Invited Review

F-18 FDG PET/CT imaging of cardiac and vascular inflammation and infection

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Abstract

Introduction: Inflammation forms an important core of the aetiopathogenic process involved in many diseases affecting the heart and the blood vessels. These diseases include infections as well as inflammatory non-infectious cardiovascular conditions. The common feature of this is invasion of the heart or blood vessel by inflammatory cells. F-18 2-fluoro 2-deoxy-D glucose (FDG) is an analogue of glucose and like glucose it is taken up by activated inflammatory cells that accumulate at the site of infection. This has formed the basis of the use of F-18 FDG PET/CT in the non-invasive evaluation of human inflammatory diseases.

Sources of data: This review is based on the published academic articles as well as our clinical experience.

Areas of agreement: F-18 FDG PET/CT is a useful imaging modality in the evaluation of cardiovascular inflammatory disorders. Accumulation and distribution of F-18 FDG at the site of inflammation/infection corresponds to severity of the inflammation/infection and extent of involvement.

Areas of controversy: Most studies evaluating utility of F-18 FDG PET/CT in imaging cardiovascular inflammation are small observational studies hence are potentially prone to bias.

Growing points: Being a hybrid metabolic and morphologic imaging technique, F-18 FDG PET/CT offers combined advantage of complementary anatomic and metabolic information in disease process. This makes it a useful modality in the diagnosis, determination of extent of disease, prognostication as well as treatment monitoring.
Areas timely for developing research: Larger prospective studies are needed to validate the superiority of F-18 FDG PET/CT imaging over conventional anatomic imaging modalities.

Key words: FDG PET/CT, cardiovascular, inflammation

Background

Inflammatory conditions affect all layers of the heart causing endocarditis when the endocardium is involved, myocarditis in the myocardium and pericarditis in the pericardium. Inflammation of the vessels causes vasculitis. Cardiovascular inflammation, compared with atherosclerosis, is uncommon. It is, however, associated with high mortality and morbidity.

Infection is a common cause of cardiovascular inflammation. Other causes include drugs, toxins, radiation and uraemia. Timely diagnosis of infection is crucial in order to minimize morbidity and mortality. Clinical symptoms are usually non-specific necessitating the use of imaging modality.

Echocardiography is the most commonly used modality in the evaluation of cardiac disorders. Transesophageal echocardiography (TEE) is more sensitive than transthoracic echocardiography (TTE). Morphological imaging with computed tomography (CT) and magnetic resonance imaging (MRI) is also used because of their good tissue characterization.

Positron emission tomography (PET) imaging with F-18-labelled 2-fluoro 2-deoxy-D glucose (F-18 FDG) is a well-utilized functional imaging modality in the diagnosis and management of malignancies. This is premised on increased glucose utilization by malignant cells. F-18 FDG use in imaging inflammation and infection is increasing. Acute and chronic inflammatory cells accumulate F-18 FDG causing its accumulation at the site of infection and inflammation. Combined PET and CT imaging provides complementary morphologic and metabolic information of lesions.

This review describes the utility of F-18 FDG PET/CT as a diagnostic tool in the imaging of cardiovascular infection and inflammation.

Pericarditis

Pericarditis is defined as inflammation of the pericardium. It has several aetiologies that may be categorized into specific or idiopathic causes. Specific causes of pericarditis include infections, connective tissue disorders, uraemia and post-radiotherapy for treatment of malignancies. Infectious pericarditis caused by tuberculosis (Tb) is responsible for most cases in Africa, Asia and other regions where Tb is endemic. In the developed countries, most cases are idiopathic with Tb pericarditis mostly seen in immigrants from endemic regions and in patients with human immunodeficiency virus (HIV) infection.

Pericardial spread of the tubercle bacilli occurs via three routes: retrograde spread from mediastinal, peri-bronchial and para-tracheal nodes, haematogeneously from the primary focus, although rare in immunocompetent patients, is a common mechanism of spread in HIV-infected patients due to the associated immune suppression and lastly via direct spread from adjacent infected lung, pleura, rib cage and diaphragm.

In the pericardium, the tubercle antigen activates a delayed type hypersensitivity reaction characterized by lymphocyte activation leading to release of lymphokines. The lymphokines cause activation of macrophages with resultant cytolysis and granuloma formation.

Four pathological phases of tuberculous pericarditis have been described:

Dry phase characterized by features of acute pericarditis. It is the least common phase seen clinically and pericardial effusion is absent.

Effusive phase that presents with moderate to large pericardial effusion associated with features of heart failure and/or cardiac tamponade. This is the most common stage seen clinically.
Adsorptive phase presents similarly as the effusive phase, but has a finding of thick fibrinous exudate around the heart seen on imaging.

Constrictive phase is characterized by features of constrictive pericarditis resulting from loss of pericardial elasticity from post-inflammatory scarring, thickening, fibrosis and calcification. No pericardial fluid is seen at this stage. HIV-infected patient is less likely to progress to this phase.

Definitive diagnosis of tuberculous pericarditis rests on demonstration of the acid fast bacilli in the pericardial fluid or biopsy sample of pericardial tissue. The yields from these invasive studies are however low due to paucibacillary nature of pericardial fluid. In HIV co-infected patients, diagnostic yield of Ziehl-Neelsen staining and culture is even lower, and poor formation of granuloma has been documented.

Morphologic imaging of tuberculous pericarditis using echocardiography, CT and MRI shows thickened pericardium with pericardial fluid collection in the effusive phase. Due to limited acoustic window, the entire pericardium is not visualized on echocardiography.

