilesomab show acceptable diagnostic performance without the need for the tedious process of ex-vivo labeling. ^{67}Ga scintigraphy used to be popular for cardiac and vascular infection imaging. Its use has run out of favor following the availability of more effective molecular imaging methods.

Conclusion: SPECT techniques with radiolabeled leucocytes scintigraphy has a high diagnostic performance in the evaluation of patients with suspected cardiac or vascular infection. It is able to confirm or reject the presence of infection when results of anatomic imaging or culture remain inconclusive. Its diagnostic performance is not compromised by sterile inflammation occurring in the early post-operative period or in response to implanted prosthetic materials.

Graphical abstract
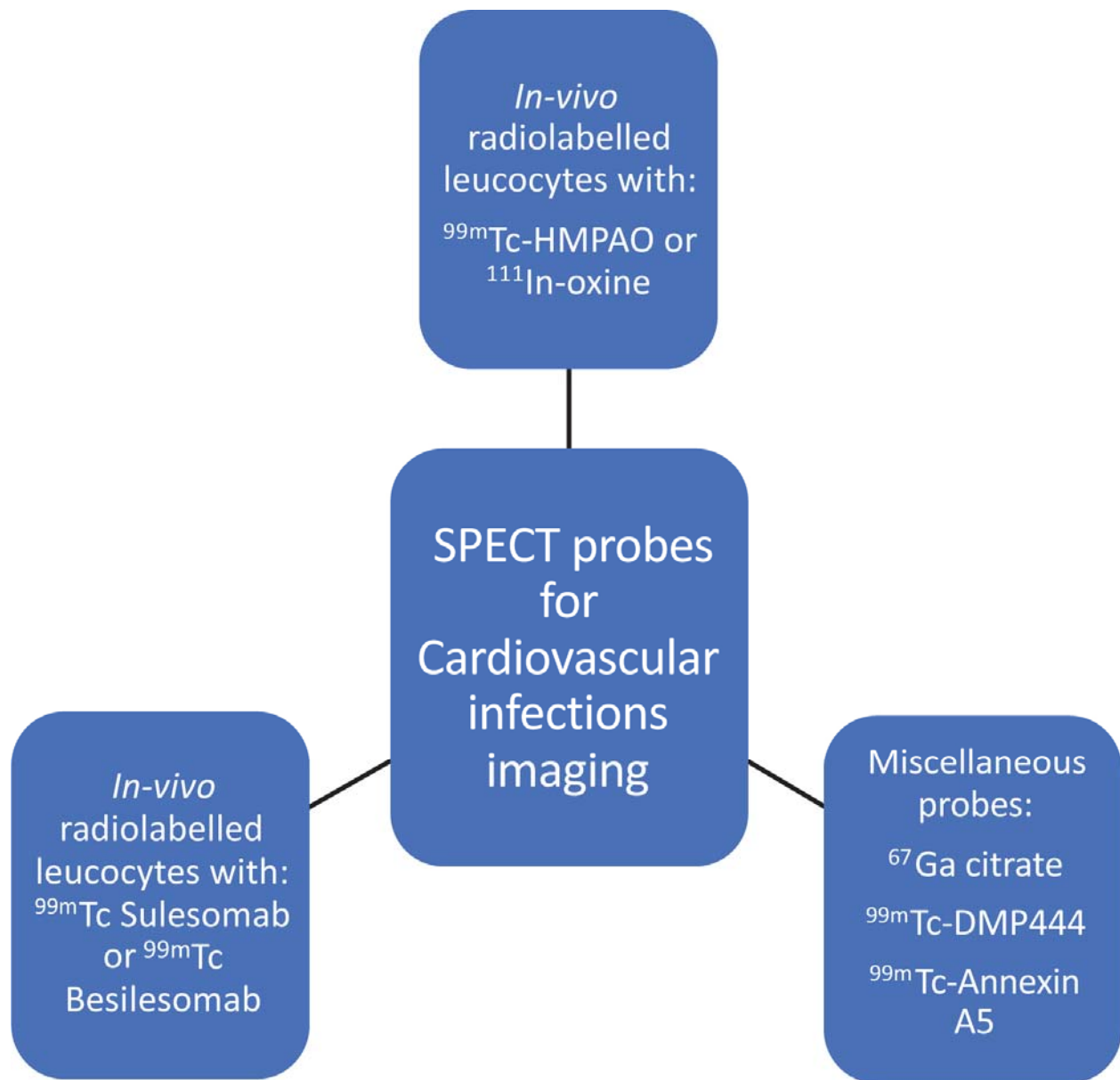
SPECT probes for cardiovascular infection imaging.

Keywords: Infective endocarditis; Prosthetic valve; Cardiac implantable electronic device; left ventricular assist device; Vascular graft infection; Radiolabeled leucocyte scan; SPECT imaging

1. INTRODUCTION

The use of prosthetic devices in the treatment of cardiovascular diseases has been on the increase in recent times [1]. This increase in utilization is in part contributed by an ageing population, expanding indications, and an improvement in devise design and the techniques for their placement. Infection of the native tissue or prosthetic devices of the cardiovascular system is associated with substantial mortality and morbidity as well as a significant drain of the health budget. Infection can involve the various tissues of the cardiovascular system including the pericardium, myocardium, endocardial lining of the native and prosthetic heart materials (such as native valves, prosthetic valves, intra-cardiac patches, and shunts), cardiac implantable electronic devices (CIED), left ventricular assist device (LVAD) and vascular grafts [1].

Infectious endocarditis (IE) remains a fatal disease with rising incidence despite improvement in prevention and management [2]. The reasons for the rising incidence and poor prognosis of IE include an ageing patient population requiring prosthetic valves and CIED, affectation of older people with multiple co-morbidities, changing epidemiological profiles, and challenges with its diagnosis and treatment [2,3]. This, therefore, calls for a concerted effort among different specialist groups in a multidisciplinary team including cardiologist, cardiothoracic surgeon, microbiologist, infectious disease experts and imaging specialist, for the diagnosis and treatment of IE [1,4,5].

The diagnosis of IE is challenging. Clinical presentation is highly variable depending on the virulence of the causative organism and co-morbid conditions. No single clinical sign or symptom, laboratory or imaging finding is diagnostic of IE. Diagnosis is based on the combination of clinical signs and symptoms, imaging findings and positive microbial culture using the modified Duke criteria [4]. Blood culture-negative IE can occur in as many as 21 - 31% of cases [2,4]. Negative blood culture in a patient with IE may be a result of prior antibiotic use, infection due to fastidious bacteria, non-culturable organisms, or non-bacterial etiology. Echocardiography, trans-thoracic echocardiography (TTE) followed by trans-esophageal echocardiography (TEE), is the imaging technique of choice in the initial assessment of patients with suspected IE. It is also useful for monitoring response to therapy and to predict the risk of septic embolism [6]. Three echocardiographic findings (vegetation, abscess or pseudoaneurysm

and new dehiscence of a prosthetic valve) are major criteria in the diagnosis of IE [4]. TTE has sensitivity and specific of 71% and 80%, respectively for the diagnosis of native valve endocarditis [7]. For the diagnosis of vegetations, TTE has a sensitivity of 75%. Sensitivity is reduced with vegetations that are small, of low echogenicity, affecting intracardiac devices or prostheses [8]. TEE has a better sensitivity for the diagnosis of vegetations with a sensitivity of about 85-90%. The sensitivity of TTE and TEE for the diagnosis of abscess is 50% and 90%, respectively [8].

Using the Duke criteria, IE is diagnosed in 80% of patients [9]. Further testing may, therefore, be necessary to diagnose IE in patients with clinical suspicion of IE but inconclusive diagnosis based on Duke criteria. In its latest guidelines on the management of IE, the European Society of Cardiology (ESC) incorporated abnormal tracer accumulation on Florine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) or radiolabeled leucocytes single-photon emission tomography/ computed tomography (SPECT/CT) scan as major criteria in the diagnostic algorithm of patients with prosthetic valve who are suspected to have IE [4]. Since the ESC published its guidelines, a couple of studies have been published demonstrating the utility of radiolabeled leucocytes SPECT/CT in IE associated with prosthetic valves, CIED and LVAD. In this review, we aimed to summarize the diagnostic performance of radiolabeled leucocytes SPECT/CT in the diagnosis of cardiac and vascular infections. Our main focus will be with on IE, CIED and LVAD-related infections, and vascular graft infection (VGI). We will briefly describe the rationale for using radiolabeled leucocytes scintigraphy for infection imaging, discuss the technical issues related to radiolabeling, image acquisition and scan interpretation. We will compare the clinical utility of radiolabeled leucocyte SPECT/CT with ^{18}F-FDG PET/CT. A few other SPECT tracers have been used in the clinical imaging of cardiac and vascular infections. We shall briefly review these tracers as well. Inflammation plays a critical role in the formation, progression and fatal complication of atherosclerotic cardiovascular diseases. Excellent reviews on SPECT tracers for imaging inflammation in atherosclerotic cardiovascular diseases including in people living with human immunodeficiency virus infection have been recently published and will not be discuss in this current review [10,11]. Infection may also involve the pericardium and myocardium. ^{18}F-FDG PET/CT is the most common radionuclide imaging modality for myocarditis and pericarditis [12]. Due to the limited published

data on SPECT imaging of these forms of cardiac infection, it will not be discussed in the current review.

