Building Up the Diagnosis of Cardiac Device Infections: The Role of Imaging

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5.1 Introduction

Imaging represents only a part of the workup for the diagnosis of cardiac implantable electronic device (CIED) infection. Clinical examination, laboratory exams, blood cultures, and swabs all are mandatory steps for the diagnostic process, similarly to what occurs during diagnosis of endocarditis. However, since the diagnosis of CIED infection (CIEDI) may often be challenging, because signs and symptom may be mild or confusing [1], imaging has a key role in the management of a patient with suspect CIEDI, especially in patients without overt involvement of CIED pocket. Notably, the role of imaging techniques in CIEDI is not limited to rule out the diagnosis but also for the assessment of the extension of the infectious process, evaluation of presence of infective endocarditis, detection of complications of secondary localizations of infection and follow-up and as a help during transvenous lead extraction (TLE), and for planning CIED reimplantation. Echocardiography was the first of these imaging techniques introduced and it still represents the gold standard for detection of cardiac involvement in CIEDI, being echocardiographic positivity the only imaging data included as a standard major criteria for the assessment of endocarditis according to modified Duke criteria [2]. However other approaches, either anatomical like computed tomography or functional like nuclear imaging, are involved in a growing expanse of their indications and are currently included in guidelines [3].

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5.2 Echocardiography

Echocardiography, both transthoracic (TTE) and transesophageal (TEE), represents the gold standard for diagnosis of infective endocarditis [3], being the imaging technique of choice for the assessment of modified Duke criteria [2]. Standard TTE is an easy accessible methodic and should be always performed in patients with a suspicion of CIEDI during the initial evaluation; in addition, TEE should be considered in patients with possible CIEDI [3], given their complementary data.

5.2.1 Vegetations in Patients with CIEDI

Presence of vegetations is the most important findings provided by echocardiography when CIEDI is suspected (Fig. 5.1). Vegetations are defined as oscillating masses with motion independent from the heart, attached to a native cardiac valve, to endocardial surface, or to prosthetic material like prophetic valve or CIED leads [4]. When these characteristics are met this finding fulfills one of the major criteria for modified Duke criteria used for diagnosis of endocarditis (Table 5.1) [2]. In general vegetations can be identified in 20–25% of patients with CIEDI [5, 6].

The superior sensitivity of TEE vs. TTE for identification of infective vegetations, for the closer distance to involved structures without interposition of lungs, is well known. TEE sensitivity and specificity for the detection of tricuspid valve vegetations are 70% and 96% for native cardiac valves, while it is lower for prosthetic valves 50% and 92%, respectively [7]. For comparison, the reported sensitivity of

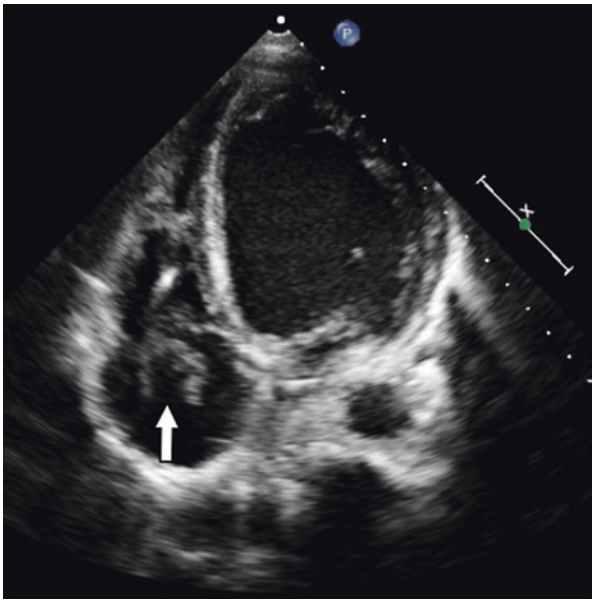

Fig. 5.1 Valvular vegetations in CIED-related endocarditis. Transthoracic echocardiogram in a patient with CIED infection, which shows a large vegetation (pointed by the arrow) attached to the atrial side of the tricuspid valve

