Prosthetic Valve Endocarditis

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Epidemiology, Microbiology, and Pathophysiology of PVE

Cardiovascular infections are a heterogenous group of conditions that can affect various components of the native structure of the heart (pericardium, muscle, endocardium, valves, autonomic nerves, and the vessels) as well as implanted devices such as valve prostheses (all types of prosthetic valves, annuloplasty rings, intracardiac patches, and shunts), cardiovascular implantable electronic devices (CIED), left ventricular assist device catheters, and vascular grafts. The increased use of implantable devices and surgical biomaterials during the last decades have resulted in an increase in related infections as well as associated complications. For example, the expected number of heart valve interventions is estimated to reach more than 800,000 annual procedures worldwide by 2050 [1]. Healthcare-associated infections are the most common non-cardiac complication following cardiac surgery and device implantation affecting about 1.7 million patients each year and associated with nearly 100,000 deaths in the US alone [2, 3].

Infective endocarditis (IE) is a severe disease associated with high morbidity and mortality and whose incidence and severity have remained unchanged or even increased, despite improvements in diagnostic and therapeutic strategies [4, 5]. Recent data such as from the EuroEndo registry, the most comprehensive and far-reaching observational international study involving a cohort of 3116 adult with IE recruited between January 2016 and March 2018 in 40 countries, showed that in-hospital mortality remains very high—around 17.1% of patients—and was more frequent in prosthetic valve endocarditis (PVE). Independent predictors of mortality were the Charlson index, creatinine >2 mg/dL, congestive heart failure, vegetation length >10 mm, cerebral complications, abscess, and failure to undertake surgery when indicated [6].

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PVE accounts for 20% of all cases of endocarditis and occurs in up to 6% of patients with a prosthetic valve [7]. The frequency of PVE in the EuroEndo registry is also increasing, accounting for 30% of cases [6] as compared to the 26% of cases in the EuroHeart survey [8], 25% in the 2008 French registry [9], and 21% in the International Collaboration on Endocarditis-Prospective Cohort Study reported in 2009 [10].

The epidemiology of aortic PVE is different in patients with surgical aortic valve replacement (SAVR) versus transcatheter aortic valve replacement (TAVR). In SAVR, the incidence of PVE is about 6 per 1000 cases [11] with higher infection rates in cases of bioprosthetic compared to mechanical valves [12]. In TAVR, the incidence rate of PVE is similar to patients with bioprosthetic SAVR [13]. However, TAVR is increasingly being used, and the number of post-TAVR IE is also expected to rise [14]. A major problem with post-TAVR IE is that SAVR is often required to replace the infected valve. However, TAVR patients are often elderly and with more comorbidities, rendering them inoperable or at high risk, thus resulting in a general worst prognosis [15]. In addition, the leaflets of transcatheter valve prostheses contain a greater quantity of metal in the stent frame in contrast to the surgical valves, leading to significant changes in the outcome and management of IE [16].

Early SAVR PVE is typically the result of peri-procedural bacterial contamination of the prosthetic valve, often secondary to seeding from a distant focus of infection such as a catheter or wound infection [17]. In the first days following valve implantation organisms have direct access to the prothesis–annulus interface and the tissue along the sutures in the paravalvular area. They can easily adhere to the fibrinogen and fibronectin in the paravalvular area, resulting in the formation of abscesses. *Staphylococcus aureus*, *Staphylococcus epidermidis*, Gram-negative bacteria, and fungi are the most frequent isolated microorganisms. Staphylococci and streptococci have a penchant for transcatheter valves. Interestingly, in TAVR PVE, enterococci have also been a prominent causative agent in the peri-procedural period [16], likely related to the femoral access in the groin.

Data from the EuroEndo registry confirmed that the microorganisms most often identified were staphylococci (44.1%), oral streptococci (12.3%), enterococci (15.8%), and *Streptococcus gallolyticus* (6.6%). Finally, the number of culture-negative IE observed in the EuroEndo registry (21%) was higher than those previously reported; 14% and 11% observed in the 2002 French survey [9] and 2009 International Collaboration on Endocarditis Prospective Cohort Study [10], respectively.

Late-onset PVE acquired in the community is usually caused by endogenous microbiota organisms also seen in native valve endocarditis, such as streptococci, staphylococci, and enterococci. The prostheses do not allow the organism to adhere to leaflets in the absence of thrombotic material. The sewing ring and sutures become endothelialized a few months after the valve implementation. Alterations in the valve and the paravalvular surface can lead to the formation of microthrombi, to which bacterial organisms can adhere, multiply, and cause an infection [18].

The severity of PVE infection depends upon several factors including the involved microorganism, the maturity of the biofilm developed on the device, the location and type of the biomaterial, and the host defence status [19, 20]. The presence of a biofilm, a community of adherent microorganisms embedded within a self-produced matrix of extracellular polymeric substances, provides a physical barrier leading to antibiotic resistance and host phagocytic defences. Therefore, the only strategy to effectively eradicate the infection is often surgical removal of the infected device.

PVE cannot be diagnosed from a single symptom, sign, or diagnostic test. The heterogeneity of clinical presentations makes a multidisciplinary team approach integrating diagnostic criteria necessary. Microbiology and imaging are currently the benchmarks for a prompt and accurate diagnosis. The standard microbiological investigation includes microorganism identification, and antibiotic susceptibility tests for treatment guidance. Blood culture is the most important initial laboratory test. If antibiotic therapy has been administered prior to the collection of blood

cultures, the rate of positive cultures declines, reducing the sensitivity of the diagnostic criteria [21]. Multimodality imaging, including molecular hybrid imaging techniques, is widely used in conjunction with traditional diagnostic criteria.

In this chapter, we will focus on the use of ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) in PVE. In addition, we will give some insight into recent new developments that might be of particular interest for this field.

Diagnostic Workout

Evidence of valve or intracardiac material involvement on imaging is a major diagnostic criterion of PVE, with echocardiography (ECHO) representing the first-line imaging method. However, it is well known that ECHO has several limitations [22] and other imaging modalities such as CT, MR, and nuclear imaging have progressively been shown to be useful to demonstrate both valve involvement and the presence of IE-related peripheral complications (metastatic infection and septic embolism), as well as occult predisposing lesions that may be the source of infection. Hybrid imaging combining anatomical imaging and metabolic information as in PET/CT or SPECT/CT has been shown to be particularly useful in the presence of implantable/prosthetic material [23, 24]. Therefore, these techniques have been gradually included in the global assessment of patients with suspected IE, and the 2015 ESC guidelines [25] and the American Heart Association (AHA) 2020 guidelines for the management of patients with valvular heart disease [26] which also recognize the value of the multimodality approach and the importance of team work in the assessment of patients with IE.