**Interpretation**

Intense F-18 FDG uptake has been described in tuberculous pericarditis on PET/CT. The intensity of uptake is greater than seen in idiopathic pericarditis. Dong et al retrospectively reviewed the F-18 FDG PET/CT images of patients with tuberculous pericarditis and compared them with images from patients with idiopathic pericarditis. They found that tuberculous pericarditis was associated with higher mean pericardial thickness, more intense F-18 FDG accumulation in the pericardium and lymph nodes in the mediastinum and supraclavicular region. Higher F-18 FDG update demonstrated in tuberculous pericarditis is a result of infiltration of the pericardium by lymphocytes and macrophages, which accumulate F-18 FDG intensely. Non-caseous tuberculoma formed by tuberculous infection results in thickened pericardium seen on imaging. Pericardial involvement with tuberculous infection is most commonly a result of spread of infection from a focus of tuberculous lymphadenitis either of mediastinal nodes, cervical nodes or nodes elsewhere. Invariably, F-18 FDG PET/CT imaging commonly demonstrates involvement of these nodes (Fig. 1). Lymph-node involvement may or may not be an associated finding in other forms of pericarditis and when present are usually fewer in number and are less metabolically active.

Tuberculosis is a multi-systemic infection with multi-organ involvement. While involvement of some organs may be clinically apparent, infections in some other organs may remain quiescent and undetectable clinically. Being a whole-body study, F-18 FDG PET/CT is useful in identifying these foci of infection not apparent clinically. The bone is commonly the site of such hidden infection focus.

Another important utility of F-18 FDG PET/CT is in evaluating response to therapy. FDG uptake in the pericardium returns to background with resolution of inflammation associated with successful treatment of infection.

Clinical application in patient management

Demonstration of F-18 FDG uptake in the pericardium of a patient with clinical suspicion of tuberculous pericarditis will raise the index of suspicion for this disease. This can further guide biopsy if invasive confirmatory testing is intended. Alternatively, F-18 FDG PET/CT may be useful to confirm resolution of abnormal pericardial F-18 FDG uptake upon successful anti-tuberculous therapy. Whole-body imaging avails the clinician opportunity to detect other tuberculous foci in the body. Additionally, F-18 FDG PET/CT may be useful in differentiating tuberculous from non-tuberculous pericarditis.

Myocardial inflammation

Myocarditis

Myocarditis results from myriad of aetiologies including infection (mostly viral), radiotherapy and systemic illnesses such as autoimmune diseases, toxin and drugs (especially cardiotoxic chemotherapeutic agents). Definitive diagnosis is by histopathologic demonstration of inflammatory infiltrates within the
myocardium associated with myocyte degeneration and necrosis of non-ischaemic origin (Dallas criteria). Myocardial biopsy is invasive and may be subjected to sampling error when myocardial involvement is patchy.

Non-invasive imaging of myocarditis using echocardiography may show normal wall motion, or regional or global motion abnormality. Cardiovascular magnetic resonance (CMR) imaging performs better in acute than in subacute or chronic myocarditis. Even in acute type, the presentation type affects diagnostic sensitivity of CMR, 80% in infarct-like type versus 40% in arrhythmic pattern.

Myocardial F-18 FDG uptake has been demonstrated in myocarditis caused by chronic active Epstein-Barr virus infection. It may be possible to evaluate response to therapy with F-18 FDG PET since myocardial uptake is expected to normalize with successful treatment.

Cardiac sarcoidosis

Sarcoidosis is a multi-systemic inflammatory disorder characterized by non-caseating granuloma in many organs. It most commonly affects the lungs and the lymph nodes. Clinically, 5% of patients with sarcoidosis have involvement of the heart but higher prevalence of cardiac sarcoidosis (CS) has been reported in autopsy series of cases of sarcoidosis. This suggests that many cases of CS go undiagnosed.

The diagnosis of CS is based on the guidelines by the Japanese Ministry of Health and Welfare (JMHW). The guidelines do not incorporate many of the recently developed diagnostic modalities such as cardiac magnetic resonance imaging (CMRI) and positron emission tomography (PET) imaging.
as F-18 FDG PET/CT. These guidelines are largely outdated. The JMHW guidelines provides for clinical diagnosis of CS when biopsy of myocardium cannot be under taken to demonstrate non-caseating epithelioid granuloma characteristic of CS. It consists of major and minor criteria. In a patient with extracardiac sarcoidosis, two major criteria or one major plus two minor criteria are diagnostic of CS (Table 1).

CS presents as global or regional wall motion abnormality associated with systolic dysfunction on echocardiography. These findings are non-specific and may be seen in myriad of other cardiac conditions. When myocardial involvement is patchy, echocardiography may be falsely normal.23

CMR imaging allows direct visualization of the myocardium. Areas of involvement are seen with late gadolinium enhancement on CMR both in acute and in chronic disease. CMR has limited utility because many of these patients have arrhythmias and heart failure hence have cardiac implantable electronic devices in place, which is a contraindication to MRI.24,25

In a meta-analysis of 7 studies involving 164 patients with systemic sarcoidosis and suspected or confirmed CS, Youssef et al.26 found pooled sensitivity and specificity of 89% (95% confidence interval (CI), 79–96) and 78% (95% CI, 68–86) respectively for F-18 FDG PET/CT.26

Potential sources of error exist in interpretation of FDG PET imaging for diagnosis of CS. The myocardium demonstrates variable physiologic uptake and may persist despite adequate preparation. This physiologic uptake may result in false positive finding in a patient without CS. Ohira et al.27 and Ishimaru et al.28 demonstrated such physiologic diffuse or focal uptake in the lateral wall in the patients from their studies.27,28

Corticosteroid and other immunosuppressive therapy remains the cornerstone treatment of sarcoidosis. With successful treatment, inflammation subsides and left ventricular function improves. F-18 FDG PET/CT has been used to demonstrate response to steroid therapy.