Table 5.1 Modified Duke criteria for the diagnosis of endocarditis

Major Criteria
1. Positive blood cultures, either by: (a) Microorganism typical for IE (viridans streptococci, *Streptococcus gallolyticus*, HACEK group, *Staphylococcus aureus*, community-acquired enterococci), found in at least two separate BC (b) Microorganism consistent with IE from repeated positive blood cultures (at least two positive BC obtained with a time interval >12 h; all of three or the majority of four positive separated BC; a positive BC for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800) 2. Evidence of cardiac involvement at imaging (a) Echocardiogram positive for IE (perform TEE if there is at least a "possible IE" according to clinical criteria, in patients with suspected complicated IE (i.e., paravalvular abscess) and in patients with prosthetic valves; TTE first in other cases)
Minor Criteria
1. Predisposition: predisposing heart condition or injection drug use 2. Fever as temperature >38 °C 3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, intracranial hemorrhage, conjunctival hemorrhages, Janeway's lesions 4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor 5. Microbiological evidence: positive blood culture that does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE

A diagnosis of "definite" endocarditis requires two major criteria, or one major and three minor criteria, or five minor criteria [2]. If those criteria are not met, a diagnosis of "possible" endocarditis is performed with one major criterion and one minor criterion or three minor criteria. *BC*, blood cultures; *HACEK*, *Haemophilus parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*, *H. influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*, and *K. denitrificans*; *IE*, infective endocarditis; *Ig*, immunoglobulin; *TEE*, transesophageal echocardiography; *TTE*, transthoracic echocardiography

TTE is far lower (22–43%) [8]. For CIED infections, the detection of lead-related vegetations is also well performed by TEE with a reported sensitivity of 91–96% [9–11], while the sensitivity of TTE is lower at 22–30% [12] (Figs. 5.2 and 5.3). Another advantage of TEE over TTE is the possibility to visualize vegetations in atypical locations hardly visible to standard TTE such as: the right atrium, the proximal portion of the superior vena cava, and some portions of the right ventricle [7], even if it should be underlined that TEE accuracy may be lower in these cases [8] which in specific cases can be overcome by intracardiac echocardiography (ICE; see below) [13]. Notably, use of TEE is particularly relevant in planning CIED removal to rule out involvement of native/prosthetic valve beyond CIED hardware. It has been estimated that a similar event occurs in 13–30% of all CIEDI [9, 10, 14] [for additional information see also Chaps. 1, 2, and 4] [7] and a similar evidence may drive the choice of preference to a complete surgical reparation in spite of standard transvenous lead extraction (TLE). Cardiac abscess is another CIEDI-related echocardiographic finding (Fig. 5.4), which is better visualized using TEE (90% sensitivity of TEE vs. 50% sensitivity of TTE) [7].

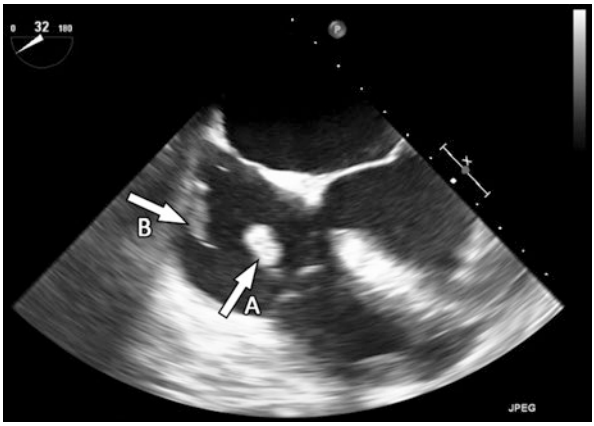

Fig. 5.2 Echocardiographic findings in CIED-related endocarditis. Transesophageal echocardiogram (TEE) provides a better visualization and a higher sensitivity for the detection of endocarditic vegetations. In this picture, TEE shows a large tricuspid valve vegetation (**a**) and also a vegetation attached to the right atrium wall (**b**)

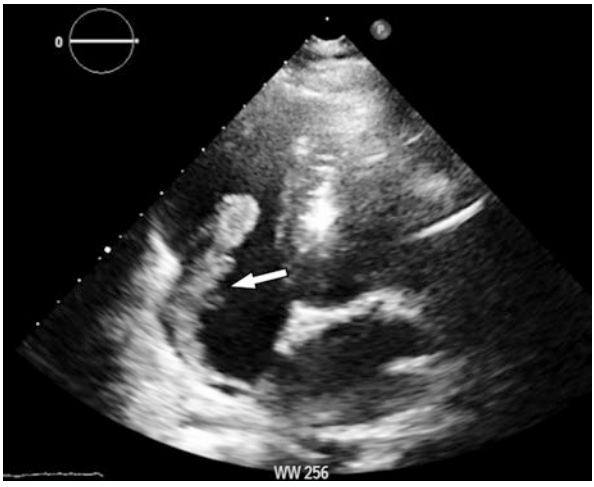

Fig. 5.3 Lead-related endocarditis. Transthoracic echocardiogram in a patient carrier of an infected CIED. The arrow points a large vegetation attached to the CIED lead