2. RADIOLABELED LEUCOCYTES SPECT/CT IMAGING OF CARDIAC AND VASCULAR INFECTIONS

2.1. Rationale

Pathogenic organisms perturb the internal milieu of the living system. In response to the presence of a microbe, the body's immune system initiates an inflammatory response to curtail the spread and exterminate the offending microbe. Inflammation is a series of vascular, cellular and chemical events mounted by the host system to neutralize a foreign antigen such as seen in microbial agents. The hallmark of the cellular events taking place during inflammation include leucocytes migration towards the site of infection and their migration from the vascular compartment to the tissue space at the site of infection. The use of radiolabeled leucocytes SPECT/CT for infection imaging is premised on this phenomenon of leucocytes migration to the site of suppurative bacterial infection [13]. Radiolabeled leucocytes accumulate at the sites of suppurative infection allowing the ex-vivo detection of the site of infection in SPECT/CT imaging.

2.2. Radiolabeling of leucocytes

Technetium-99m hexamethylpropyleneamine oxime (^{99}Tc-HMPAO) and Indium-111 oxine are commonly used for radiolabeling of leucocytes for SPECT imaging. The energy of the gamma photon emitted by ^{99m}Tc emits is 140 KeV and is most suited for the gamma camera's sodium iodide detector. 370 – 740 MBq of ^{99m}Tc is used for leucocytes labeling. A higher injected activity and a gamma photon energy that is optimum for detection by the gamma camera, makes image quality with ^{99m}Tc-HMPAO labeled leucocytes much better compared with ^{111}In-oxine labeled leucocytes. The other merits of ^{99m}Tc-HMPAO for leucocytes labeling are shorter physical half-life of six hours (compared with 2.8 days for ^{111}In) which confers lower radiation burden to patient and its ready availability from a Molybdenum generator. ^{99m}Tc-HMPAO specifically label to granulocytes which are the predominant inflammatory cells in acute infection while ^{111}In-oxine label to all categories of

leucocytes (granulocytes, monocytes and nonnuclear lymphocytes). In view of this preferential affinity of these radionuclides, it may be safe to speculate that ^{99m}Tc-HMPAO-labeled leucocytes will perform better in the setting of acute infections while ^{111}In-oxine will be useful in acute and chronic phases of infections.

The details for labeling leucocytes with either ^{99m}Tc-HMPAO or ^{111}In-oxine have been published by the European Association of Nuclear Medicine [14,15]. About 50mls of patients own blood is required. A leucocyte count of at least 2×10^8 is required to achieve an optimum labeling efficiency. Acceptable labeling efficiency ranges between 40 and 80%.

2.3.Image acquisition

Leucocytes accumulate progressively over time. Imaging is designed to capture this time-dependent leucocytes migration. Standard imaging acquisition protocol for radiolabeled leucocytes SPECT/CT imaging has been published recently [1,5,16]. Standard imaging protocol recommend planar imaging at 30 minutes, 4-6 hours and 20-24 hours post reinjection of radiolabeled leucocytes. Delayed imaging at 20-24 hours post reinjection should be acquired for longer, corrected for radionuclide decay. Planar imaging should include whole-body imaging and static imaging over the chest region or site of vascular graft. The whole-body imaging offers the opportunity to localize sites of septic emboli or portal of entry of infection. Additional static imaging may be necessary to further elucidate findings on whole-body imaging. SPECT/CT imaging is performed (over the chest region in cardiac infections or over the region of vascular graft in suspected vascular graft infection) at 4-6 hours and 24 hours post reinjection. The better contrast resolution afforded by SPECT imaging is useful in delineating area of radiolabeled leucocyte accumulation at site of infection from an overlying area of physiologic radiolabeled leucocytes accumulation such as the sternum, ribs or vertebrae. Addition of low-dose CT to SPECT imaging is useful for attenuation correction and more importantly for anatomic co-localization of the site of infection. Defining the extent of infection with CT may help in guiding therapeutic intervention.

2.4.Image interpretation

Image processing and interpretation should be done on a standard nuclear medicine workstation. Attenuation corrected and non-attenuation corrected SPECT/CT images must be reviewed especially since attenuation correction may introduce artifact into images in patients with prosthetic materials which may be mis-interpreted as abnormal increased tracer accumulation.

Infection appears as single or multiple foci of radiolabeled leucocytes accumulation seen on early images (30 minutes or 4-6 hour images) with increasing intensity or changing spatial distribution on the delayed imaging (20 – 24 hour images) [16]. This phenomenon of increase in intensity of abnormal radiolabeled leucocytes accumulation at the site of infection reflects the time-dependent leucocytes migration.

During image interpretation, care must be taken to avoid potential pitfalls and artifacts [17]. The early images are particularly useful for quality control of the leucocytes labeling process. High blood pool background activity suggests radiolabeling of red cells. This limits signal-to-noise ratio and may impair visualization of subtle foci of abnormal radiolabeled leucocytes accumulation. The spleen shows very intense normal accumulation of tracer on a radiolabeled leucocytes scintigraphy. Intense liver uptake greater than the liver suggests damage to the leucocytes prior to reinjection [14,15]. There is a normal initial diffuse pulmonary activity that clears promptly with time. This has been attributed to leucocytes activation as they come in contact with the glass wares during radiolabeling making them sluggish as they traverse the pulmonary micro-circulation. Persistence of diffuse pulmonary activity may suggest damage to the leucocytes prior to reinjection [14,15].

Whole-body images should be assessed for foci of septic emboli or portal of entry of infection. While most sites of infection outside of the area of primary infection in the heart or heart-associated devices will appear as foci on increased radiolabeled leucocytes accumulation, septic emboli in organs like spleen which shows intense physiologic tracer accumulation may appear photopenic. The spine is a common area of septic embolus in patients with IE. Spinal infection has a variable appearance on radiolabeled leucocyte scintigraphy (may appear normal, photopenic or with intense accumulation) [18]. This pattern must be borne in mind when reviewing the spine for septic emboli.

3. RADIOLABELED LEUCOCYTES SPECT/CT IMAGING OF INFECTIVE ENDOCARDITIS

IE frequently affects old frail patients with multiple co-morbidities [2]. Prompt diagnosis for early institution of treatment is necessary to limit morbidity and mortality. Diagnosis of IE may remain inconclusive after clinical evaluation, blood culture and echocardiography (possible IE). Additional imaging may, therefore, be necessary for further evaluation of these patients in order to confirm or exclude IE.

3.1.Prosthetic valve endocarditis
Prosthetic valve-related endocarditis (PVE) is a rising cause of cardiac infection. It accounted for 30% of all cases of IE in the recent report on the EURO-ENDO registry [2], compared with 26% in the Euro Heart survey of 2005 [19], or 21% reported in the International Collaboration on Endocarditis Prospected Cohort Study of 2009 [20]. PVIE is very difficult to diagnose on both TTE and TEE for reasons including (1) poor visualization of vegetation or abscess due to the presence of the prosthetic material, (2) difficulty in differentiating thrombus or strand from a vegetation, (3) difficulty in differentiating bioprosthetic degeneration and infective lesions, and (4) post-operative changes, such as thickening of the aortic root after a Bentall procedures which may mimic abscess [8]. These shortcomings of echocardiography have made additional advanced imaging necessary for the diagnosis of PVE.

Studies have shown excellent performance of radiolabeled leucocytes SPECT/CT imaging in PVE. Sensitivity and specificity of radiolabeled leucocytes SPECT/CT imaging for IE range between 64-91%, and 87-100%, respectively [21-25]. In a group of 42 patients with suspected PVE but inconclusive echocardiographic findings, Hyafil et al. found radiolabeled leucocytes scintigraphy to be a useful guide for management [22]. Intense tracer accumulation at the site of infection was 100% sensitive for the presence of abscess requiring surgical intervention (figure 1). Patients with mild tracer accumulation at the site of infection did well on antibiotic therapy without the need for surgery (figure 2). None of the patients with negative finding on radiolabeled leucocytes imaging had abscess giving a 100%

negative predictive value [22]. In a follow-up study by the same group, radiolabeled leucocytes scintigraphy showed sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 64%, 100%, 100%, 81%, and 86%, respectively for the diagnosis of PVE [23]. Other studies evaluating the diagnostic utility of radiolabeled leucocytes SPECT/CT in patients with IE have included mixed group of patients including those with native and prosthetic valve-associated IE [21,26]. A recent systematic review of studies with study population that included at least 50% of patients with prosthetic valves evaluated with radiolabeled leucocytes scintigraphy for IE reported sensitivity of 64-90%, specificity of 36-100%, positive predictive value of 85-100%, and negative predictive value of 47-81% [27]. For the diagnosis of abscess, radiolabeled leucocyte scintigraphy had a sensitivity, specificity, positive predictive value, and a negative predictive value of 83-100%, 78-87%, 43-71%, and 93-100%, respectively [27].