Myocardial F-18 FDG uptake in patients with suspected or confirmed with CS has prognostic value and is useful in patients stratification. Blankstein et al. followed 118 of such patients for a median follow-up period of 1.5 years and found 5-fold higher event rate (death and sustained ventricular tachycardia) among patients who demonstrated abnormal myocardial F-18 FDG uptake compared to those with normal uptake (Fig. 2). Among patients with normal F-18 FDG uptake in the heart, those with no uptake at all have significantly lower event rate than those with a diffuse myocardial uptake pattern.29

In a serial F-18 FDG PET studies performed by Osborne et al.30 in patients with CS on treatment, they found improving ejection fraction as demonstrated on Rubidium-82 rest myocardial perfusion study with reducing myocardial F-18 FDG uptake.

**Clinical application in patient management**

Clinical utility of F-18 FDG PET/CT in CS will include to support clinical suspicion of CS, to localize segment of cardiac involvement and guide biopsy, to follow-up treatment and in prognostication.

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**Table 1** Japanese Ministry of Health and welfare diagnostic criteria for cardiac sarcoid

<table>
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<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tr>
<td>Advanced AV block.</td>
<td>Abnormal ECG finding: ventricular arrhythmias (VT or multifocal or frequent PVCs), complete RBBB, axis deviation or abnormal Q waves.</td>
</tr>
<tr>
<td>Basal thinning of the interventricular septum.</td>
<td>Abnormal ECHO: wall motion abnormality or morphologic abnormalities such as aneurysm, wall thinning and ventricular dilation.</td>
</tr>
<tr>
<td>Myocardial uptake on gallium-67 scan.</td>
<td>Perfusion defect on myocardial perfusion imaging with Thallium-201 or 99 mTc labelled SestaMIBI or Tetrofosmin SPECT imaging.</td>
</tr>
<tr>
<td>Depressed left ventricular ejection fraction &lt;50%.</td>
<td>Delayed gadolinium enhancement on cardiac magnetic resonance imaging/Interstitial fibrosis or monocyte infiltration on cardiac biopsy.</td>
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Infective endocarditis

Infective endocarditis (IE) is a severe disease with an increasing incidence rate globally especially in the elderly.\textsuperscript{31,32} An incidence rate of 3.5/100,000 inhabitants with an in-hospital mortality rate of 28.9\% and a 1-year mortality rate of 11.2\% has been reported.\textsuperscript{33} Factors contributing to the changing epidemiological characteristics of IE are mostly due to increase in invasive cardiovascular procedures, prosthetic valve placement and intravenous drug abuse. Rheumatic heart disease (RHD) remains a predisposing factor to IE in developing countries.\textsuperscript{34}

RHD is the most severe manifestation of rheumatic fever (RF), which is a post streptococcal autoimmune disorder affecting the joints, skin, brain, serosal surfaces and heart valves. The diagnosis of RHD is made using the modified Jones criteria. The 2015 modified Jones criteria consists of major and minor manifestations and essential criteria. The major criteria are carditis, polyarthritis (or monarthritis or polyarthralgia), chorea, subcutaneous nodules and erythema marginatum. The minor criteria are fever, monoarthralgia, elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and prolonged PR interval on ECG. The essential criteria are evidence of preceding group A streptococcal infection: rising ASO or other streptococcal antibody, positive throat infection and positive rapid antigen test. Two major or one major and two minor plus evidence of preceding infection is diagnostic. For recurrent disease, three minor plus evidence of preceding infection is diagnostic.\textsuperscript{35}

The current diagnostic gold standard for IE is the modified Duke criteria, which is based on clinical, echocardiographic, microbiological and histological findings. These criteria provide diagnostic probability, which is classified as definite, possible or rejected endocarditis.\textsuperscript{36}

The diagnosis of IE is suspected clinically in a patient with fever of unknown origin associated with features of infection, anaemia, microscopic haematuria and findings consistent with septic embolism. Cardiac features include new or changing heart murmurs and worsening heart failure.\textsuperscript{37} These symptoms are non-specific as they may overlap with symptoms of other conditions.

Vegetation, abscess, new dehiscence in a prosthetic valve and new para-valvular regurgitation are major diagnostic findings on echocardiography. TEE has better sensitivity than TTE in native heart valve endocarditis (96 vs 70\%, respectively) and less doubtful finding (1.5 vs 16\%, respectively).\textsuperscript{38} TTE has poor diagnostic performance in prosthetic heart valve endocarditis with a sensitivity of 36\% for abscess and 29\% for identifying vegetation (86 and 88\%, respectively, for TEE) due to acoustic shadowing. Echocardiography is also useful for monitoring purposes while patient is on antimicrobial therapy by demonstrating changes in size and mobility of vegetation.\textsuperscript{39} Limited utility of both TEE and TTE have however been described in small vegetations (<2 mm), pre-existent severe lesions (valvular prolapse, calcification), recent embolization and non-vegetant IE. Echocardiography may result in false positive finding in thrombus, ruptured...
chordae tendinae, cusp prolapse, rheumatoid conditions and small intracardiac tumours.\textsuperscript{40}

Clinical presentation, echocardiographic findings and blood culture remain the cornerstone of IE diagnosis. Blood culture-negative IE may however be seen in up to 31\% of cases. This results in delay in instituting anti-microbial treatment. Causes of negative blood culture include fungi, fastidious organisms especially intracellular bacteria and prior use of antibiotics.\textsuperscript{40}

Overall, the sensitivity of Duke criteria is 80\%.\textsuperscript{41} Negative blood culture and inability to demonstrate vegetation on echocardiography are leading causes of unconfirmed IE in suspected cases. This has led to up to 24\% of cases being misclassified as possible IE based on Duke criteria alone.\textsuperscript{41}

The short fall of Duke criteria in the diagnosis of IE has triggered interest in molecular imaging with F-18 FDG PET, which demonstrates increased metabolic activity at the site of infection before morphologic changes occur. Combine PET/CT imaging provides complimentary morphologic and metabolic information at the site of infection.