Figure 12.1 presents the diagnostic algorithm currently used at our centre. ECHO is the first-

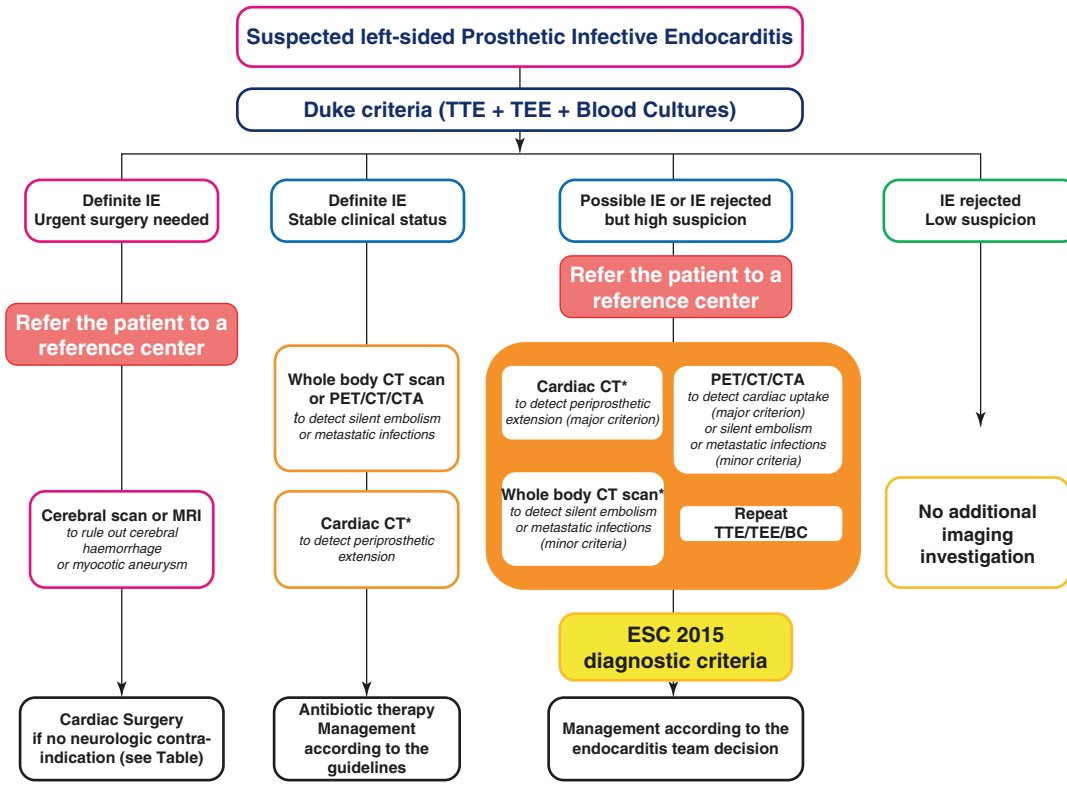

Fig. 12.1 Diagnosis algorithm in suspected prosthetic valve infective endocarditis, reprint with permission from Erba et al. [22]. * If contrast-agent injection is not contra-indicated

line imaging modality performed in suspected IE [22]. Both transthoracic (TTE) and transoesophageal (TEE) echocardiography should be performed [27], with TEE allowing a better evaluation in several situations where TTE has a limited sensitivity [28], such as prosthetic valve IE small vegetations, and in the presence of perivalvular abscess [29]. ECHO is of major importance for the diagnosis of IE, the assessment of the severity of the disease, providing prognostic data including embolic risk, and patient follow-up assessments. The typical ECHO findings in PVE are vegetations and perivalvular complications such as abscess, pseudoaneurysm, new dehiscence of a prosthetic valve, intracardiac fistula, and valve perforation or aneurysm [25]. ECHO is also useful in predicting embolic events, with the size and mobility of vegetations being the stronger predictors of embolic events [30].

In cases of suspected PVE, abnormal uptake at the site of the prosthetic valve on FDG-PET/CT or WBC SPECT/CT is considered a major criterion. Identification on imaging of recent embolic events or infectious aneurysms (silent events) is considered as a minor criterion. The identification of paravalvular lesions by cardiac CT is also a major criterion of the ESC 2015 diagnostic criteria. In fact, ECG-gated cardiac CT (A) enables assessment of both the valve and perivalvular IE lesions with the ability to detect perivalvular lesions (abscesses and pseudoaneurysms) with very high sensitivity and specificity (>95%) [31], especially for the aortic valve [32]. Detection of valvular lesions such as vegetations, leaflet thickening, valve perforation, or valve aneurysm is also feasible [31].

FDG PET/CT and PET/MR Imaging

Two different strategies might be used for molecular imaging of infection. The first is based on the use of agents targeting the microorganism responsible for the infection while the second targets components of the pathophysiological changes of the inflammatory process and/or the host response to the infectious pathogen. FDG is actively incorporated by inflammatory cells (i.e., activated leukocytes, monocyte-macrophages, and CD4+ T-lymphocytes) at the sites of infection due to their overexpression of glucose transporters. FDG-PET/CT in PVE is generally performed using a single acquisition time point (generally at 45–60 min) after the administration of FDG (Fig. 12.2). Advantages of FDG-PET/CT over other nuclear imaging modalities, such as radiolabelled WBC, are the lack of blood handling, a shorter study time that allows the conclusion of the scan within 1–2 h after tracer administration (excluding preparation time), and high target-to-background ratio and higher image resolution.

FDG-PET/CT and PET/MR have an increasingly relevant role in cardiovascular infections and inflammation imaging. They can be used throughout the disease course for different purposes (Fig. 12.3). In the very early phase of the disease, bacteraemia might result in the microorganism adhering to native and/or prosthetic valves. At this stage, the main manifestations of the disease are local as a direct consequence of the vegetation formation. In this phase, ECHO is very useful for identifying valvular abnormalities and early vegetation development. Based on their ability to directly identify the microorganisms sustaining the infection, it could be hypothesized that bacterial specific agents might be the radiopharmaceutical of choice for this early disease phase. At a later phase, once the host immune response to infections has been activated, WBC and other inflammatory cells are recruited at the vegetation site, imaging using radiolabelled WBC and FDG has become effective for detecting local disease extension and/or complication as well as for