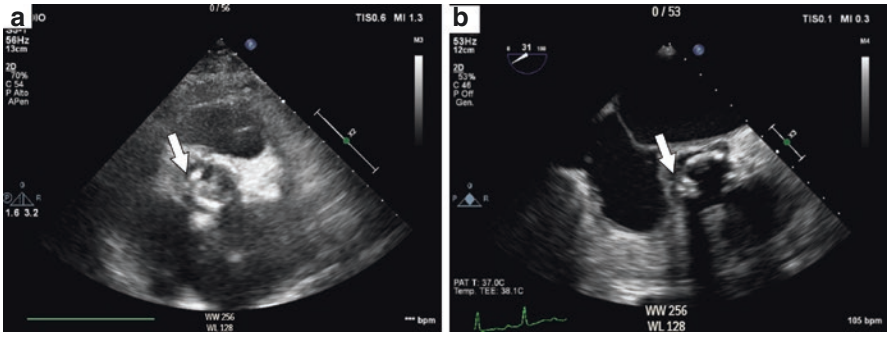

Fig. 5.4 Perivalvular abscess as an echocardiographic finding. Endocarditis-related abscess around aortic valve, visualized as an echogenic space in view of its liquid content. Both images have been obtained from the same patient, adopting transthoracic echocardiogram in (**a**) and transesophageal echocardiogram in (**b**)

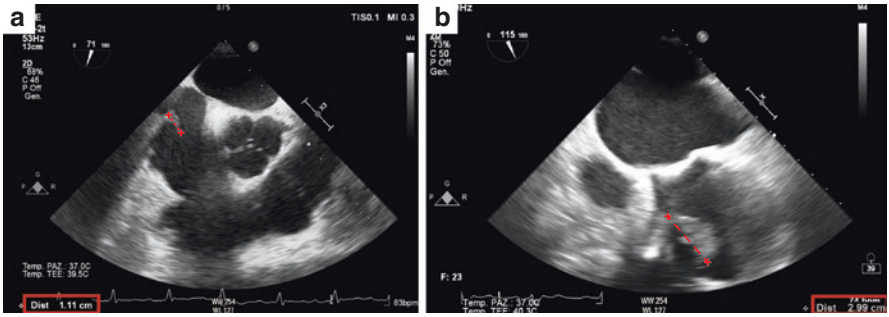

Fig. 5.5 Measurement of endocarditic vegetations. Echocardiography represents a useful tool for the measurement of endocarditic vegetations. Pictures **a** and **b**, obtained from transesophageal echocardiogram of two different patients with CIED infection, show vegetations of different size (highlighted in red)

Accurate visualization of infective vegetations is not only relevant for assessing the presence of CIEDI-related endocarditis but also to properly estimate their size, which is a factor of extreme relevance to plan CIED removal strategy (Fig. 5.5). Presence of vegetations in a patient with patent foramen ovale is a particular issue for the risk of paradoxical systemic embolization (e.g., risk of septic stroke) which is generally managed with surgical treatment [3]. The second major concern in patients candidate to TLE and vegetations is the risk of pulmonary embolism during TLE. In general during TLE it is expected to have limited pulmonary embolism from the thrombotic/infective material surrounding the leads; however it is really infrequent that this phenomenon is associated with relevant sequelae. Formerly, a cutoff of vegetation size >10 mm was proposed [11] to perform a surgical extraction, based on initial experience on complications after extraction. However, the same authors highlighted that while two of the five patients undergoing TLE with vegetations >10 mm presented scintigraphy evidence of embolism only one with a vegetation >40 mm presented nonlethal, hemodynamic consequences. On the opposite the four in-hospital deaths among 52 patients (7.6%) occurred either pre-extraction (two patients) or after surgical extraction (two patients with vegetation sizes of 14 and 20 mm, respectively). Subsequent studies demonstrated the safety of TLE even in patients with vegetations larger than 20 mm [15]. A retrospective review from Mayo Clinic [14] reported the absence of clinical relevant pulmonary embolism even in patients with large vegetations (range 0.3–7 cm). A consistent result was reported also in another retrospective study published by Baman et al. [16], in which the vegetation size and the presence of pulmonary embolism was not associated to patients' outcome. However, it should be underlined how in this study was reported a higher prevalence of patients with elevated (higher than 60 mmHg) right ventricular pressure and with pulmonary embolism among the death cohort. This may be due to the presence of a more severe disease in these patients, but another explanation is that these factors may represent the consequences of a prior embolization of larger vegetations. It should be noted, indeed, that the sizing of endocarditic vegetation depends by the timing in which echocardiogram is performed.