In a prospective study of 92 patients, Pizzi et al. found F-18 FDG PET/CT imaging to outperform Duke criteria in the diagnosis of IE in native and prosthetic valve with a sensitivity of 87.2\% in prosthetic heart value for FDG PET/CT versus 51.3\% for Duke criteria. In 42 discordant cases between Duke criteria and PET/CT, PET/CT was correct in identifying IE in 18 cases and ruled it out in 13 patients. Two cases of false negative results in the study were in patients with very small vegetations who had been on antibiotics for >48 h.\textsuperscript{42}

F-18 FDG PET/CT has the unique attribute of imaging the whole body. This is useful in identifying sites of metastatic infections. Relapse of IE commonly occur due to insufficient duration of treatment of metastatic foci.\textsuperscript{43} In a prospective study of patients with IE affecting the native and prosthetic valves, PET/CT identified sites of septic emboli in 74.5\% of patients, the lung was the commonest site. Septic emboli were also localized to the brain; brain is, however, a possible for false negative due to high uptake of FDG in the brain.\textsuperscript{44} In the series by Orvin et al., they found significant extracardiac findings in 75\% of patients with confirmed IE, 38.1\% of whom were asymptomatic at the time of imaging. The commonest sites of septic emboli were in the spleen and the musculoskeletal system and PET/CT findings led to change in management in one-third of patients. High number of patients with no symptoms in their series may be due to prevalence of antibiotic use among the patients reported in 40\% of their study participants.\textsuperscript{45}

Determination of extent of infection is important in deciding the treatment modality in prosthetic valve IE. When infection extends into the perivalvular area, early surgical intervention is necessary. In this early phase, echocardiography may still be negative since an abscess is not yet formed. F-18 FDG PET/CT does show abnormal accumulation in the prosthetic valve with extension into the perivalvular area consistent with peri-valvular spread.\textsuperscript{46}

Following successful antibiotic therapy and resolution of inflammation at the site of infection, FDG uptake normalizes returning to background level. This is an important role of F-18 FDG PET/CT in the evaluation of therapeutic response.\textsuperscript{47}

Saby et al. (Fig. 3) reported sensitivity and specificity of 73 and 80\%, respectively, for F-18 FDG PET/CT in suspected prosthetic valve endocarditis. There was an improvement in the sensitivity of Duke criteria in diagnosing IE in these patients from 70 to 97\%.\textsuperscript{48}

Nagesh et al.\textsuperscript{49} did not find that F-18 FDG PET/CT is useful in differentiating acute or chronic RHD in children from normal control group. Our group has however reported heterogeneously intense F-18 FDG uptake in myocardium and valves of a patient with histologically confirmed RHD presenting as pyrexia of unknown origin (Fig. 4).\textsuperscript{50}

**Interpretation**

It is important to know that the heart demonstrates variable physiologic uptake of F-18 FDG and different patterns of uptake may be seen in the same individual under different conditions.\textsuperscript{51} Factors affecting myocardial uptake of FDG include blood levels of glucose, fatty acid and insulin. The left
ventricle has the highest uptake. The right ventricle has uptake usually less than but may be equal to uptake in the left ventricle. The atria and normal blood vessels do not demonstrate any visible uptake on PET imaging. Extended fasting and dietary modification (low carbohydrate, high fat and protein permitted diet) are necessary to prevent physiologic myocardial uptake of FDG.

The advantages and limitations of F-18 FDG PET/CT are presented in Table 2.

Clinical application in patient management

Based on its utility in reducing the rate of classifying patients as ‘possible IE’ using modified Duke criteria alone and its ability to demonstrate foci of metastatic infection, the European Society of Cardiology (ESC) has recommended use of F-18 FDG PET/CT in the evaluation of patients for IE. Other possible roles will include follow-up of patient to evaluate for effectiveness of therapy and in the determination of disease extent for therapy selection—medical versus surgical.

Cardiovascular implantable electronic device infections

Increasing cardiovascular implantable electronic devices (CIED) use in medical practice has been seen in the last few decades mostly due to the ageing population. These devices, majorly cardiac resynchronization therapy (CRT) devices, implantable cardiac defibrillators (ICD) and pacemakers, consist of a pocket placed subcutaneously or deep to the pectoral muscle on the anterior chest wall and leads placed endovascularly or on the epicardial surface. About 400,000 CIED were inserted in the UK in 2010 with annual increase in ICD and CRT devices of 12–15%.

Despite improvement in technique, design of device and prophylactic antibiotic use, CIED infection rate is on the increase. An estimated infection rate of 1.82/1000 device year has been reported in recipients of pace makers, with more infections seen in the first year of placement. Infection rate of 1.2% has been reported in recipients of ICD and 3.5% in the more complex CRT. Factors associated
with higher rate of infection include early pocket re-exploration, male gender, diabetes mellitus, upgrade procedure, heart failure, renal failure and hypertension.\textsuperscript{56}

Severe infection involving the pocket, intravascular and epicardial leads requires removal of device. Superficial soft tissue infection at pocket site however only require antibiotic therapy without the need for device removal. Both deep pocket and superficial soft tissue infection present clinically with signs and symptoms of local inflammation including pain, erythema, swelling, wound discharge and wound dehiscence. These clinical features are not sufficient to differentiate between the two entities.\textsuperscript{57} Severe lead infection causes device-associated IE. This is diagnosed using Duke criteria by demonstration of vegetations in the heart on TEE and positive blood culture.