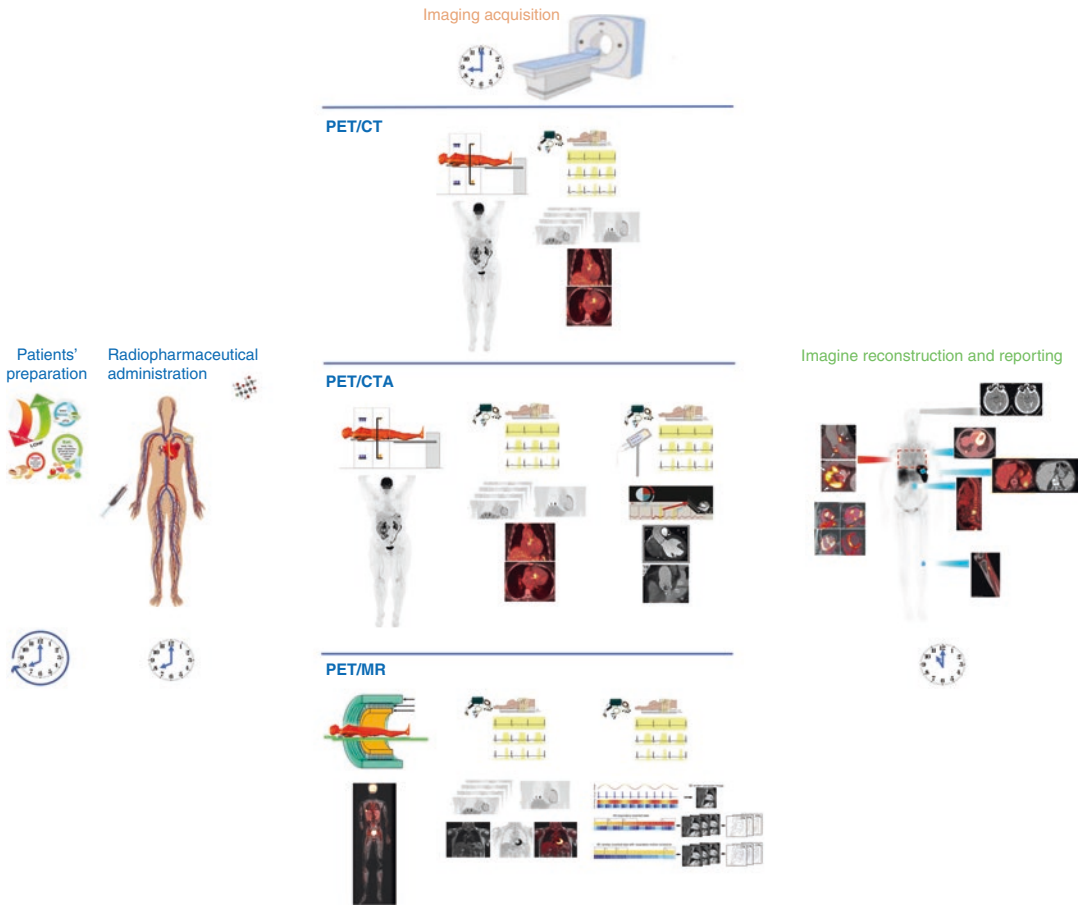

Fig. 12.2 Schematic summary of the use of FDG-PET/CT(A) and PET/MR in the context of cardiovascular infections. First in the right panel, the patient should be properly prepared by at least 24 h of high-fat-low-carb diet followed by 12 h fasting before the radiopharmaceutical administration. After about 1 h, the patient is imaged according to the specific protocol (middle panel, upper row PET/CT, middle row PET/CTA, and lower panel PET/MR). Finally, the images are reconstructed, reoriented, and assessed for the presence of uptake at the valve and extracardiac disease involvement, as in case of septic embolisms, metastatic sites of infection and the portal of entry or alternative source of infections (left panel)

identifying systemic manifestation of the disease caused by embolic detachment from the vegetation/valve. PET/MR, an exciting novel hybrid imaging tool which can assess disease activity together with cardiac anatomy, function, and tissue composition has not been evaluated yet in the context of PVE except in an anecdotal case (Fig. 12.4) [33, 34].

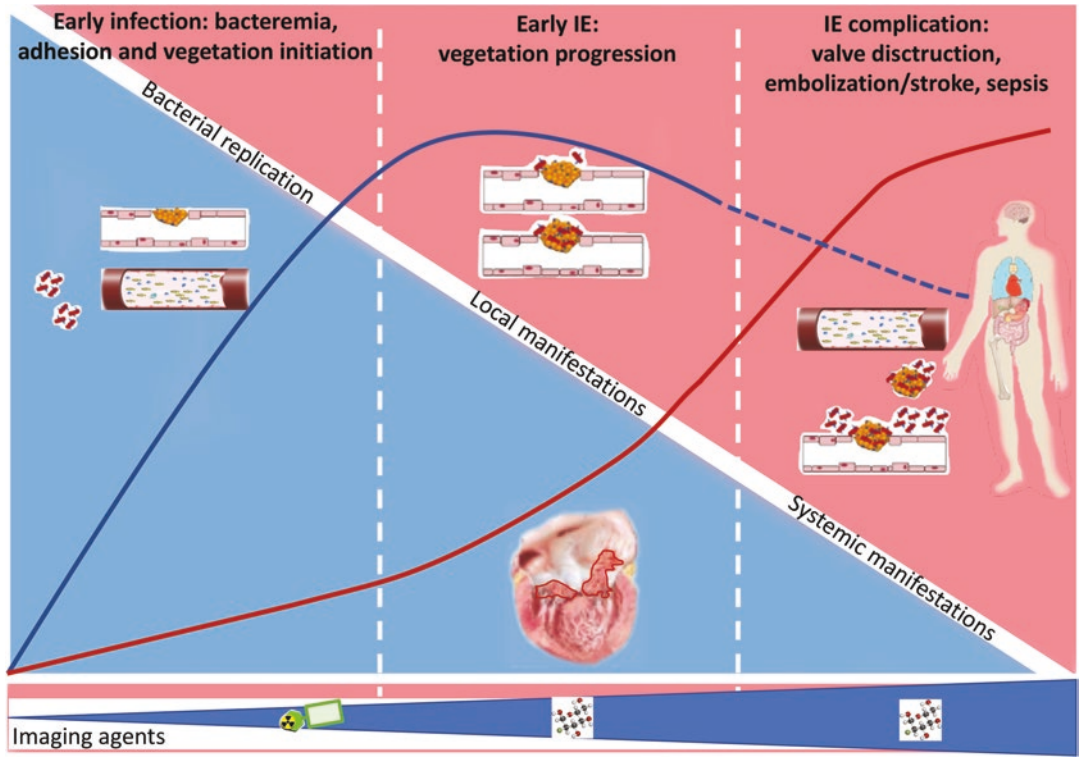

Fig. 12.3 Schematic representation of IE pathogenesis from the microorganism entrance and subsequent heart native valve/prosthetic valve adhesion to local and systemic manifestations of the disease. In the lower panel, the type of radiopharmaceutical agents to be used in relation to the different disease phase: bacterial specific agents potentially leading to early diagnosis or agents identifying the host immune response to infections such as WBC imaging and FDG. The blue curve indicates the intensity of the local infection burden while the red curve the intensity of systemic infection