Infection by organisms that form biofilm such as *Candida species*, *Enterococcal species* and *Staphylococcus epidermidis* have been found to be associated with false negative finding on radiolabeled leucocytes scintigraphy [21]. Biofilms are formed when microbes lived in aggregates under the protective cover of secreted extracellular polymeric substance [28]. Biofilms offer the organism protection against antibiotic penetration leading to treatment failure and to attack by the host immune system [29]. Radiolabeled leucocytes may similarly fail to concentrate at the site infection due to protective effect of the biofilm causing false negative finding. Similarly, microbes that do not stimulate significant host reaction including chemotaxis of endogenous leucocytes may produce false negative finding on radiolabeled leucocytes imaging. The gamma camera has a limited resolution hence small infected vegetations may be missed on radiolabeled leucocytes SPECT/CT imaging.
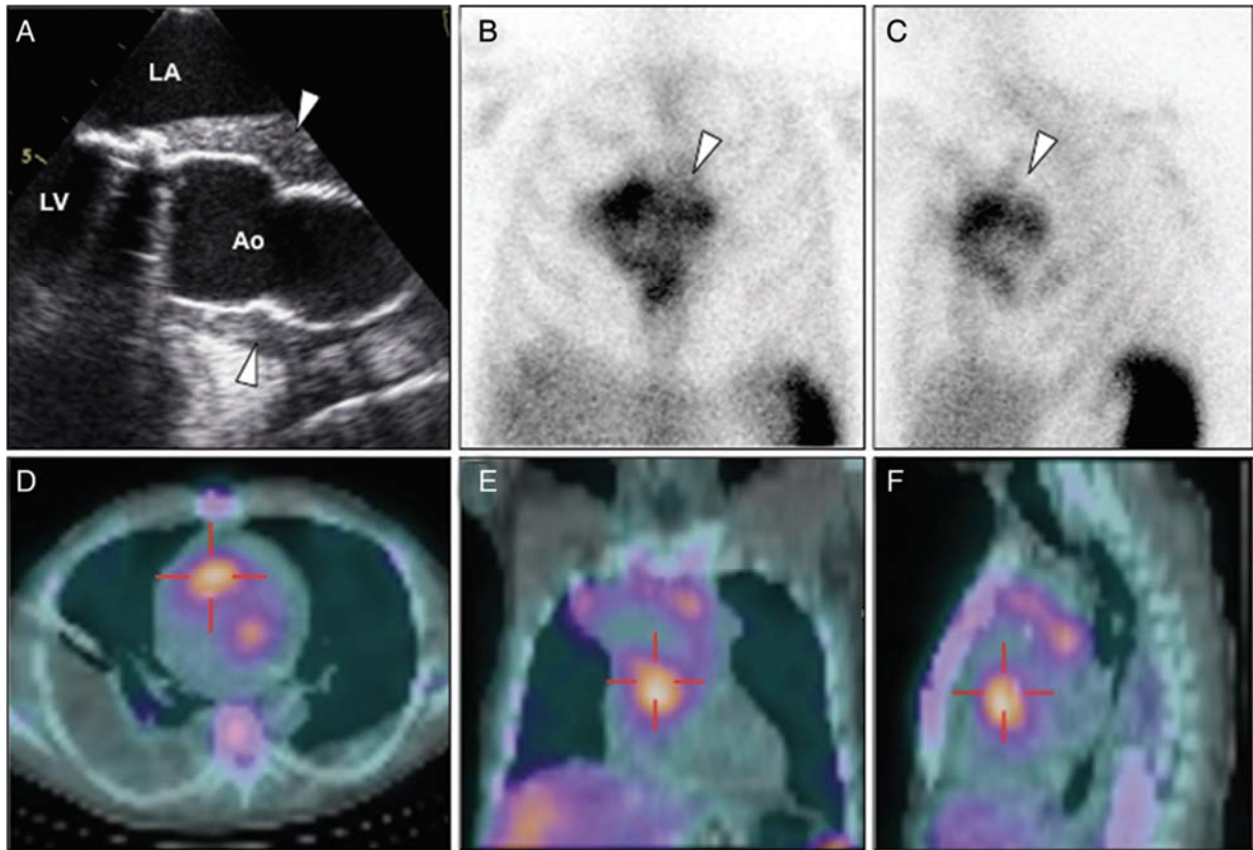
Figure 1: A 50-year-old admitted with pleuro-pneumonia and meningitis associated with pneumococcal septicemia. The patient had a history of bicuspid aortic valve with severe aortic stenosis and aneurysm of the ascending aorta for which had aortic valve replacement with mechanical prosthesis and replacement of ascending aorta 5 years earlier. TEE showed a 20mm heterogeneous thickening around the aortic tube (A, white arrowheads). Diffuse accumulation of radiolabeled leucocyte along the aortic tube was detected in the cardiac area (white arrowheads) on anterior (B) and oblique (C) planar scintigraphic acquisitions and co-localized with the aortic tube (red crosses) on axial (D), coronal (E), and sagittal (F) views of reconstructed fused SPECT/CT images. Based on the results of cardiac echocardiography, radiolabeled leucocyte scintigraphy, and the persistence of biological inflammatory syndrome after the initiation of antibiotic treatment, the patient underwent redo surgery with the excision of all the material. Intra-operative analysis confirmed the presence of pus around the aortic tube and partial dehiscence of the proximal anastomosis of the tube. Adapted with permission from Hyafil et al. [22].
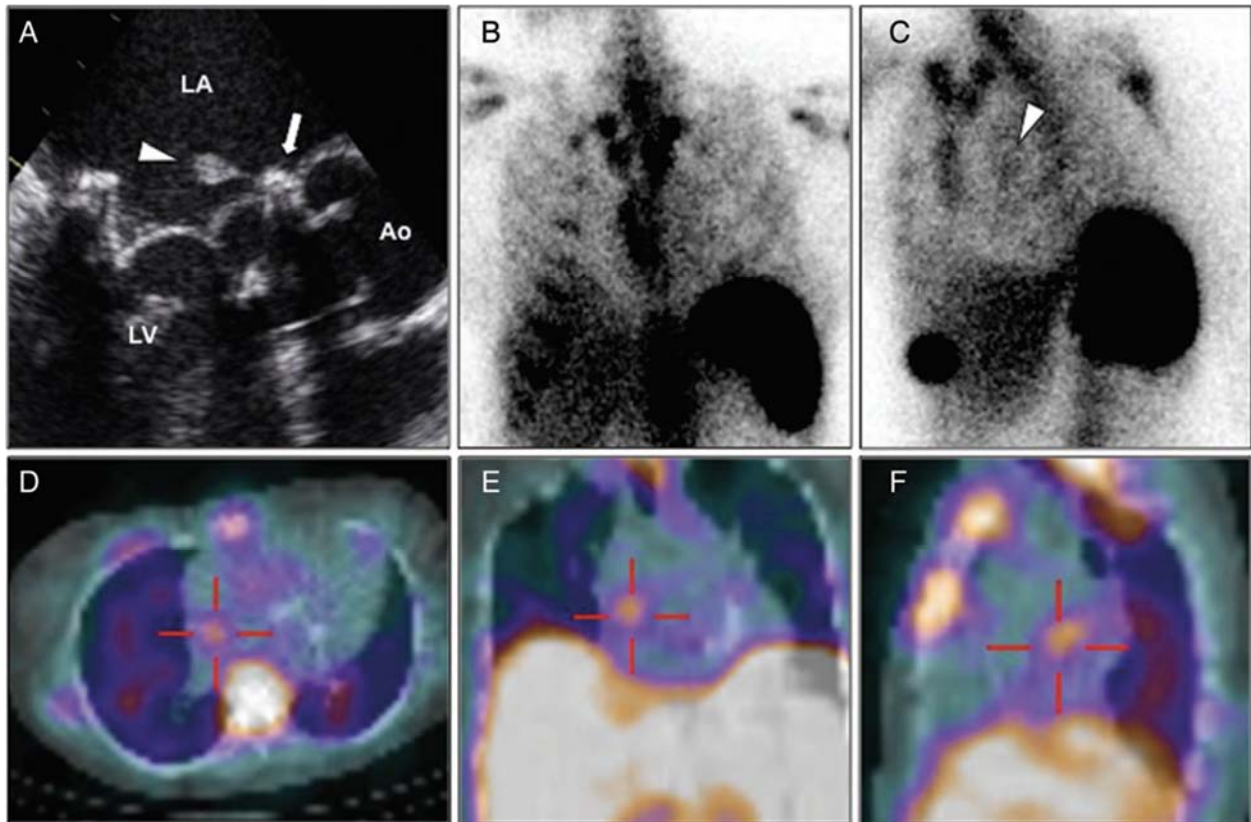
Figure 2: A 28-year-old woman was admitted for massive mitral regurgitation caused by an acute endocarditis and underwent urgent replacement of the mitral valve with biological prosthesis. Antibiotic therapy and anticoagulation were started immediately after the intervention. Two weeks later, a 13-mm-large mobile mass attached to the mitral annulus associated with a thickening of the aorto–mitral trigone (A, white arrowheads) was detected by TEE. Only mild and focal accumulation of radiolabeled leucocytes was detected in cardiac area (white arrowheads) on anterior (B) and oblique (C) planar scintigraphic acquisitions and co-localized with the cardiac area (red crosses) on axial (D), coronal (E), and sagittal (F) views of reconstructed fused SPECT/CT images. Antibiotic and anticoagulation treatments were pursued. Two weeks later, the mass was not present anymore by TEE. The patient remained asymptomatic and did not present any recurrent endocarditis 36 months later. Adapted with permission from Hyafil et al. [22].