**Classification of CIED-related infections**

CIED-related infections can be classified based on the site of involvement or its time occurrence. Based on the site of infection, infection may involve the pocket, extracardiac lead(s) or intracardiac lead(s).

Table 2 Advantages and limitations of F-18 FDG PET/CT imaging of IE

<table>
<thead>
<tr>
<th>F-18 FDG PET/CT imaging of IE provides the following advantages</th>
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<tr>
<td>High sensitivity compared with other imaging modalities.</td>
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<tr>
<td>Whole-body imaging allows for the detection of septic embolic foci which when not properly treated often leads to recurrence.</td>
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<tr>
<td>High negative predictive value for both IE and septic emboli.</td>
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**Limitations of F-18 FDG PET/CT imaging of IE**

| Physiologic uptake in the heart may be erroneously reported as positive for IE.       |
| FDG uptake in unrelated cardiac pathologies such as recent thrombi, soft atherosclerotic plaques, primary and secondary heart tumours causing false positive interpretation. |
| Post-surgical inflammation may cause FDG uptake if imaging is done within 1 month after surgery. |
| Sterile inflammation to BioGlue surgical adhesive causing false positive interpretation. |
| Prolonged prior antibiotic use may reduce sensitivity of the study.                   |
| Low-grade infection with minimal inflammation may not show significant FDG uptake.    |
study. In addition, FDG PET was able to differentiate between inflammatory reaction occurring following recent surgery at the site of suspected infection and intense FDG accumulation due to infection. Overall sensitivity and specificity of F-18 FDG PET/CT for diagnosing CIED infection were 88.6 and 85.7%, respectively.58

Interpretation

FDG uptake in the lead is consistent with lead infection. Sensitivity of F-18 FDG PET/CT for infection in the lead may be lower due to its small size.59 Because of its high negative predictive value, F-18 FDG PET/CT is useful in ruling out CIED infection so that alternative causes of patient’s symptoms are explored.47

The advantages and limitations of F-18 FDG PET/CT imaging of CIED-related infection are shown in Table 3.

Clinical utility in patient management

F-18 FDG PET/CT has been found useful in the differentiation of superficial from deep pocket infection, to support suspicion of CIED-related endocarditis and to detect metastatic extracardiac focus of infection.

Large vessel vasculitis

According to the 2012 revised Chapel Hill classification of vasculitides, large vessel vasculitis (LVV) is vasculitis that affects large arteries more than do other vasculitides and are typified by Takayasu arteritis and giant cell arteritis. Large vessels are the aorta and its major branches and analogous veins.60 The histopathologic features of the two entities are not distinguishable with both characterized by chronic granulomatous inflammation. Whereas TA most commonly affects the aorta and/or its branches with onset before age 50 years, GCA has predilection for branches of the carotid and vertebra arteries and is seen above age 50 years.

The exact trigger for the vessel inflammation seen in LVV is unknown.61 The process however starts with invasion of all layers of vessel wall through the vasa vasorum by the dendritic cells normally resident in the adventitial layer of the vessel. There is subsequent activation macrophages and T lymphocytes leading to the formation of granulomas, which consists of activated macrophages (histiocytes) surrounded by T lymphocytes.62

Diagnosis of LVV is based on the histopathologic demonstration of vessel inflammatory. Biopsy is rarely done because it is invasive and many false negatives due to sampling error may result from normal segments intervening between diseased vessel segments.63 Laboratory test findings and imaging modalities are used in evaluating suspected cases. Angiography is important in demonstrating vessel narrowing and occlusion. Doppler ultrasound, CT and MRI are useful to define vessel wall oedema and thickening.

Table 3 Advantages and limitations of F-18 FDG PET/CT in the imaging of CIED-related infection

| Advantages | Excellent sensitivity for the detection of pocket infection. |
| Inclusion of F-18 FDG PET/CT into Dukes criteria improves the diagnostic yield of the latter. |
| Ability to differentiate isolated superficial soft tissue infection, which does not require device removal from deep pocket infection. |
| Whole-body imaging allows for detection of metastatic foci of infection. |
| High negative predictive value allows for ruling out CIED-related metastatic infection. |

| Limitations | The smallness in size of the leads may lead to lower sensitivity for the detection of infection in them due to limited resolution of the PET system. |
| Reduced specificity may be encountered in the evaluation of early infection due to FDG accumulation caused by post-surgical inflammation. |
| Prolonged prior antibiotic use with consequent reduction in inflammation may reduce the sensitivity of the study. |
Interpretation

F-18 FDG is accumulated in activated inflammatory cells such as lymphocytes and macrophages. This has formed the basis of F-18 FDG PET/CT imaging of LVV. Uptake of F-18 FDG in vessel wall have been quantified using different assessment scales.

Visual scoring system using four-point scale scores uptake as 0 if no uptake is seen, 1 if minimal but negligible uptake which is less than liver uptake, 2 if intermediate uptake that is similar to liver uptake is seen and as 3 if high-grade uptake higher than liver uptake is seen in the affected vessel wall. Vascular F-18 FDG uptake ≥2 (equal or higher than liver uptake) is considered positive for vasculitis in treatment-naïve patients.

Alternatively, semi-quantitative indices such as SUVmax, which is activity of F-18 FDG in a region of interest divided by total activity of F-18 FDG injected into the patient corrected for patient’s body weight, may be used. Many other semi-quantitative methods have been used to quantify F-18 FDG uptake in LVV including ratio of SUVmax in vasculitic vessel to SUVmax in liver (SUVmax ratio vessel-to-liver) and ratio of SUVmax in diseased vessel and non-affected vessel.