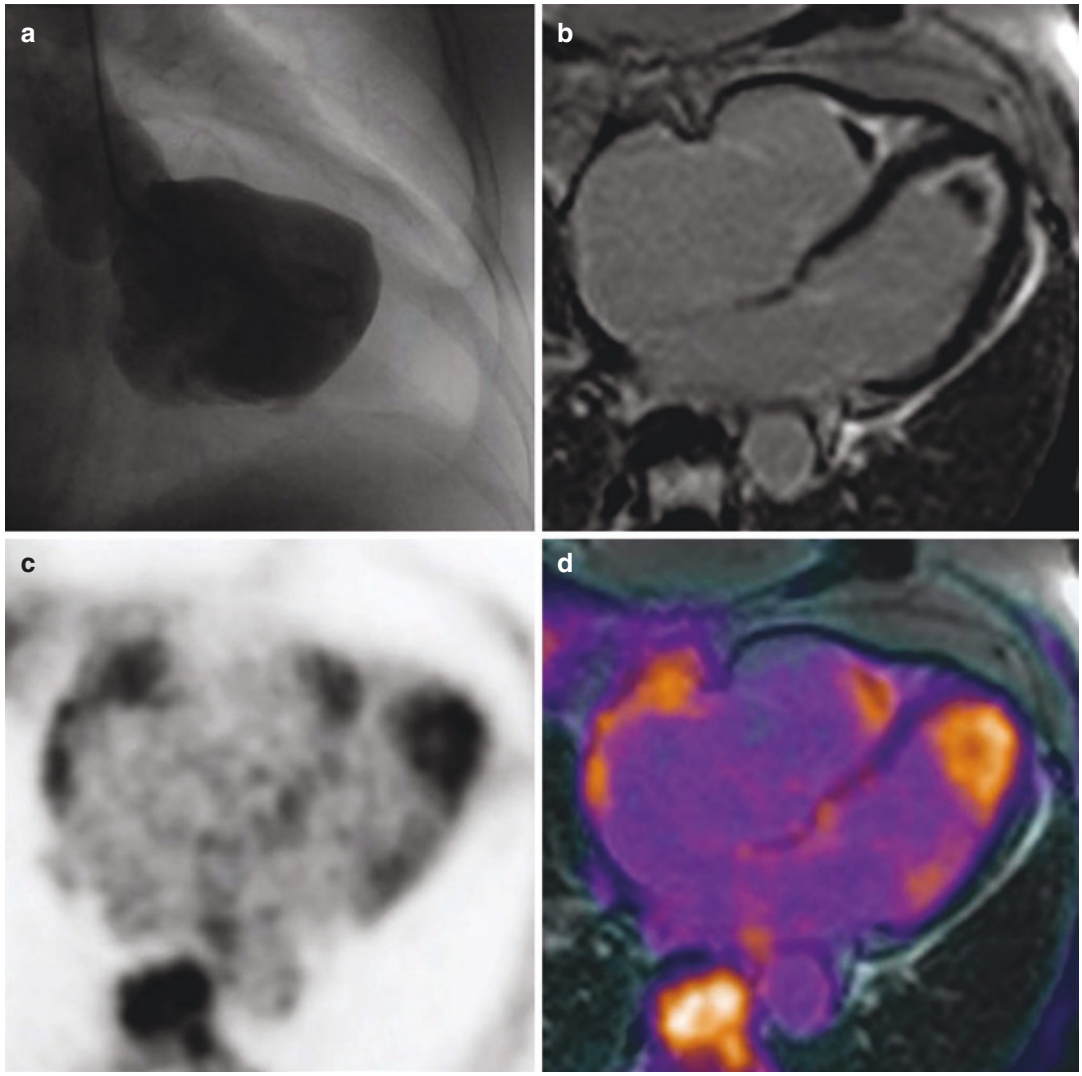

Fig. 12.4 FDG PET/MR images in a case of Loeffler endocarditis. (**a**) Left ventriculography showing thickening of the apical endocardium of the left ventricle. (**b**) Magnetic resonance imaging in four-chamber orientation depicting late gadolinium contrast-enhanced (LGE) lesions restricted circumferentially to the endocardium within the apical region of both ventricles in contrast to an apical mass in the left and right ventricle without LGE. (**c**) FDG-PET in four-chamber orientation demonstrating significant FDG uptake within the whole-apical region of both ventricles. (**d**) Superimposed MRI and FDG-PET in four-chamber orientation, confirming FDG uptake not only in the LGE region but particularly within the apical mass of both ventricles identifying the presence of active inflammatory tissue. (Reprinted from Langwieser et al. [34])

Specific Technical Considerations

For an optimal test, special attention must be paid to the patients' preparation, the imaging protocol, and the study interpretation. An extensive review of the main critical technical issues is provided in the "Recommendation on nuclear and multi-modality imaging in IE and CIED Infections" and in the "EANM Procedural recommendations of cardiac PET/CT imaging standardization in inflammatory-, infective-, infiltrative-, and innervation (4Is)-related cardiovascular diseases: a joint collaboration of the EACVI and the EANM" [35].

Patient Preparation

Patient preparation is very important to reduce the physiological uptake of FDG of the myocardium (see Chap. 4). There is a general agreement to use patient preparation protocols including a high-fat diet lacking carbohydrates for 12–24 h prior to the scan combined with a prolonged fasting period of 12–18 h, with or without the use of intravenous heparin of 50 IU/kg approximately 15 min prior to FDG injection [36–38]. In addition, strenuous exercise should be avoided for at least 12 h prior to the exam. Following FDG injection, and before images are obtained, the patient should continue to fast and should refrain from any physical activity, as both will enhance myocardial glucose uptake. Hyperglycaemia does not represent an absolute contraindication to performing the study [39]. In fact, a study by Rabkin et al. demonstrated that neither diabetes nor hyperglycaemia at the time of the study had a significant effect on the false-negative rate in infection and inflammation imaging [40]. FDG should be injected no sooner than 4 h after subcutaneous injection of rapid-acting insulin or 6 h after subcutaneous injection of short-acting insulin. FDG administration is not recommended on the same day after the injection of intermediate-acting and/or long-acting insulin [41].

Radiopharmaceutical: Administered Activity

The administered activity can vary based on the type of PET scanner used and acquisition duration. The EANM guidelines on FDG-PET imaging in inflammation/infection suggest an administered activity of 2.5–5.0 MBq/kg, which represents 175–350 MBq or 4.7–9.5 mCi for a 70-kg standard adult. In the USA, the recommended FDG administered activity is 370–740 MBq (10–20 mCi) for adults and 3.7–5.2 MBq/kg (0.10–0.14 mCi/kg) for children [39].

Concomitant Treatments

Although antimicrobial treatment for cardiac infection is expected to decrease the intensity of inflammation and therefore FDG accumulation [42], there is currently no evidence to routinely recommend treatment discontinuation before performing PET/CT. The risk of false-negative FDG-PET scans is probably the lowest if the patients are imaged when their CRP is >40 mg/L [43]. This contrasts with inflammatory disorders such as large vessel vasculitis where treatment with steroids can lead to false-negative results [44].

Other Special Considerations

FDG imaging can be safely performed in patients with kidney failure, although image quality may be suboptimal and prone to interpretation pitfalls [45]. Creatinine and/or glomerular filtration should be evaluated, according to national guidelines, if intravenous contrast agents will be administered. If renal function is impaired and FDG-PET/CT examination with intravenous CT contrast agent is deemed necessary, then adequate prevention of nephrotoxicity should be performed according to local or society guidelines.

Image Acquisition Protocol and Postprocessing

Image acquisition generally starts 45–60 min following radiotracer administration, and acquisition duration depends on the sensitivity of the scanner and administered dose. The time interval between FDG injection and scanning is critical if semiquantification using SUV is intended, but less important for visual reading only. Although the recommended interval is 60–90 min for cardiovascular imaging (similar to tumour imaging), 120–180 min is sometimes applied to help assess inflammatory activity in the vascular wall and

left ventricle due to lower background activity in the blood pool [39, 46, 47], but these extended time intervals could be less effective in infection detection [48].

A specific acquisition protocol is used for IE imaging. First, a total body acquisition with a field of view extending from skull base to mid thighs is performed. Imaging of the lower limbs and brain can also be considered. Total body FDG-PET imaging is particularly useful in patients with suspected systemic involvement and can identify septic emboli, mycotic aneurysms, and the portal of entry (POE). This first acquisition can be ECG-gated and include a prolonged acquisition of the cardiac region, which can be separately reconstructed to improve evaluation of the heart. A separate and dedicated cardiac bed ECG-gated acquisition may improve image quality, particularly in coronary atherosclerosis assessment and PVE, but supporting literature is scarce [49]. A respiration-averaged low-dose CT can be considered for attenuation correction of the thorax, as this will likely give better alignment between PET and CT over the heart. Otherwise, the recommendations for low-dose CT attenuation correction for tumour imaging with FDG can be followed.

Diagnostic CT angiography (CTA) scan might also be performed, to maximize the diagnostic information provided by the exam. The technical requirements for performing PET/CTA with a hybrid PET/CT scanner are cardiac gating for both techniques and at least a 64-detector row CT. For the evaluation of left-sided PVE, an arterial phase ECG-gated CTA must be performed. When PET/CTA is performed to diagnose device infection, a prospective, ECG-gated, venous phase CTA sequence is recommended to evaluate local soft tissue changes, lead vegetation, and venous thrombosis of the vascular accesses [35]. The routine iodinated contrast injection protocol should be adjusted individually to the patient's body mass index and the scan duration. A typical injection consists of 50–120 mL of isomolar iodinated contrast medium at a flow rate of 4–7 mL/s, followed by a 30–50-mL saline chaser [50]. Optional is the use of diluted contrast which may help define the four heart chambers and make anatomic localization of endocarditis easier (triphasic contrast administration for better delineation of the right and left cardiac chambers).