Newer cardiocentric cameras with semiconductor cadmium-zinc-telluride (CZT) detectors allows for faster image acquisition, have improved energy response reducing the scatter contribution to measured data, and have superior intrinsic spatial resolution compared with Anger cameras [30]. CZT detectors directly converts radiation to electric signal without the need for photomultiplier tubes improving the camera sensitivity signal. The improved performance of the CZT cameras has been explored for IE imaging. Caobelli et al. explored dual-isotope imaging with ^{111}In-leucocyte and ^{99m}Tc-Sestamibi using a CZT camera for combined infection and myocardial perfusion imaging in patients with possible IE by Duke criteria [24]. At 24 hours following re-injection of radiolabeled leucocytes, all patients had

whole-body planar followed by SPECT/CT imaging using a convention SPECT/CT camera. Thereafter, ^{99m}Tc-sestamibi was administered followed by dual-isotope imaging on a CZT camera. CZT imaging had the best sensitivity and specificity of 83% and 95%, respectively compared with planar (21% and 30%) or conventional SPECT/CT (58% and 70%) imaging [24]. Dual isotope imaging was possible with the CZT camera due to its improved energy resolution preventing cross-talk between the photons from the two radionuclides. The diagnostic performance of radiolabeled leucocytes scintigraphy in patients with suspected IE is summarized in table 1.

Table 1: Diagnostic performance of radiolabeled leucocytes scintigraphy in patients with suspected infective endocarditis.

Study	Population	Sensitivity (%)	Specificity (%)	PPV (%)	NNP (%)	Accuracy (%)
Erba et al. 2012 [21]	131 patients with suspected IE	90.0	100.0	100.0	94.0	NR
Rouzet et al. 2014 [23]	39 patients with suspected PVE	64.0	100.0	100.0	81.0	86.0
Caobelli et al. 2017 [24]	34 patients with possible IE according to modified Duke criteria	83.0	95.0	NP	NR	NR
Holcman et al. 2019 [26]	40 patients with suspected IE	93.0	88.0	81.0	96.0	90.0

PPV: Positive Predictive Value; **NNP**: Negative Predictive Value; **IE**: Infective Endocarditis; **PVE**: Prosthetic Valve Endocarditis; **NP**: Not Reported.

3.2. Native Valve Endocarditis

Native valve endocarditis (NVE) present much less diagnostic conundrum compared with PVE. This is due to the excellent diagnostic performance of echocardiography in NVE. Additional imaging beyond echocardiography is, therefore, less requested in the diagnostic work-up of patients with suspected NVE. Clinical experience with radiolabeled leucocytes imaging of NVE is limited. Studies that included a mixed population of patients with suspected NVE and PVE show sensitivity and specificity of 83-90% and 95%, respectively [31].

4. RADIOLABELED LEUCOCYTE SPECT/CT IMAGING OF CARDIAC IMPLANTABLE ELECTRONIC DEVICE INFECTION

Implantation of cardiac implantable electronic devices (CIED) have seen a dramatic increase in the last decade, a result of several reasons including expanding indications, improvement in the performance of these devices with survival advantage, and ageing of the population [32,33]. CIED is an umbrella term for cardiac electrophysiological devices including permanent pacemakers (PM), implantable cardioverter-defibrillators (ICD) and cardiac resynchronization devices. Infection is one of the most serious complications of CIED implantation. Despite improvement in device design, surgical improvement and other preventive measures, CIED infection is on the increase with an attendant high morbidity, mortality and cost [34-37].

There are different types of CIED-related infections including:

- Superficial incisional infection which is infection that involves only the skin and the subcutaneous tissue without extension to the generator pocket. Treatment of superficial infection involves local wound care and antibiotic therapy, and may not require CIED system extraction [38].

- Pocket infection which is defined as the infection limited to the generator pocket. Pocket infection is characterized by local signs and symptoms of inflammation such as erythema, warmth, and fluctuant mas. Other features of pocket infection include deformation of the pocket and adherence or threatened erosion of the device generator [34]. Pocket infection may extend to the CIED leads and endocardium causing lead infections, CIED systemic infection and infective endocarditis.

- CIED systemic infection and infective endocarditis may occur in isolation without associated pocket infection. This form of CIED presents diagnostic challenges as symptoms may be non-specific and may present long after system implantation. Septic embolus may be the presenting symptom.

The diagnosis of CIED infection is based on echocardiography and blood culture using the ESC 2015 criteria [4]. This diagnostic algorithm was designed for IE and may be inadequate for CIED infection. The 2019 International CIED Infection Criteria was developed to cater

for this need [34]. The 2019 international CIED criteria recommends radiolabeled leucocytes scan or ^{18}F-FDG PET/CT for the evaluation of patients with clinical suspicion of CIED infection with or without clinical generator pocket infection to determine extent of the disease, portal of entry and sites of septic emboli [34]. Tracer uptake on either of these two radionuclide imaging techniques at the site of generator pocket, along the leads or valve site is considered a major criterion for the diagnosis of CIED infection [34].

Erba and colleagues were among the workers to provide the earliest evidence supporting the use of radiolabeled leucocytes scintigraphy in patients with suspected CIED infection [39]. In a group of 63 patients, ^{99m}Tc-HMPAO-labeled leucocyte SPECT/CT imaging performed better than echocardiography with a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 93.7%, 100%, 100%, 93.9%, and 96.8%, respectively for the diagnosis of CIED infection. Combined SPECT/CT imaging had a superior diagnostic performance compared with planar or SPECT imaging alone. In 7 of 9 patients who had repeat radiolabeled leucocytes scintigraphy after six to nine months of antibiotic therapy, earlier identified area of abnormal radiolabeled leucocytes accumulation had resolved and antibiotic treatment was stopped based on this finding. The remaining two patients with residual radiolabeled leucocytes accumulation at the sites of infection had their antibiotic treatment prolonged, and treatment was stopped when findings normalized on the second follow-up imaging. In this study, the author showed evidence supporting the utility of radiolabeled leucocytes scintigraphy for the diagnosis of CIED infection, determine the extent of disease and guide the duration of antibiotic treatment [39]. The diagnostic performance of radiolabeled leucocytes scintigraphy in the evaluation of patients with suspected CIED infections is summarized in table 2.