Increased F-18 FDG uptake in LVV is characterized by lineal diffuse uptake in the vessel wall. This must be differentiated from low-grade (mostly grade 1) patchy uptake seen in atherosclerotic vessels. This distinction is important to prevent false positive diagnosis.

F-18 FDG PET/CT has a very high sensitivity and specificity for the diagnosis of LVV. In a recent meta-analysis evaluating the diagnostic performance of F-18 FDG PET/CT in the diagnosis of TA and GCA, analysis of 57 patients from four studies showed pooled sensitivity and specificity of 89.9 and 97.7%, respectively, for GCA. Similar analysis in 191 patients from 7 studies, 96 of whom had active TA showed a pooled sensitivity and specificity of 87 and 73%, respectively.

Giant cell arteritis commonly co-exist with polymyalgia rheumatica (PMR) so that the two entities have been recognized as different manifestation of the same disease. PMR may occur before, with, after the diagnosis of GCA or may only develop during immunosuppressive therapy for GCA. In a subset of patients, isolated PMR precedes clinical diagnosis of GCA. In this group of patients, subclinical vasculitis occurs with associated high risk of developing disease-related ischaemic complications reported in up to 50% of them. F-18 FDG PET/CT imaging in this group with subclinical GCA have been found useful in demonstrating disease activity in joints, pattern of joint involvement and identify subclinical GCA. In a study of 67 patients who fulfilled the Healey’s diagnostic criteria for PMR with no clinically apparent or symptomatic GCA, Rehak et al. found associated vasculitis in ~40% of patients. Median number of involved joint was 4, proximal joints were most commonly involved—shoulders in 86.6% and hip in 70.1% of cases.

In the clinical evaluation of patients with suspected vasculitis, F-18 FDG PET/CT can be used to define pattern of vascular involvement, differentiate between the different vasculitides and guide biopsy. GCA is associated with disease involvement in the aorta, subclavian, axillary, carotid, iliac and femoral with or without large joints involvement. TA involves more centrally placed aorta and its thoracic branches. Rarely, the abdominal aorta may be involved. Polymyalgia nodosa and polychondritis represent medium and small vessel vasculitis. F-18 FDG is most commonly seen in the medium and small vessels of the extremities associated with uptake in the ears, nose and costochondral regions when polychondritis is present.

Immunosuppressive therapy with steroid remains the cornerstone of treatment of LVV. Immunosuppression reduces vessel inflammation and consequently reducing F-18 FDG accumulation on PET/CT imaging. This is important in evaluating patient response to therapy and disease activity. Level of F-18 FDG uptake also correlates with clinical symptoms and laboratory findings. It is however important to know that sensitivity for detection of disease is less in patient already on steroid therapy. For these patients, a minimal uptake less than uptake in liver (Grade 1) is suspicious for vasculitis. PET scan is also useful in evaluating...
response of PMR to immunosuppressive therapy. F-18 FDG uptake normalizes in affected joints with successful treatment.  

Clinical utility in patient management
Demonstration of linear intense F-18 FDG uptake in vessels is an aid to the diagnosis of LVV. This portion of the involved vessel may be biopsied if invasive confirmatory testing is necessary. F-18 FDG PET/CT imaging is an additional tool to differentiate between types of LVV, detect complications such as vascular occlusion or aneurysmal dilatation of vessel wall as well as evaluate for adequacy of immunosuppressive therapy.

HIV-associated vasculitis
Vasculitis is present in 1% of HIV-infected patients. A wide spectrum of vasculitis has been described in these patients with almost all types of vasculitis described in the Chapel Hill classification seen in them. Vasculitis in HIV-affected patients is non-discriminatory affecting large, medium and small vessels.

The major aetiopathogenic patterns of vasculitis in HIV-infected individuals are as follows:

**Infective vasculitides**—HIV infection causes immunosuppression, which provides an enabling environment for opportunistic infections to thrive. Infectious agents cause vascular inflammation in large, medium and small arteries and veins in different organs. These agents include herpes viruses (Cytomegalovirus (CMV), Epstein-Barr virus, Varicella-Zoaster virus), hepatitis B virus (HBV), *Mycobacterium tuberculosis*, toxoplasmosis, *Pneumocystis jiroveci* and salmonellosis. These organisms cause vasculitis either by direct invasion and subsequent damage to vessel wall or by immune-mediated mechanisms that may be cellular or humoral.

**Necrotizing vasculitides**—these include polyarteritis nodosa-like (PAN) vasculitis not associated with HBV infection. It occurs on the background of moderate to severe immunosuppression and presents clinically with features less severe than in HIV non-reactive patients.

**Hypersensitivity vasculitides**—these affect small vessels and manifest in the skin with purpura. Henoch–Schonlein purpura, drug-induced hypersensitivity vasculitis and cryoglobulinaemia are examples.

**Primary angitis of the central nervous system (CNS)**—it has predilection for small arteries and veins of the brain surface and adjacent leptomeninges. It is characterized by chronic granulomatous inflammation with accumulation of giant cells. It has been suspected to be associated with increased risk of stroke in young HIV patients.

**Large vessel vasculopathy**—occlusive and aneurysmal disease involving large vessels have been described in HIV-infected individuals. Direct invasion of vessel wall by infectious agents causing mycotic aneurysm is known. In HIV-infected individuals, however, occlusive and aneurysmal diseases of large vessels have been reported without associated vessel wall invasion by micro-organisms. It results from obliterative endarteritis of vasa vasora of these large vessels leading to fragmentation of the internal elastic lamina and consequently aneurysmal dilation. Alternatively, variable intima proliferation occurs, leading to occlusive disease. Affected individuals are young males aged 30–40 years, with multiple aneurysms in femoral, popliteal and carotid vessels and without background predisposing atherosclerosis.