Medication potentially interacting with intravenous contrast agents (e.g., metformin) and relevant medical history (e.g., compromised renal function) should be taken into consideration. Renal function should generally be assessed in this group of patients before administration of contrast agents because of possible nephrotoxicity. Patients with a higher risk of contrast agent-induced nephrotoxicity include those with an eGFR < 30 mL/min/1.73 m^2 [51]. Furthermore, attention must be paid to patients with a history of previous contrast agent hypersensitivity reactions. Premedication with glucocorticoids and H1- and H2-blockers reduce the risk of an anaphylactic reaction, but unenhanced CT should generally be performed in patients with a known severe contrast reaction.

In cases of IE and CIED infection, combining FDG-PET with CTA is helpful in the identification of a larger number of anatomic lesions and in reducing the number of equivocal scans [52, 53]. CTA can help in the diagnosis of pseudoaneurysm, fistulas, and abscesses associated with infected valves and for the accurate assessment of valve prostheses. CTA is especially useful in patients with aortic grafts, or congenital heart diseases and complex anatomy. Another advantage is that in case of aortic valve IE, CTA can provide useful information about the anatomy of the valve, such as the size or extent of any calcification of the valve and ascending aorta, as it can also differentiate between pannus vs. thrombus/vegetation in case of elevated transvalvular pressure gradients. This information is important for a proper surgical management.

The protocol for cardiac PET/MR in IE requires the acquisition of MR attenuation cor-

rection sequences, total body PET, followed by an ECG-gated cardiac PET including the area from the aortic arch to the upper border of the diaphragm (12 cm, with an approximate duration of 30 min). Multiparametric MR sequences are performed simultaneously with PET with different sequences possible such as cine sequences, T1- or T2-weighted turbo spin echo, perfusion, and valvular phase contrast sequences. In case of contrast use, short-axis delayed-enhancement sequences at 10 min following contrast agent injection, with coverage from the base to apex of the heart. Figure 12.2 shows a schematic summary of the FDG-PET/CT, PET/CTA and PET/MR protocol generally used for imaging patients with PVE.

Image Reconstruction

Image reconstruction with and without attenuation correction is recommended to identify potential reconstruction artefacts. Metal artefact reduction techniques are useful to minimize overcorrection. In general, images should be reconstructed according to the guidelines for tumour imaging with FDG-PET/CT [35], using iterative reconstruction with a product of subsets and iterations between 40 and 60. Use of TOF and resolution recovery is recommended as it has been shown to improve disease detectability in cardiac PET [54]. All corrections necessary to obtain quantitative images should be applied during the reconstruction. More advanced image reconstruction methods, such as penalized reconstruction, are possible; however, the use of these methods is rather limited to visual assessment and should not be used interchangeably with regular iterative reconstruction methods [55].

Image Quality Assessment

Image quality should be assessed as suggested in the procedural recommendations of cardiac PET/CT imaging [35] as follows: overall quality (good, average, low), motion artefacts, abnormal biodistribution, quality of FDG suppression in the myocardium (full suppression, partial suppression, unsuppressed). In particular, the proper suppression of FDG signal in the myocardium should be considered before reporting. Physiological myocardial FDG uptake usually occurs in a diffuse intense pattern across the myocardium but can also demonstrate regional variation. In the absence of adequate myocardial suppression, the compliance of the patient to the preparative procedures should be verified, and this information is included in the report. Standard commercial software programs can be applied for reading and quantifying FDG data.

Image Analysis and Interpretation Criteria

FDG-PET/CT images must be visually evaluated. Both CT-attenuation corrected and non-corrected PET images are evaluated in the coronal, transaxial, and sagittal planes, as well as in tridimensional maximum intensity projection (MIP) cine mode. FDG-PET images are visually analysed by assessing increased myocardial FDG uptake, taking into consideration the pattern (focal, focal on diffuse, linear, diffuse), intensity, and relationship to adjacent areas of physiologic distribution (Fig. 12.5). The location, pattern, and intensity of the FDG uptake at the valve should be described and localized as intravalvular (in the leaflets), valvular (following the supporting structure of the valve), or perivalvular (next to the valve). Focal and/or heterogenous perivalvular uptake is the most common finding in case of PVE. In TAVR IE cases, focal or multifocal activity surrounding the prosthetic ring, more intense than the normal pulmonary parenchyma on the non-attenuation-corrected images, is highly suspicious of PVE.

PET information should always be compared with the morphologic information available from the CT, including contrast-enhanced CT scans when available. It must be kept in mind that the sensitivity of FDG for infection and inflammation is not perfect and that even in the absence of significant FDG uptake, a thorough analysis of the CT component is essential.

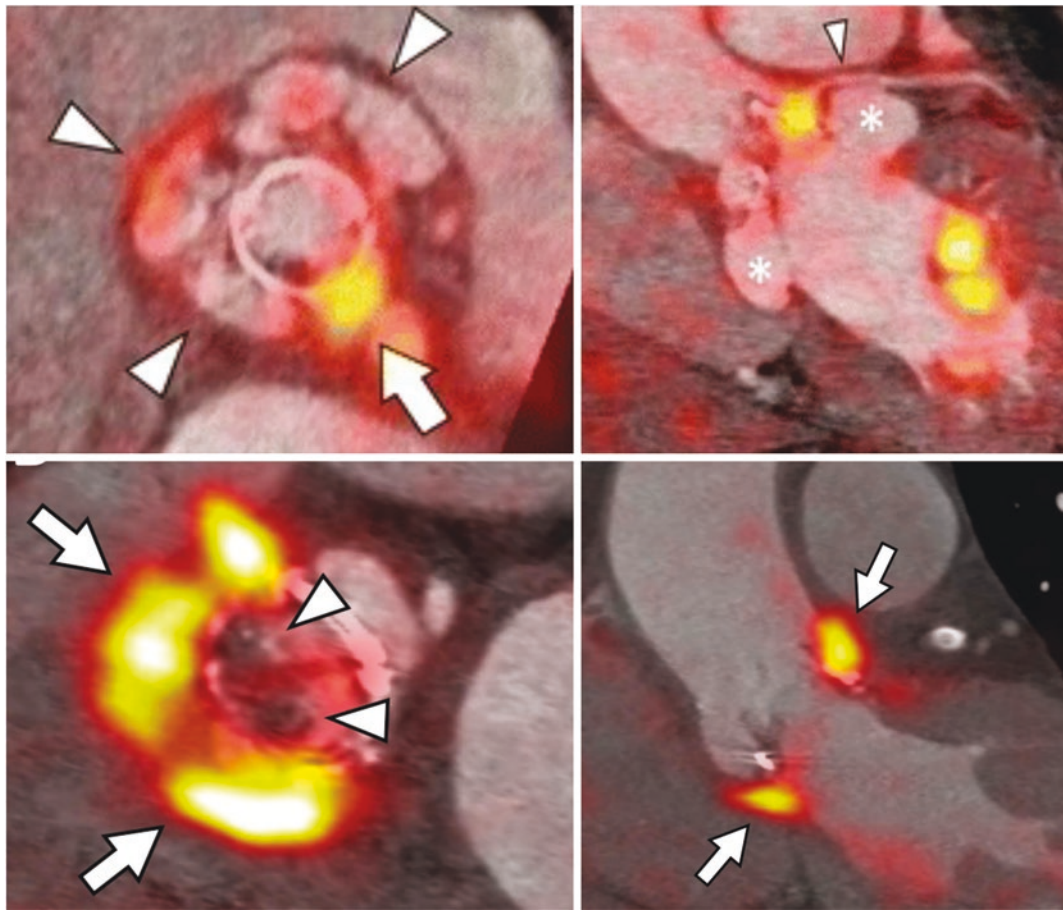

Fig. 12.5 Example of the typical pattern of focal heterogeneous peri-valvular uptake considered a positive finding for FDG-PET/CT in patients with PVE

Semi-quantitative analysis with the standard uptake value (SUV) is possible. However, as opposed to oncology applications, SUV has not been validated in inflammation and infection. If SUV is used, all the factors influencing its quantification should be carefully considered, including those related to patient preparation (glycaemia, concurrent treatment, etc), time of uptake and the use of positive contrast. Although higher SUV may be more suggestive of infection, there is significant overlap with inflammation and uptake distribution must be taken into account in the interpretation.