Table 2: Diagnostic performance of radiolabeled leucocyte scintigraphy in patients with suspected cardiac implantable electronic device infection

Study	Population	Sensitivity (%)	Specificity (%)	PPV (%)	NNP (%)	Accuracy (%)
Erba et al. 2013 [39]	63 patients with suspected device-related infections	93.7	100	100	93.9	96.8
Małecka et al. 2019 [40]	40 patients with suspected lead-dependent IE	73.7	81.0	77.8	77.3	77.5
Calais et al. 2019 [41]	48 patients with suspected CIED-related infection	60.0	100.0	100.0	84.6	80.0

PPV: Positive Predictive Value; **NNP**: Negative Predictive Value; **IE**: Infective Endocarditis

CIED infection affecting the intravascular and intracardiac leads is the most difficult to diagnose and the subtype of CIED infection associated with the highest mortality and morbidity [34]. A recent study explored the diagnostic performance of radiolabeled leucocytes scintigraphy in the diagnosis of lead-dependent infective endocarditis (LDIE) in patients with CIED [40]. Radiolabeled leucocytes SPECT/CT imaging had a sensitivity, specificity, positive predictive value, negative predictive, and accuracy of 73.7%, 81.0%, 77.8%, 77.3%, and 77.5%, respectively. Five patients who were on antibiotic therapy at the time of imaging had false negative image findings. When these five patients were excluded from analysis, the respective sensitivity, specificity, positive predictive value, negative predictive value and accuracy improved to 100.0%, 81.0%, 77.8%, 100%, and 88.6%. In this study, four of 21 patients without LDIE had positive imaging finding (false positive) [40]. This is rather an unusual finding since radiolabeled leucocytes scintigraphy is known to have a very high specificity and many studies have reported no case of false positivity in the evaluation of patients with different types of cardiac infections. The four cases with false positive imaging finding may be related to non-uniformity in the tracer used in the study where a quarter of the patients where imaged with an in vivo leucocytes technique using ^{99m}Tc-Besilesomab [40].

Patients are often commenced on empirical antibiotic treatment before or during diagnostic work-up for CIED infection. Antibiotic treatment may reduce the sensitivity of radiolabeled

leucocytes scintigraphy [39]. Calais et al. recently reported the outcome of their head-to-head comparison of ^{18}F-FDG PET/CT and radiolabeled leucocytes scintigraphy in patients suspected with chronic CIED infection [41]. Two-third of the study patients were on antibiotic for an average of about 36 days before radiolabeled leucocytes scintigraphy. The respective sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of radiolabeled leucocytes scintigraphy for CIED infection in this patient population was 60.0%, 100%, 100%, 84.6%, and 80%. ^{18}F-FDG PET/CT had a better sensitivity (80%) but lower specificity (90.9%) compared with radiolabeled leucocytes scintigraphy. When both radionuclide techniques were combined with Duke criteria for the diagnosis of chronic CIED infection, the respective sensitivity, specificity, positive predictive value, negative predictive value, and accuracy improved to 100%, 84.9%, 75.0%, 100%, and 92%. The duration of antibiotic treatment is important since all 5 patients who received antibiotic for less than nine days had true positive imaging finding [41]. Prolonged antibiotic is likely to cause reduced chemotaxis of leucocytes to the site of infection either due to sterilization of the infection site or adaption by the microbes such as formation of protective biofilm.

5. RADIOLABELED LEUCOCYTE SPECT/CT IMAGING OF LEFT VENTRICULAR ASSIST DEVICE INFECTIONS

Communicable and non-communicable diseases affecting the heart results in heart failure in the long run. This makes heart failure a major cause of morbidity and mortality and a condition with a rising prevalence and incidence among the adult population [42]. There is insufficient donor organ to cater for patients with heart failure refractory to medical therapy. Left ventricular assist device (LVAD) has come to fill this void which is increasingly use as a destination therapy or a bridge-to-heart transplantation intervention [43]. Like most implanted device, LVAD is susceptible to infection. Infection is common and has a rising incidence among patients with LVAD [43,44]. LVAD consists of a percutaneous driveline that carries electrical signal from the batteries to the implanted pump which connects to the cannula. The skin piecing for the driveline, therefore, serves as an ever-present entry point for infection which may spread via the subcutaneous tunnel to the implanted pump and

cannula. Classification and diagnostic criteria of LVAD infection has been provided by the International Society for Heart and Lung Transplantation [45]. Initial evaluation is with blood culture and echocardiography. Radionuclide imaging may be used in patients in whom suspicion of infection remains despite negative echocardiography.

An early preliminary study by Litzler and colleagues showed an excellent diagnostic performance [46]. Infection involved the percutaneous site of the driveline in the subcutaneous tissue in all patients with LVAD infection. Radiolabeled leucocytes scintigraphy was true positive in all patients with LVAD infections and true negative in those without. Five patients had follow-up imaging for therapy response assessment. Radiolabeled leucocyte scintigraphy was accurate in identifying three patients in whom infection had resolved and two patients with residual infection [46]. This study provided evidence supporting the diagnostic utility of radiolabeled leucocytes scintigraphy in the diagnosis of LVAD infection and in assessing response to antibiotic therapy.

A recent study has provided more evidence supporting the diagnostic utility of radiolabeled leucocytes scintigraphy in patients with LVAD infection [47]. In a group of 22 patients imaged with 24 scans, radiolabeled leucocytes scintigraphy had a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 71.4%, 100%, 100%, 33.3%, and 75%, respectively. No case of false positive scan was reported. False negative scans were found in seven patients, five of whom were already on antibiotic treatment at the time of imaging [47]. Figure 3 shows the images of a patient with infected localized to the region of the outflow cannula of a LVAD.
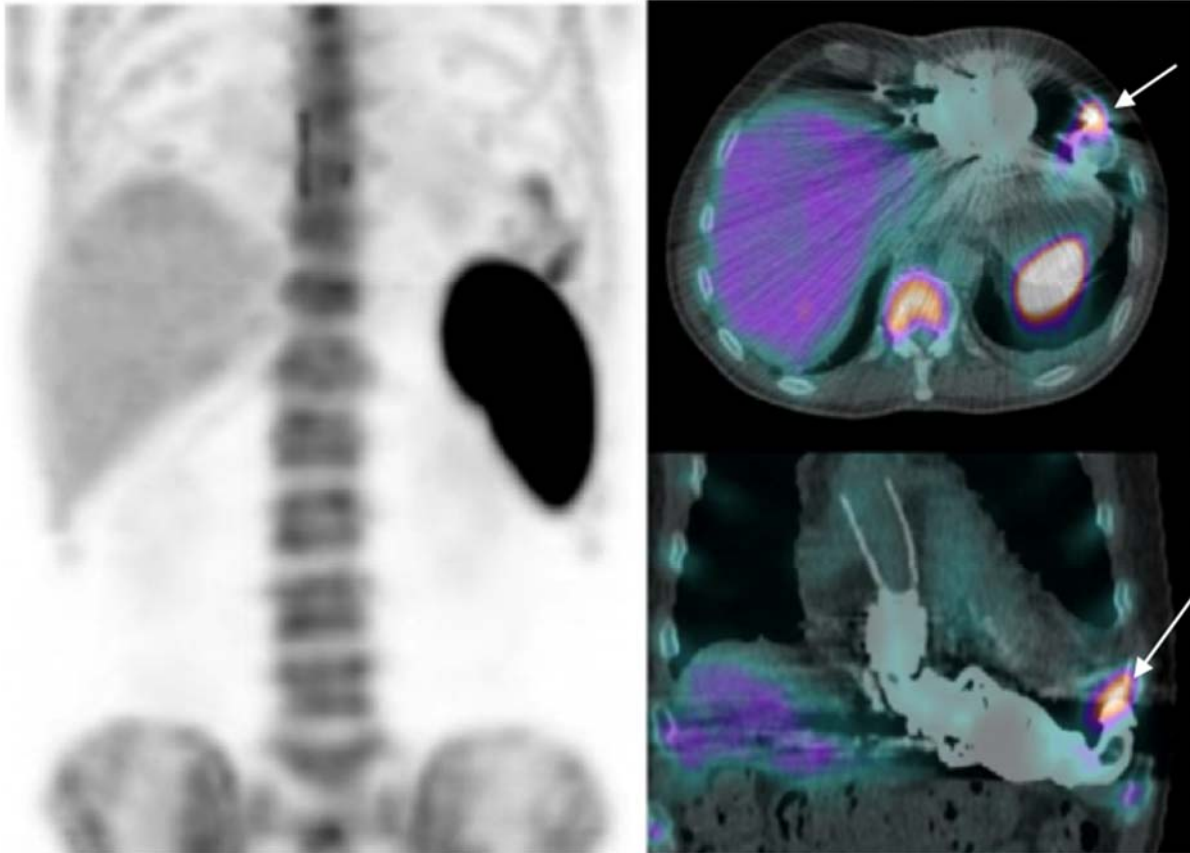
Figure 3: A 58-year-old male with Heartmate II-type LVAD in situ. He was admitted with purulent discharge at the driveline exit site associated with abdominal pain and fever. Culture of pus and blood showed no microbial growth. Radiolabeled leucocytes scintigraphy showed uptake on outflow canula (white arrows, axial and coronal views). These findings were visible on both corrected and uncorrected for attenuation acquisitions. The patient had a heart transplant 2 months after the onset of symptoms. The culture of the Heartmate II device was positive to *Propionibacterium acnes*. Adapted with permission from de Vaugelade et al. [47].