**Angiocentric immunoproliferative lesions**—seen in HIV-infected patients with lymphoma. It results from HIV-associated immune dysregulation leading to T-cell proliferation with angiocentric proclivity. The exact aetiopathogenic cause of vascular inflammation in HIV-infected patients is unknown. It is likely that multiple aetiologies play roles in pathogenesis of vascular inflammation, the common underlying finding in HIV-associated vasculopathy. Potential pathogenic mechanisms are presented in Table 4.

Interpretation and potential clinical utility in patient management
Potential utilities of F-18 FDG PET/CT imaging of HIV-associated vasculitis include demonstration of
abnormal F-18 FDG accumulation in involved vessel in a suspected case (Fig. 5). This will aid in identifying disease pattern, determining group of vessels involved, determining activity of disease and guide targeted biopsy for histological confirmation. Repeat scan may be used for follow-up in patient on treatment. This will aid in assessing response or otherwise to treatment. Owing to limited PET resolution, this imaging modality is not useful in evaluating disease in small vessels.

Atherosclerosis

The immune system plays a central role in the formation and sustenance of atherosclerotic plaques in medium and large vessels. The process starts following vascular endothelial injury leading to recruitment of inflammatory cells especially macrophage. Activated macrophages engulf lipoprotein to form foam cells. Progression of this lesion leads to occlusion of the involved vascular bed or plaque rupture.\(^8^5\) Plaque rupture causes exposure of its highly thrombogenic core to circulating platelets and clotting factors leading to intraluminal thrombus formation.\(^8^6\) Inflammation is an important trigger of plaque rupture. Identification of susceptible plaque is important in the prevention of catastrophic clinical events such as acute coronary syndrome in both high risk and patients with low traditional cardiovascular risk.\(^8^7\)

Morphologic imaging of atherosclerotic disease is commonly done using endovascular ultrasound, CT and MRI to demonstrate burden of atherosclerotic plaque, vessel wall thickening, luminal stenosis or dilatation, and in identifying complications such as aneurysm, dissection and thrombosis.\(^8^6\)

Interpretation

F-18 FDG uptake in a plaque has been correlated with region of macrophage accumulation representing region of plaque inflammation at risk of rupture.\(^8^9\) F-18-FDG accumulation is significantly higher in symptomatic arterial plaques compared with asymptomatic ones.\(^9^0,9^1\) Focal F-18 FDG uptake at the sites of inflamed plaques is
characteristic of atherosclerosis in contradistinction to diffuse uptake in vessel wall seen in vasculitides. This inflammatory uptake has been demonstrated to precede plaque calcification.  

Statins have anti-inflammatory property and are commonly used in patients with atherosclerosis. F-18 FDG uptake in plaques reflects response to therapy. With successful statin therapy, plaque inflammation reduces and so does F-18 FDG uptake. In the same way, uptake also correlates with disease progression. This has been demonstrated in patients with atherosclerotic plaques in different vascular bed followed up with F-18 FDG PET/CT. Chen et al. found uptake of F-18 FDG in plaque to correlate with risk of cardiovascular events.

Physiologic FDG uptake in the myocardium, when not completely suppressed, may interfere with assessment of abnormal uptake in atherosclerotic coronary artery imaging. F-18-labelled sodium fluoride (F-18 NAF) is a positron emitting tracer that localizes to areas of calcium deposition, a feature shared by atherosclerotic plaque and bone osteoid. F-18 NAF localizes to inflammatory and vulnerable plaques. Joshi et al. in a prospective clinical trial of patients with myocardial infarction and control group with stable angina who underwent PET/CT and coronary angiography found intense F-18 NAF accumulation in recently ruptured plaques and plaques from patient with symptomatic carotid disease. Focal F-18 FDG accumulation seen in patient with stable coronary artery disease occurred in plaques with greater remodelling, more microcalcification and a larger necrotic core.

Derlin et al. demonstrated differences in uptake of F-18 FDG and F-18 NAF in atherosclerotic plaques of oncologic patients. Out of 503 calcified plaques studied, F-18 NAF uptake was demonstrated in 81 arterial calcifications contrary to only 18 arterial calcification showing F-18 FDG uptake. Uptake of both traces in same lesion was only seen in 6.5% of total lesion studied. This indicates that different mechanisms are in play in the localization of these tracers to arterial plaques. F-18 FDG accumulates to inflammatory plaques whereas F-18 NAF localizes to plaques with ongoing calcium deposition. Among lesions showing avidity for F-18 NAF, those with microcalcification which sometimes are not even visible on CT are more predisposing to acute clinical events than the densely calcified lesions. Fiz et al. demonstrated an inverse relationship between density of arterial plaque and F-18 NAF uptake. Highest F-18 NAF uptake was seen in arterial segments without visible calcification on CT.

F-18 FDG accumulation in atherosclerotic plaque represents ongoing inflammation. This indicates vulnerability to plaque rupture and has been found to predict mortality, occurrence of ischaemic stroke and a propensity to re-stenosis after stenting for revascularization. Calcification of atherosclerotic plaque occurs in a biphasic manner. The initial phase is the phase of microcalcification, which is below the spatial resolution of CT and is not visualized during imaging. F-18 NAF localizes to this region of the diseased vessel. Presence of microcalcification in the thin cap of an atherosclerotic plaque, during changes in shear pressure on the cap arising from changes in blood flow, causes plaque rupture. Accumulation of F-18 NAF therefore helps to identify these vulnerable plaques.