Several physiological variants and pathological conditions should be recognized to prevent false-positive scan. A physiological variant that might be misinterpreted as PVE is increased activity along the posterior aspect of the heart, which may represent lipomatous hypertrophy of the interatrial septum, presenting as a fat-containing mass with increased FDG uptake [56]. Focally increased FDG uptake might be found in many other conditions such as active thrombi [57], soft atherosclerotic plaques [58], vasculitis [59], primary cardiac tumours [60], cardiac metastases [61], post-surgical inflammation [62], foreign body reactions [63], stitches [64], and Libman-Sacks endocarditis [65]. The use of surgical adhesives (i.e., Bioglue) can result in false-positive scan findings after valve surgery [66]. Post-operative inflammation characterized as diffuse, homogeneous distribution of FDG in the absence of associated anatomic lesions, can also lead to a false-positive scan and can persist for at

least 1 year after surgery as suggested by a recent prospective study in patients undergoing FDG-PET/CTA at 1, 6, and 12 months. In fact, the results of this study show that FDG uptake might be present in implanted prosthetic valves from the recent post-operative period, with a typical diffuse and homogenous distribution pattern and mild intensity in relation to post-operative inflammation which can be defined a "normal" FDG morphological and metabolic pattern of non-infected prosthetic valves (Fig. 12.6). Such uptake is very different from the focal/heterogeneous pattern of infected prosthetic valves and remains stable during the first year after surgery [67]. Therefore, based on these results, the 3-month interval recommended in the ESC 2015 guideline [25] seems to lose value, and depending on the level of risk for infection in the presence of noncomplicated valve surgery, scans <3 weeks surgery can be considered [66].

On the other hand, prolonged antimicrobial therapy can reduce FDG intensity despite persistent infections. All these confounder factors should be taken into consideration when interpreting the images. In all cases, correlation with clinical features, ECHO, and CTA findings is necessary. In doubtful cases, white blood cell single-positron emission tomography (WBC-SPECT) can further help define the presence/absence of infection at PVE.

Several semiquantitative parameters have been tested to quantify the FDG uptake in PVE, such as the highest SUV (SUV_{max}) in the valvular region and the prosthetic to background ratio (PBR) which takes into account the variability of the signal related to blood pool activity and image noise, by correcting valve SUV values by background activity in non-affected myocardium. Nonetheless, final interpretation relies on the integration of several parameters

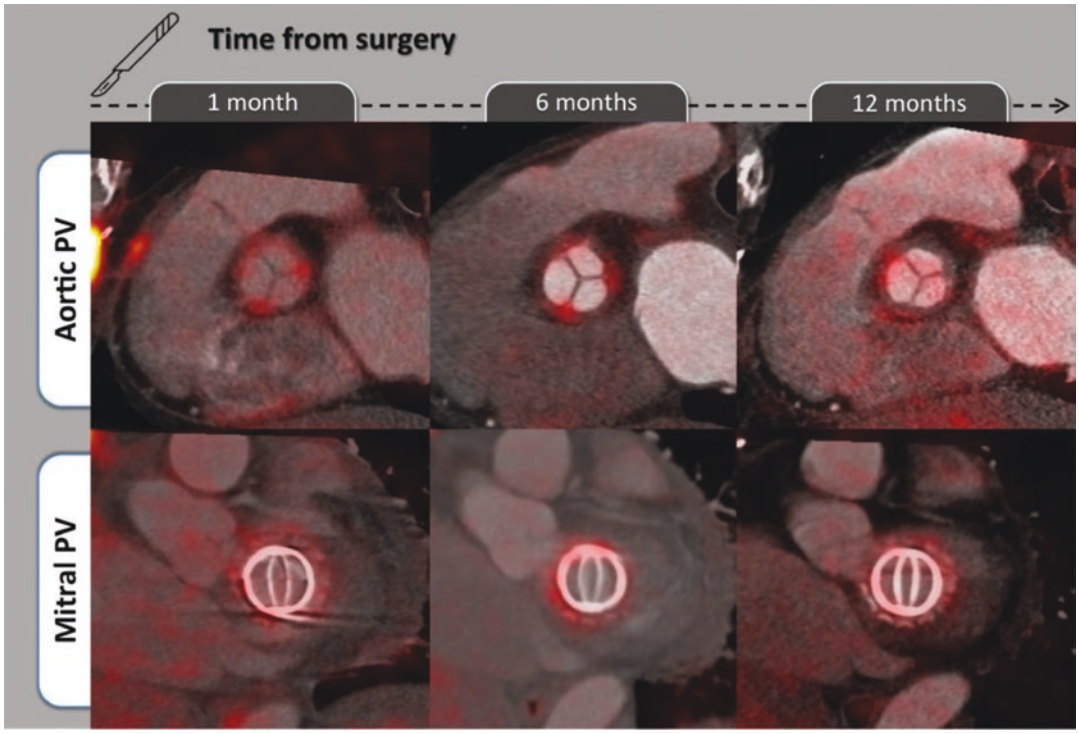

Fig. 12.6 Changes in anatomic and metabolic features over time. Aortic bioprosthesis (upper row) and mitral mechanical prosthesis (lower row) show stable FDG uptake distribution and intensity at 1, 6, and 12 months after surgery. No anatomic lesions appeared at any time point of follow-up. (Reproduced from Roque et al. [67])

including visual analysis and should not rely on a single quantitative index.

Overall Clinical Performance

A recent meta-analysis showed an overall pooled sensitivity and specificity (95% CI, inconsistency I-square statistic) of 0.74 (0.70–0.77, 71.5%) and 0.88 (0.86–0.91, 78.5%) for all cases of endocarditis. For native valve IE, sensitivity was 0.31 (0.21–0.41, 29.4%) and specificity was 0.98 (0.95–0.99, 34.4%). For PVE, sensitivity was 0.86 (0.81–0.89, 60.0%) and specificity was 0.84 (0.79–0.88, 75.2%). Interestingly, the pooled sensitivities and specificities were higher for the 17 most recent studies published after 2015 compared to the nine studies published before 2015, which could be explained by improved imaging techniques and interpretation [68]. The addition of FDG-PET/CT to the modified Duke criteria increased sensitivity for a definite IE from 52–70% to 91–97% [69] by reducing the number of possible PVE cases. This finding has been confirmed in several series [52, 70–76]. The presence of FDG-PET/CT uptake as a major criterion of the ESC 2015 was present in 40.9% of patients without major echo criteria (in this study, ECHO sensitivity was 68.1% [57.5–77.5%] with a specificity of 62.5% [40.6–81.2%] while the sensitivity of FDG-PET/CT was 73.6% [63.3–82.3%] and specificity 75.0% [53.3–90.2%.]). Therefore, by adding FDG-PET/CT in the ESC 2015 classification, the sensitivity of the Duke criteria increased from 57.1% (95% CI: 46.3–67.5%) to 83.5% (95% CI: 74.3–90.5%) ($p < 0.001$), with a relative decrease in specificity from 95.8% (95% CI: 78.9–99.9%) to 70.8% (95% CI: 48.9–87.4%). However, in cases of high clinical suspicion of IE, the absolute increase in true positive findings was higher than the absolute decrease in the occurrence of false positive using the ESC 2015 classification instead of the Duke criteria [77]. Indeed, applying the proper interpretation criteria, high sensitivity (87%) and high specificity (92%) have been reported [52, 78], underlying the need to use specific PET/CT criteria (typical findings) in imaging reading and proper discussions of the results within the Endocarditis Team [77].