6. RADIOLABELED LEUCOCYTE SPECT/CT IMAGING FOR WORK-UP OF SEPTIC EMBOLI

IE of heart native structures and implanted prosthetic devices (valves, CIED and VAD) present a peculiar risk of systemic embolism. The pulmonary and systemic circulation serve as suitable conduits for the dissemination of infected vegetations from the heart to distant sites. The lungs are the commonest destination of septic emboli arising from the right-sided IE while the brain and spleen are the most frequent sites of emboli in left-sided IE [4]. Other common sites of systemic embolization are the bones and kidneys. Embolization is seen in up to 80% of patients with IE, and contribute significantly to morbidity and mortality [2,48]. Vegetation size greater than 10mm is a very strong risk factor for embolization [48]. A

significant proportion of systemic embolization may be asymptomatic. Unidentified site of embolization that is not optimally treated is a frequent cause of recurrent IE. It is, therefore, important to search for systemic embolization in the evaluation of patients suspected with IE. In the 2015 ESC guidelines on IE, presence of asymptomatic embolic event is considered a minor criterion in the diagnostic algorithm for IE [4]. The American Heart Association considers symptomatic embolic event as a minor criterion in their diagnostic algorithm for IE [49].

Radiolabeled leucocytes scintigraphy is a whole-body imaging that affords the opportunity to localize sites of asymptomatic emboli event. Sites of septic embolization are commonly seen as foci of increased radiolabeled leucocytes accumulation. An exception to this is when embolization occurs in organs such as spleen with high physiologic radiolabeled leucocytes uptake where it is seen as area of photopenia. A Danish group recently performed intra-individual comparison of ^{18}F-FDG PET/CT and ^{99m}Tc-HMPAO-labeled leucocytes for the detection of extra-cardiac sites of infection in a mixed population of patients with IE (valvular and device-related IE) [50]. ^{18}F-FDG PET/CT identified more lesions (91 lesions in 32 positive scans) compared with radiolabeled leucocytes scintigraphy (37 lesions in 24 positive scans) [50]. Apart from dental region where radiolabeled leucocyte scintigraphy identified more lesions than ^{18}F-FDG PET/CT, the latter imaging test identified more lesions in every other region of the body with positive finding. ^{18}F-FDG PET/CT is a highly sensitive modality that is able to detect inflammation and infection. It is unknown the actual relationship of the positive findings in this study to infection. For example, seven patients had positive ^{18}F-FDG PET/CT finding in the lymph nodes compared with no patient with positive lymph node finding on radiolabeled leucocytes scintigraphy [50]. This may suggest reactive lymphadenopathy in the lymph node basin draining the site of an infection rather than actual suppurative lymphadenitis.

Radiolabeled leucocytes scintigraphy has been shown to be useful in identifying extra-cardiac sites of infection. Among 131 patients with suspected NVE or PVE (97 of whom had positive scan findings), septic emboli were identified in 41% of them [21]. Three cases that were wrongly classified as septic embolism were active vasculitis involving the aortic arch,

prostate cancer metastasis to the spine and a case of vertebral collapse. Eight cases of extra-cardiac infection that were missed were found in the kidney (n=3) and brain (n=5) [21]. In the series by Holcman and colleagues, septic emboli were detected in 47.5% of patients [26]. In the majority of patients with extra-cardiac involvement, the foci were found in the gastro-intestinal tract (47.3%). This finding must be considered bearing in mind the gastrointestinal excretion of free radiotracer in ^{99m}Tc-HMPAO-labeled leucocytes scintigraphy. Other sites of extra-cardiac involvement were bones (15.8%), lungs (10.5%), and urinary tract (5.3%) [26].

Radiolabeled leucocyte scintigraphy is similarly able to detect septic embolism in patients with CIED infection. In a series of 63 patients with suspected CIED infection (32 of whom had definite CIED infection), radiolabeled leucocytes scintigraphy identified 38 extra-cardiac foci of infection [39]. Sites of septic embolism included bones (n=6), vascular graft (n=4), lungs (n=4), and spleen (n=1). Two cases of septic embolism causing ophthalmitis and cerebral infection were missed on radiolabeled leucocytes scintigraphy [39]. In another series of 48 patients with suspected CIED infection imaged with both ^{18}F-FDG PET/CT and radiolabeled leucocyte SPECT/CT, ^{18}F-FDG PET/CT identified septic embolism in 12 patients involving the spine (n=5), spleen (n=1), joint space (n=2), aorta (n=1), aortic prosthesis (n=1), and lungs (n=6) [41]. None of these extra-cardiac sites were visualized on radiolabeled leucocytes SPECT/CT imaging. This disparity between the two imaging modalities may be related to the prolonged antibiotic therapy with about two-thirds of the study population on antibiotic for an average of 36 days before radiolabeled leucocytes scan [41]. Antibiotic therapy has been reported to have less impact on the diagnostic performance of ^{18}F-FDG PET/CT in infection imaging [51].

7. OTHER SPECT TRACERS FOR CARDIAC INFECTION IMAGING

Radiolabeled leucocytes scintigraphy is, by far, the most common SPECT technique for cardiac infection imaging. Prior to the widespread availability of PET/CT scanners for clinical imaging, other SPECT tracers had been used. Also, the technical demands of in vitro leucocytes labeling has popularized techniques exploiting in vivo leucocytes labeling for

infection imaging. Clinical experience regarding in vivo leucocyte labeling for cardiac infection imaging is, however, limited.

7.1.Gallium-67 Citrate SPECT/CT imaging of cardiac infections

In the period prior to the widespread availability of PET/CT scanners, several cases of Gallium-67 (^{67}Ga) citrate imaging of IE were reported [52-55]. A few more cases have been reported in recent years [56,57]. Beyond these case reports and case series, a recent study reported the diagnostic performance of ^{67}Ga SPECT/CT in 36 patients with suspected LVAD infection [58]. ^{67}Ga SPECT/CT was 61% sensitive for driveline infection [58]. This performance is inferior compared with results from ^{18}F-FDG PET/CT or radiolabeled leucocytes SPECT/CT imaging. Beyond this inferior diagnostic performance, there are several other factors that will militate against widespread use of ^{67}Ga SPECT/CT for cardiac infection imaging. These factors include: (1) relatively poor image quality resulting from the low abundance and energy of the four photopeaks of ^{67}Ga photons, (2) the long physical half-life of the radionuclide constitute significant radiation burden to the patients, (3) imaging is done over 48 to 72 hours, and (4) ^{67}Ga is cyclotron-produced which makes it expensive and not readily available.

Gallium-68 citrate (^{68}Ga-citrate), a congener of ^{67}Ga, is a positron emitter which is available from a generator (Germanium-68/Gallium-68) and can be used for PET imaging of inflammation and infection [59,60]. It does not suffer from any of the limitations associated with ^{67}Ga. ^{68}Ga-citrate for PET imaging has a high blood pool background activity and is unlikely to be a successful tracer for cardiovascular infection imaging [61].

7.2.Tracers for in vivo leucocyte labelling for cardiac infection imaging

In vitro labelling of leucocytes with ^{99m}Tc-HMPAO or ^{111}In-oxine is laborious, time-consuming and requires skilled technicians. The technician is exposed to blood with an attendant risk of contracting blood-borne infection. Monoclonal antibody and antibody fragments have been developed for in vivo labeling of leucocytes obviating the need for blood collection and separation of blood components. Sulesomab is a monoclonal murine IgG antibody Fab' fragment that has affinity for a 42 kDa glycoprotein (nonspecific cross-

reacting antigen 90, NCA-90) expressed on granulocytes and their precursors in the bone marrow [62]. Radiolabeled sulesomab with [99mTc] (LeucoScan®) has been used in clinical imaging of infection especially for the evaluation of infected peripheral limb prostheses mostly in Europe [63,64]. Clinical experience on the use of [99mTc]-sulesomab SPECT for imaging IE is limited [65, 66]. In a small series of patients with suspected IE, [99mTc]-sulesomab SPECT had a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 66%, 79%, 26%, 87%, and 78%, respectively [66].

Besilesomab is a monoclonal IgG1 antibody. Like sulesomab, it binds to NCA-95 expressed on granulocytes and their bone marrow precursor. Being a whole antibody, it has a slower biokinetics compared with sulesomab. About 10% of [99mTc]-labeled besilesomab (scintimum®) is bound to neutrophils while about 20% circulates free in plasma localizing to the site of infection by nonspecific mechanisms [67]. A risk of human antimurine antibody response exists with repeated re-injection of [99mTc]-besilesomab [68]. [99mTc]-besilesomab was approved by the European Medicines Agency for the evaluation of osteomyelitis of peripheral bones in adults and has been shown to have similar diagnostic performance as radiolabeled leucocyte scintigraphy for this indication [68]. [99mTc]-besilesomab SPECT has been explored for imaging subactute endocarditis. In a group of 72 patients with suspected subacute endocarditis, 33 of whom were proven to have the infection, [99mTc]-besilesomab SPECT had a sensitivity of 79% and a specificity of 82% [69]. Since the results of this study was reported, there has been a significant improvement in SPECT camera design. CT co-localization is especially important since blood-pool activity of [99mTc]-sulesomab is usually high on the early images obtained at 4 hours post-tracer injection. A recent study utilizing SPECT/CT imaging of [99mTc]-besilesomab in patients with suspected IE showed a better sensitivity (86-100%) and specificity (100%) [70].