Clinical utility in patient management
F-18 FDG accumulation occurs in vulnerable atherosclerotic plaque. This can serve as a guide to recognize plaques with potential for causing acute events. Reduction in F-18 FDG accumulation in atherosclerotic vessel following treatment is a useful biomarker in patient follow-up.

Prosthetic vascular graft infection
Vascular grafts are indicated in occlusive vascular disease. The incidence of vascular graft infection is low, ~1–5%. It is however associated with high mortality and morbidity. A delay in diagnosis may result in limb loss or death. Up to 75% mortality has been reported. Infection may involve the graft from peri-graft soft tissue infection, tissue contamination at the time of surgery or haematogenously from a distant focus of infection. Prosthetic vascular graft infection (PVGI) is considered early if
it occurs within 3 months of placement or late when it occurs beyond 3 months after surgery. Factors predisposing to vascular graft infection have been categorized into three groups, which can be patient related, procedure related or pathogen related.103,104

Patient-related factors are diabetes mellitus, immunosuppression, heart failure, renal failure, malignancy, old age, remote infection focus and overweight or frank obesity. Procedure-related factors are prolonged duration of procedure, emergency re-do procedure, breach in sterility, post-operative seroma or haematoma, pseudo-aneurysm and adjacent soft tissue infection. Pathogen-related factor is the pathogenic attributes of the invading organism.

When PVGI is suspected, timely and accurate confirmation is essential to prevent morbidity and mortality. It is important at this point to differentiate between peri-graft soft tissue infection without vascular graft involvement from PVGI. This is so because isolated soft tissue infection requires antibiotic therapy and local wound care without the need for graft replacement. Failure to differentiate between these two entities will lead to unnecessary graft replacement with its attendant morbidity. Definitive diagnosis of PVGI is by histopathologic examination of excised vascular graft.102

CT is the most common imaging modality used in the evaluation of PVGI. It identifies peri-graft fluid collection and air bubble, thickened graft wall, peri-graft fat stranding and soft tissue swelling associated with PVGI.102

**Interpretation**

Focal intense uptake of F-18 FDG is consistent with graft infection (Fig. 6). In a prospective study of 69 vascular grafts, 40 of which were infected, sensitivity, specificity, positive predictive value and negative predictive value of 93, 91, 88 and 96% respectively were reported. Two cases of false positives in the study were due to adjacent haematoma.88 Similar findings were reported by authors of a more recent study.105

Several uptake patterns have been described that may potentially lead to false positive report. Uptake limited to soft tissue without involvement of the graft is in favour of soft tissue infection, which does not require graft replacement. Non-infected graft may be associated with low-grade uniform F-18 FDG uptake along the graft wall. Absence of clinical signs and symptoms of infection as well as non-elevated systemic inflammation markers will boost diagnostic confidence in these cases.106–108

It is important to be familiar with patterns of F-18 FDG uptake in non-infected vascular graft. In a comprehensive study of 107 non-infected vascular grafts, Keidar et al found both homogeneous and non-homogeneous uptake pattern in 92% of non-infected grafts. More intense and inhomogeneous uptake was seen more commonly with Dacron vascular graft whereas homogeneous uptake pattern was more significantly associated with Gore-Tex vascular graft. None of the graft showed focal F-18 FDG uptake. Whereas native vein graft showed significantly little or no F-18 FDG that reduced over time, no significant change in intensity of uptake was seen in the synthetic vascular graft over the 1- to 5-year follow-up period.107 F-18 FDG uptake demonstrated with synthetic graft material is due to sterile inflammatory reaction to the foreign vascular graft material characterized by invasion by macrophages, fibroblast and foreign body giant cells all of which take up F-18 FDG.109 Other causes of diffuse F-18 FDG uptake at the site of a vascular graft include level of metabolic activity within the peri-graft tissue, physiologic F-18 FDG uptake in native vessels and uptake within scar tissue.102 Uptake within peri-graft tissue occurring as a result of post-operative sterile inflammation is prominent in the early post-operative period and may remain so for years thereafter.

**Clinical utility in patient management**

F-18 FDG PET/CT has been found to be a useful tool in the diagnosis of vascular graft infection. It can be used to differentiate isolated wound infection from vascular graft infection.
Emerging role of PET/MRI imaging of cardiovascular inflammation and infection

With resolution of most of the initial problems encountered in the fusion of PET and MRI technologies, integrated PET/MRI machines are now appearing on the clinical scene proving an expanded role for molecular imaging of cardiovascular diseases. In addition to a better soft tissue resolution than CT, MRI provides additional functional information (such as in diffusion-weighted imaging, magnetic resonance spectroscopy and perfusion imaging) so that a hybrid PET/MRI imaging is not only more sensitive in delineating structural derangement associated with diseases but also provides superior functional information than PET/CT. Better resolution of MRI becomes complimentary to PET information in imaging of small structures such as CIED lead infections where PET performs sub-optimally. MRI does not utilize ionizing radiation. This reduces radiation dose from the study allowing for repeatability and a better role in paediatric imaging.110,111

Conclusion

In the clinical setting, F-18 FDG PET/CT imaging is useful in evaluating human cardiovascular inflammation. In most cases, its utilities include confirmation of clinical suspicion, determination of extent of the disorder, prognostication and evaluation of effectiveness of therapeutic intervention. Further development and implementation of including F-18 FDG PET/CT in clinical routine will continually increase the number of PET/CT indications.
Conflicts of interest
The authors have no potential conflicts of interest.

References


83. Pillay B, Ramdial PK, Naidoo DP. HIV-associated large vessel vasculopathy: a review of the current and
84. Mulaudzi TV. Vasculopathy is a Major Feature of HIV Disease, 27, Pretoria: University of Pretoria, 2009; 320–1.