FDG-PET/CT has been reported to have similar sensitivities for vegetations, perivalvular sequelae, and prosthetic valve dehiscence compared with ECHO [71]. However, the value of FDG-PET/CT is more limited in NVE [79, 80]. The more frequent presence of isolated valve vegetation, rare para-valvular involvement, lower predominance of polymorphonuclear cells, and increased fibrosis in NVE compared with PVE result in reduced inflammatory response and subsequently lower FDG uptake [81]. Notably, the lower sensitivity of FDG-PET/CT is offset by a near perfect specificity for the detection of NVE and an unrivalled ability for identifying septic emboli [79, 82]. Thus, in the case of NVE, the use of FDG-PET/CT is mostly useful for the detection of distant embolic events, a condition currently considered a minor criterion in the 2015 ESC guidelines. The application of gated-PET may further improve it [83].

When FDG-PET/CTA is performed, the sensitivity and specificity increased to 91%, with a positive predictive value of 93% and a negative predictive value of 88% [52, 84]. In association with the Duke criteria, FDG-PET/CTA allowed reclassification of 90% of the cases initially classified as possible IE and provided a more conclusive diagnosis (definite/reject) in 95% of the patients. By adding CTA to PET/CT, it is also possible to assess the entire chest identifying septic pulmonary infarcts and abscesses, evaluate the aorta and the coronary arteries in prevision of surgery. Figures 12.7 and 12.8 present two examples of FDG-PET/CT contribution in patients with suspected PVE.

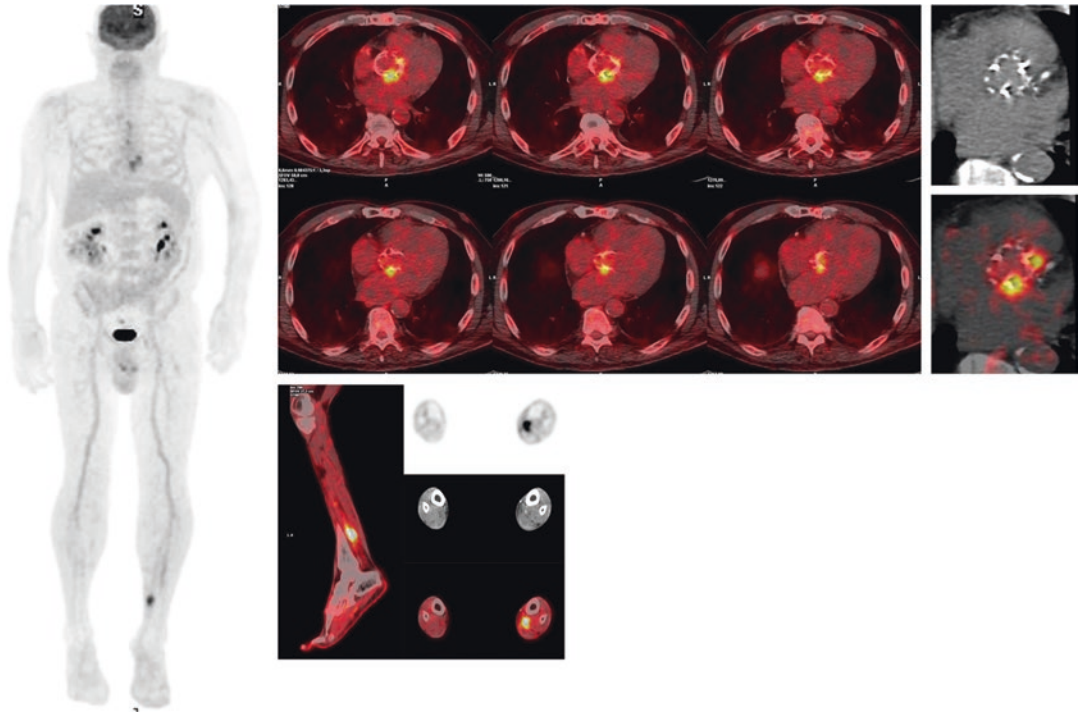

Fig. 12.7 A 73-year-old gentleman with persistent fever. Aortic valve replacement with a biological aortic valve prosthesis was performed in March 2020. TTE and TOE showed a periprosthetic leak. Repeat blood cultures were negative. FDG-PET/CT images (Discovery 710 PET/CT GE Healthcare, from left to right MIP, transaxial superimposed images of the thorax at different levels, and transaxial CT at upper level and superimposed PET/CT at lower level reconstructed) show a focal area of increased uptake at the perivalvular region, adding a major criterion to the ESC classification, thus resulting in a 'Definite IE'. Furthermore, total body images also show uptake along the tibial artery, consistent of embolic localization as confirmed by follow-up images

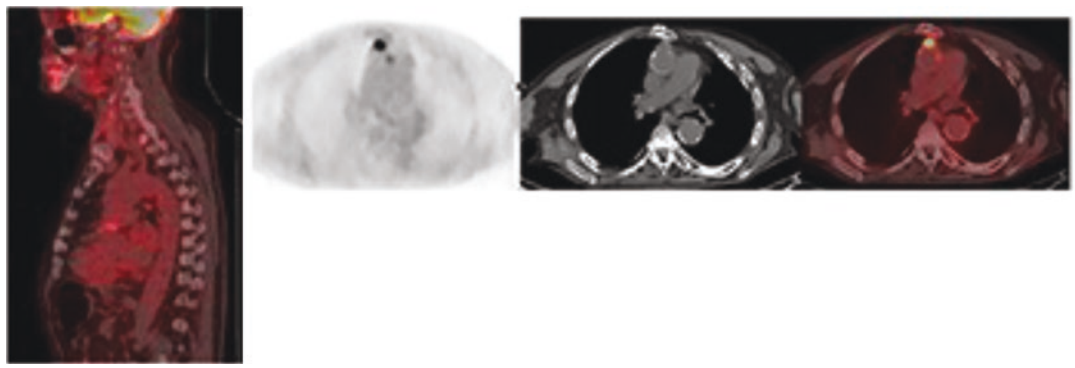

Fig. 12.8 Example of FDG-PET/CT (Discovery 710 PET/CT GE Healthcare) in patients with final diagnosis infection involving the aortic PV as shown by the PET/CT images of the thorax (from left to right, superimposed sagittal and transaxial emission, CT and superimposed images valve levels) showing an area of focal radiopharmaceutical uptake limited to the prosthetic aortic valve

Extra-Cardiac Manifestations

Extracardiac manifestations in IE (both NVE and PVE) are reported in 30–80% of patients. Most frequent are embolic stroke or septic embolization to bone, spleen, or kidneys [85]. Importantly, septic emboli are not always associated with symptoms [86–88]. The majority of emboli occur within the first 14 days after treatment initiation [89]. The localization of the emboli and their cerebral/extracerebral proportion vary according to the studies, in particular according to the frequency and modalities of imaging, and the proportion of right-sided and left-sided IE.