7.3.Miscellaneous probes for SPECT imaging of cardiac infections
Other targets within IE lesion have been explored in clinical and preclinical imaging of IE. Annexin A5 is an endogenous protein that has high affinity for phosphatidylserine (PS). PS is expressed by apoptotic cells and its expression has been explored for the identification of dying cells as a measure of response to oncologic therapies [71]. [99mTc]-Annexin A5 has

been used image apoptosis in different cardiovascular conditions including atherosclerotic vascular disease and myocardial ischemia reperfusion injury [72,73]. In a preclinical model, Benali and colleagues demonstrated localization of ^{99}Tc-HYNIC-Annexin and its congener, ^{99m}Tc-Annexin A5-128, to IE lesions seen on SPECT/CT imaging and on autoradiography. On autoradiography, tracer uptake was localized to the periphery of vegetations which corresponds to the site of vegetation growth where continued platelet recruitment was occurring. There is prompt blood clearance of tracer (<2% of injected activity of ^{99m}Tc-Annexin A5-128 remained in the blood pool at 1 hr post tracer injection) with possibility for early imaging.

Early endocarditis lesion consists mainly of platelets enmeshed in fibrin [74]. Activated platelets express glycoprotein IIb/IIIa, necessary for progression of vegetation. ^{99m}Tc-DMP444 is a molecular probe targeting glycoprotein IIb/IIIa which has been shown to localized to sites of endocarditis in a preclinical model [75]. In a follow-up human study, patients tolerated the tracer with no adverse effect [76]. ^{99m}Tc-DMP444 SPECT imaging correctly identified five out of nine patients with IE according to Duke criteria (8 definite IE and one possible IE). Imaging was true negative in seven patients without IE [76].

8. RADIOLABELED LEUCOCYTE SPECT/CT IMAGING OF VASCULAR GRAFT INFECTION

Infection is a rare but serious complication of vascular graft placement [77,78]. Failure of prompt diagnosis can lead to severe complications including fistula, fatal bleeding and limb loss. Treatment of vascular graft infection (VGI) may include partial or total removal of the infected graft, a procedure fraught with high morbidity and mortality [79]. Seriousness of the complications of VGI and treatment demands that diagnosis is made promptly with high level of accuracy and treatment be instituted accordingly. It is also important to differentiate between graft infection requiring removal of the graft from superficial wound infection requiring local wound care and antibiotic therapy. Clinical signs and symptoms of VGI are notoriously non-specific. The typical patients are elderly with co-morbid conditions such as diabetes and atherosclerotic vascular disease. Patients with VGI may present with features

including fever, abdominal pain, leukocytosis, tachycardia, tachypnea, hypotension and features suggestive of septicemia [80]. Early infection occurring within two months of surgery are usually due to virulent organisms such as *Staphylococcus aureus* introduced during surgical implantation. VGI is classified as chronic when it occurs beyond two months after surgery. Chronic VGI run a more indolent course [80]. Diagnosis of VGI is based on positive culture from fluid aspirated under ultrasound guidance or other specimens obtained from the infection site [80].

Imaging plays an important role in the diagnosis of VGI. Computed tomographic angiography (CTA) is considered the gold standard imaging for VGI. CTA helps to determine the extent of the infection, identify fluid collection for aspiration for culture, detect pseudoaneurysm or bleeding at the site of anastomosis, and define vascular anatomy which may guide medical and surgical treatment [80]. CTA features suggestive of VGI include peri-graft air, peri-graft fluid collection, peri-graft soft tissue attenuation, pseudoaneurysm, and features suggesting of aorto-enteric fistula (e.g. focal bowel thickening and contrast enhancement in the bowel during arterial phase) [81]. In the post-operative period, peri-graft air or fluid collection may be normal, making CTA less specific. Iodine allergy and renal failure are potential contraindications to CTA.

Radiolabeled leucocytes scintigraphy is a promising imaging modality in the diagnosis of VGI. Liberatore et al. explored the negative predictive value of radiolabeled leucocyte scintigraphy in a group of 23 patients with abdominal aortic aneurysm who had endovascular repair with prosthetic vascular graft [82]. Each patient had imaging at three-time-points (one week before procedure, one week after the procedure and at one month after the procedure). One patient had a 4th imaging done at 22 months after the procedure. Only two patients had a positive one-week scan. In one patient with positive one week scan, lymph accumulation was found at the surgical access site in the groin corresponding to the site of radiolabeled leucocytes accumulation. Finding normalized on the one-month scan. The other patient with positive scan finding on the one-week scan (also at the surgical access site in the groin) went on to have infection confirmed on follow-up. This study demonstrates the excellent clinical utility of radiolabeled scintigraphy in the early post-operative period, a period when CTA may be less reliable to diagnose VGI. Imaging in this study included a 3-minute dynamic

imaging post re-injection of radiolabeled leucocyte [82]. This may be an important addition to VGI imaging to serve as radionuclide angiography assessing vascular patency.

CTA is an attractive imaging modality in the work-up of patients with VGI due to its availability and usefulness. Khaja and colleagues performed a head-to-head comparison of CTA and radiolabeled leucocytes SPECT with ^{111}In-labeled leucocytes [83]. The respective sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CTA were 88%, 50%, 80%, 88%, and 50% compared with 75%, 100%, 80%, 100%, and 50% for ^{111}In-labeled leucocytes SPECT. The diagnostic performance improved when both modalities were combined for the diagnosis of VGI with a sensitivity, specificity, positive predictive value, negative predictive, and accuracy of 94%, 50%, 85%, 88%, and 67%, respectively [83]. The leucocytes scintigraphy in the study by Khaja was done on a SPECT system without CT. Addition of CT to SPECT imaging is currently considered as minimum standard in radionuclide imaging of infection [83]. A more recent series utilizing SPECT/CT imaging of radiolabeled leucocytes has demonstrated a perfect diagnostic performance (100% for sensitivity, specificity, PPV, NPV, and accuracy) [84]. Radiolabeled leucocytes SPECT/CT outperformed CTA, ultrasonography, and diagnosis bases on FitzGerald criteria. The respective sensitivity, specificity, PPV, NPD and accuracy for CTA, ultrasonography and FitzGerald criteria were 48.9/83.3/95.8/17.2/52.8%; 34.0/75.0/88.9/16.2/40.0%; and 68.1/62.5/91.4/25.0/67.3%; respectively [84]. Many of studies have confirmed the clinical utility of radiolabeled leucocytes scintigraphy in the evaluation of patients with suspected VGI [85-87].The superior performance of radiolabeled leucocytes SPECT/CT imaging over CTA was again confirmed in a recent meta-analysis that showed pooled sensitivity, pooled specificity and diagnostic odds ratio of 99% (95% CI: 92-100%), 82% (95% CI: 57-96%), and 73.59 (95% CI: 5.35-1011.76), respectively for radiolabeled leucocytes SPECT/CT imaging compared with 67% (95% CI: 57-75%), 63% (95% CI: 48-76%), and 2.90 (95% CI: 1.21-6.98), respectively for CTA [88]. The diagnostic performance of radiolabeled leucocytes scintigraphy in VGI is summarized in table 3.

Table 3: Diagnostic performance of radiolabeled leucocytes scintigraphy in patients with suspected vascular graft infection

Study	Population	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Liberatore et al. 1998 [85]	129 patients with suspected aorto-femoral graft infection	100.0	92.5	NR	NR	97.5
Shahidi et al. 2007 [86]	40 patients with suspected intra-cavitary PVGI	73.0	87.0	80.0	82.0	NR
Khaja et al. 2013 [83]	20 patients with suspected PVGI assessed with radiolabeled leucocytes fused SPECT/CTA	94.0	50.0	88.0	67.0	85.0
Erba et al. 2014 [87]	55 patients with suspected PVGI	100.0	100.0	100.0	100.0	100.0
Puges et al. 2019 [xx]	39 patients with suspected PVGI	89.5	90.9	70.8	97.2	90.6

PPV: Positive Predictive Value; **NNP**: Negative Predictive Value; **IE**: Infective Endocarditis; **PVGI**: Prosthetic Vascular Graft Infection; **NP**: Not Reported; **SPECT**: Single-Photon Emission Tomography; **CTA**: Computed Tomographic Angiography.

9. OTHER SPECT TRACERS FOR VASCULAR GRAFT INFECTION IMAGING

A few other tracers have been explored in the past for radionuclide imaging of VGI. These tracers include Gallium-67 and avidin/^{111}In-biotin scintigraphy [83,89-91]. The successful application of radiolabeled leucocytes SPECT/CT and widespread availability of ^{18}F-FDG PET/CT for this indication have rendered these other SPECT tracers obsolete as viable tools for radionuclide imaging of VGI.

10. RADIOLABELED LEUCOCYTE SPECT/CT COMPARED WITH ^{18}F-FDG PET/CT IN CARDIAC AND VASCULAR INFECTION

^{18}F-FDG PET/CT has surpassed other radionuclide imaging techniques for infection imaging, finding applications in the initial evaluation and response assessment of different types of infections including chronic granulomatous infections such as tuberculosis and in patients with non-specific symptoms as in fever of unknown origin [92-94]. ^{18}F-FDG PET/CT is a more commonly used technique in the diagnostic evaluation of cardiac infection than radiolabeled leucocytes technique [2]. There are several factors that may possibly explain this preference. In this section, the merits and demerits of both techniques will be summarized.

10.1.   Patients preparation

The myocardium uses different substrates including glucose and fatty acids during different physiologic or pathologic states. In cardiac infection imaging, it is necessary to suppress myocardial glucose utilization and by extension that of ^{18}F-FDG to enhance detection of abnormal tracer uptake. Procedures for myocardial glucose suppression including prolonged fasting for 12 to 18 hours, dietary manipulation (high fat, low carbohydrate and protein permitted diet) and pharmacologic intervention using intravenous unfractionated heparin [1,95]. Not all patients who adhere to these procedures achieve complete myocardial ^{18}F-FDG suppression. Radiolabeled leucocyte scintigraphy does not require any special patient preparation.

10.2.   Technical factors

Radiolabeled leucocytes scintigraphy requires blood collection, separating out the granulocytes for in vitro radiolabeling before re-infusion back to the patients. This process is tedious, time-consuming, technically-demanding, and risky. The risks involved include transmission of blood-borne infection to the technical staff and the possibility of injecting a patient with the wrong cells from another patient. Imaging is done at two to three-time-points usually over 24 hours. ^{18}F-FDG PET/CT is quite straightforward and does not involve blood

handling. The procedure is completed with one to two hours and test results is available almost immediately after.

10.3.   *Comparative diagnostic performance*

Excellent diagnostic performances have been reported for radiolabeled leucocytes scintigraphy and ^{18}F-FDG PET/CT in the evaluation of cardiovascular infections. Certain factors must be considered in choosing between the two imaging techniques. The PET system has a better resolution than the SPECT system. PET imaging is a whole-body tomographic imaging unlike in SPECT imaging where tomographic imaging is done around a body region of interest. These two factors generally make the ^{18}F-FDG PET/CT imaging more sensitive than radiolabeled leucocytes SPECT/CT imaging for cardiovascular infection.

^{18}F-FDG is not specific for infection. It accumulates at sites of sterile inflammation as well. ^{18}F-FDG, therefore, accumulates at the surgical sites due to post-operative inflammation associated with healing. ^{18}F-FDG similarly accumulates around cardiovascular prostheses due to sterile inflammation induced by these foreign materials [96,97]. While ^{18}F-FDG accumulation in sterile inflammation is usually diffuse and low-grade, its accumulation may also be heterogeneous as has been reported in regions of tension created by the sewing ring in patients with valvular prostheses. ^{18}F-FDG accumulation is generally higher around mechanical prostheses compared with biological and appear more intense on the attenuation corrected imaged compared with non-attenuated corrected images [96]. These physiologic uptakes induced by sterile inflammation may be mis-interpreted as positive for infection during evaluation for cardiovascular infection comprising the specificity and positive predictive value of ^{18}F-FDG PET/CT for cardiovascular infection imaging.

Radiolabeled leucocytes scintigraphy is more specific. Radiolabeled leucocytes accumulate preferentially at the sites of pyogenic infection and less so at the site of sterile inflammation. Radiolabeled leucocytes scintigraphy is, therefore, a more suitable imaging option for the evaluation of cardiac and vascular infection imaging. When specificity is of the imaging test is a more important consideration to proceeding with management, radiolabeled leucocyte scan, rather than ^{18}F-FDG PET/CT scan, is indicated. Similarly, when interpretation of [18]F-

FDG accumulation around a prosthetic cardiac and vascular device being evaluated for infection remain inconclusive, radiolabeled leucocytes scintigraphy may be useful for its excellent specificity (figure 4) [98].
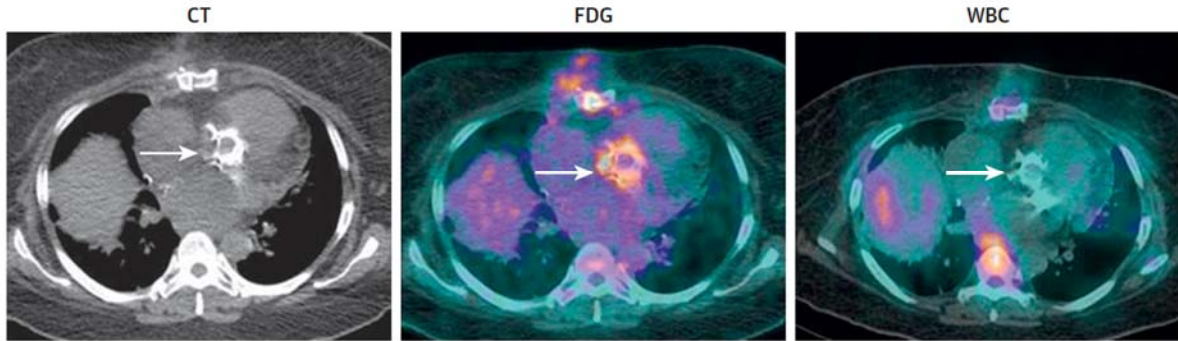
Figure 4: A 38-year-old woman with a mechanical aortic valve replacement developed acute endocarditis and underwent an urgent repeated surgery. Transesophageal echocardiography performed 40 days after the repeated intervention revealed mild perivalvular regurgitation. No criterion for endocarditis was present in blood cultures under antibiotic therapy. Moderate FDG uptake was detected around the prosthetic aortic valve on axial ^{18}F-FDG PET/CT images (middle), suspicious for prosthetic valve endocarditis. In contrast, no accumulation of radiolabeled leucocyte was detected in the prosthetic valve region on fused axial radiolabeled leucocytes SPECT/CT images (left). The corresponding location of the prosthetic valve was shown on computed tomography (right, arrow). The uptake on positron emission tomography was likely related to post-surgical inflammatory change and represented a false-positive finding. The patient remained asymptomatic and did not have any recurrent endocarditis 6 months later. Reproduced with permission from Chen et al. [96].

11. CONCLUSION AND FUTURE PERSPECTIVE

Radiolabeled leucocytes scintigraphy is the most promising SPECT technique for cardiac and vascular infection imaging. The cumbersomeness of leucocytes ex vivo labeling and the long imaging duration is well compensated for by its excellent diagnostic performance. When the diagnosis of infection remains doubtful after culture and morphologic imaging, it is able to confirm or reject the presence of cardiac or vascular infection. Its diagnostic performance is not limited by post-operative inflammation or by the sterile inflammation induced by implanted cardiac or vascular prosthetic materials. It is the imaging of choice when excellent specificity is desired in making therapy decision. It is very useful in identifying distant sites of embolic events with acceptable sensitivity and specificity. Limited evidence suggest that it may be useful to assess adequacy of antibiotic therapy, therefore, serving as guide to management.

Microbial-specific imaging where the causative organism of an infectious process is targeted rather than the inflammatory reaction mounted against it by the body is appearing promising.

Research are exploring the optimum bacterial targets for bacterial-specific imaging. A molecular probe labeled with a positron emitter for PET imaging that targets a bacterial-specific metabolic pathway will boost radionuclide imaging of cardiac and vascular infection. This imaging probe will combine the specificity afforded by targeting the causative organism and the sensitivity of a better PET resolution.

Nuclear medicine cameras are now fully integrated with morphologic imaging tools such as CT and magnetic resonance imaging (MRI) that are capable of producing images with diagnostic quality. Diagnosis of infection may be improved, for example, by combing CTA and radiolabeled leucocyte SPECT/CT at the same time. This true hybrid imaging has the potential to improve diagnostic accuracy and may better guide management. Similarly, the excellent soft tissue resolution provided by MRI may be explored in hybrid PET/MRI imaging for the diagnosis of cardiac and vascular infection in patients without contraindication to the MRI technique.

CONSENT FOR PUBLICATION

Not applicable

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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