Whole-body FDG-PET/CT imaging is particularly useful in patients with suspected or proven PVE to identify septic emboli, mycotic aneurysms, and the POE, with the notable exception of cerebral septic embolism and mycotic aneurysms of intracerebral arteries owing to the high physiological uptake of FDG in the brain (Fig. 12.3). In these cases, CT or MRI is the modality of choice. Typically, septic emboli appear as focal areas of FDG uptake and most often affect the spleen, liver, lungs, and kidneys. Uptake at the intervertebral disks and/or the vertebrae (spondylodiscitis) suggests metastatic infection and can be also observed in muscles and joints (septic arthritis). Embolic events can be clinically silent in 20% of cases, especially those affecting the spleen or brain. On CTA, septic emboli appear as hypodense lesions. FDG-PET is more sensitive and specific than CTA for the detection of septic emboli (Fig. 12.9).

Early detection of septic emboli with FDG-PET/CT has a high sensitivity (87–100%) and specificity (80%) [69], at a reasonable cost-effectiveness, especially in patients with Gram-positive bacteraemia [90]. Extracerebral septic emboli were found in 24–74% of patients with definite IE; most of these peripheral emboli were silent (50–71%) and only revealed by FDG-PET/CT. In a case-control study, FDG-PET/CT detected extra-cardiac lesions in 57.4% of IE patients, representing the only initially positive imaging technique in about half of the patients with embolic events [91]. Detection of metastatic infection by FDG-PET/CT led to change of treatment in up to 35% of patients [92] and a two-fold reduction in the number of relapses [91]. FDG-PET/CT is very accurate in organs with low physiological uptake, but is of limited utility in ruling out the presence of brain emboli [93], where the use of CT/MRI is more appropriate.

The evaluation of disease extent by the identification of extracardiac extension has consequences

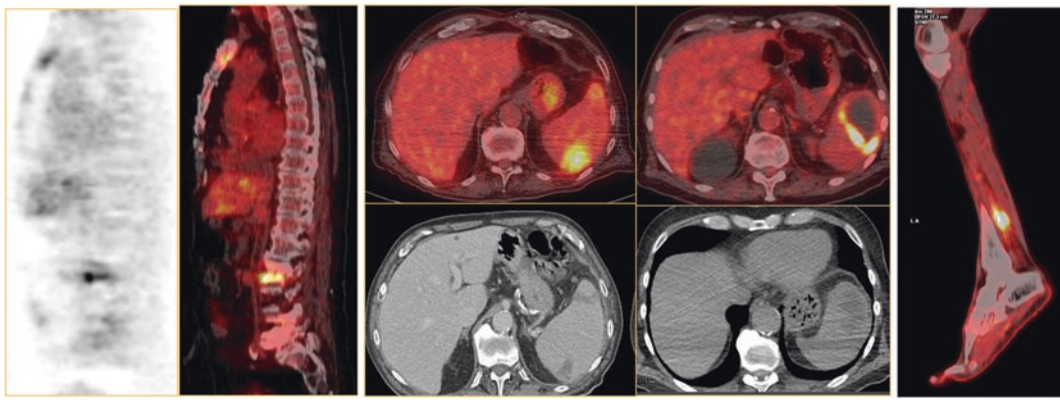

Fig. 12.9 Examples of embolic events detected at FDG-PET/CT (Discovery 710 PET/CT GE Healthcare) in the spine (right panel, sagittal emission, and superimposed images at left panel and corresponding MR images at right panel), spleen emboli (middle, upper panel superimposed PET/CT images, lower panel ceCT images) and in a case of mycotic aneurysm (left panel superimposed PET/CT images). In both cases, increased homogeneous FDG uptake is evident

on therapeutic management of IE, leading to a reduction of the risk of relapse. This has been shown particularly useful in the identification of unexpected infectious foci such as mycotic aneurysms [94], a potential life-threatening complication requiring specific treatment. Indeed, FDG-PET/CT has been demonstrated to lead to a change in therapy in 28% of patients, such as earlier cardiac surgery or initiation of a specific antimicrobial regimen for the treatment of the embolic foci [95]. In addition, in the Kestler case-control study, the systematic use of FDG-PET/CT was associated with a two-fold reduction in the number of IE relapses (9.6 vs. 4.2%) [91].

FDG-PET imaging in IE is also useful to identify the POE. Typical POE that can be identified are dental abscesses, sinusitis, infected central catheters, skin infection, and colonic cancers/polyps [6, 96]. The identification of the infection portal of entry at FDG-PET/CT and subsequent eradication of the sources of infection is particularly important in IE to prevent recurrence, either relapse and/or reinfection, a risk which varies between 2.7% and 22.5% [97–104]. The primary infectious site may be suspected based on the common biotope of the bacteria strain (digestive, skin, catheter). Yet, published research on this topic is very limited. In a recent study, systematic search for the POE identified the site of primary infection in 74% of patients, mainly cutaneous (40%), followed by oral or dental (29%) and gastrointestinal (23%) [105]. FDG-PET/CT has been demonstrated to reveal the source of infection, including cases where the sustaining POE was a neoplasia (colonic cancer) [52]. Once the portal of entry has been identified, risk modification can be attempted.

Multidisciplinary Discussion of Imaging Results

Multidisciplinary discussion of the multimodality imaging and laboratory findings is necessary to enhance their contribution into a clinical planning and decision-making process that delivers quality care in such complex contexts. A multidisciplinary team approach has been recently successfully extended beyond oncology where the work model is successfully established, such as in cases of valvular heart disease (the "Heart Valve Clinic"), particularly in the selection of patients for TAVR procedures, and coronary artery disease for revascularization decisions (Heart Team) [46, 106]. The first example of a multidisciplinary approach in the field of cardiovascular infections is represented by the Endocarditis Team (E-Team), a multidisciplinary "round table" involving specialists involving imaging, cardiologists, cardiac surgeons, infectious disease specialists, microbiologists, and others [25, 107]. This approach has been shown to significantly reduce the in-hospital and 1- and 3-year mortality in France, Italy, and Spain [37, 38]. Putting multimodality imaging in a central position in the diagnostic work-up of patients with suspected cardiovascular infections implies a new professional perspective for the "Clinical Imaging Specialist" who is called to be an active part and contributor within the E-Team. Very recently, this approach has also been recognized by the American Heart Association (AHA) 2020 guidelines for the management of patients with valvular heart disease [26] which now include FDG-PET/CT imaging and a multidisciplinary team approach in the assessment of patients with IE.

Conclusion

The application of multimodality imaging has improved the sensitivity to detect PVE, allowing for the early detection of complications such as septic emboli and metastatic infections even before these become clinically apparent. The role of multimodality imaging in the diagnostic work-up of cardiovascular infections is now well-established and supported by ample evidence. Discussion of the test results in the context of the clinical presentation in the framework of a Multidisciplinary Team Approach is recommended. Novel trends in radiopharmaceuticals developments as well as significant progress in technology, new insights on the various mechanisms that play a role in cardiovascular infections

will likely provide in the near future new diagnostic and therapeutic targets for further developments in the field.

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