For all these considerations current guidelines do not provide a limitation in terms of vegetation size to proceed with percutaneous CIEDI removal, but they suggest to tailor the extraction strategy on an individual basis [17]. At this regard, it is important to consider the evolution of tools and techniques for CIED extraction that are providing additional approaches for challenging cases. In particular, the introduction of the AngioVac (AngioDynamics, Latham, NY) system has enabled experienced operators to free leads from vegetations by aspiration without the need for open-chest extracorporeal circulatory system and pulmonary bypass (*see below*).

A latter consideration is that TTE should not be disregarded in management of CIEDI since it is not inferior to TEE for general cardiovascular evaluation before TLE (left/right ventricular function, valvular dysfunction, etc.) but also after TLE. The easier repeatability of TTE makes it useful to monitor heart recovering and assess for some complications that can manifest/progress also later after TLE: left/right ventricular dysfunction, tricuspid regurgitation, pericardial effusion, and pulmonary artery pressure (which may increase in the presence of pulmonary septic embolism) [3, 7].

5.2.2 Limitations of Echocardiography for CIEDI Diagnosis

It should be underlined that a negative echocardiogram does not rule out CIEDI. Indeed, despite being the gold standard technique, TEE still presents a non-negligible rate of false negatives. The main reasons for the under detection of cardiac vegetations are as follows: (a) early use of TEE (during a stage in which vegetations are not present yet), (b) non-floating or atypically shaped vegetations (e.g., infective material along the course of the lead without a definite mass), (c) small vegetations, and (d) inadequate visualization (usually when intracardiac prosthetic material is present, causing a shadowing effect on echoes) [13]. Given the unsatisfactory negative predictive value, especially in patients with prosthetic material, if the clinical suspicious persists, a second imaging technique should be considered according to ESC guidelines [3].

Another reported limitation of echocardiography is the risk of false-positive results. This possibility rises from the intrinsic characteristics of echocardiography which in case of vegetations it provides information on size, shape, and movement. However, composition of the identified mass can only be speculated and differentiating sterile masses or thrombus from endocarditic vegetation may become a hard task [8]. This is especially frequent among CIED carrier, since the presence of strands and fibrous material is a common finding and may represent a confounding factor. Indeed, in a comparative study of TTE and TEE including both patients with an established diagnosis of CIEDI (n = 23) and controls (n = 70), TTE was positive in 7/23 vs. 21/23 with TEE. Notably, strands were visualized by TEE in 5/70 patients. The size of strands was lower (in general

1–2 mm wide and 3–5 mm long) and they were all localized in the right atrium [9]. In other reports incidental masses attached to CIED leads have been reported in up to 22% of the patients [9, 18, 19]. For this reason, Lo et al. performed a large retrospective study reviewing about 2000 consecutive TEE to identify patients with visible leads. Fifteen among the 125 exams with "explorable" CIED lead presented a mass and only 9/15 presented a pre-TEE suspect of CIEDI. The six patients with incidental mass were treated with medical therapy alone without sequelae [18]. Downey et al. performed a similar study analyzing 177 TEE from 153 candidates to TLE. They found lead-associated masses in 14% of them without any evidence of infective origin in about three quarters [19]. For these reasons, in patients without a clinical suspicion of CIEDI or with ongoing infection with other plausible sources, a second imaging technique, like positron emission tomography or white blood cell single-photon emission computed tomography, should be considered to define the nature of unclear masses.

5.2.3 Intracardiac Echocardiography

Intracardiac echocardiography (ICE) has been recently proposed as a further evolution of echocardiography with the potential to overcome some of the limitations of extravascular techniques, especially in CIEDI settings. This derives from a higher resolution and the possibility to closely study distant area (e.g., vena cava) (Fig. 5.6) [13]. A prospective study comparing the diagnostic accuracy of TEE and ICE was conducted by Narducci et al. [13] in 162 patients with a diagnosis of CIEDI and all referred for TLE. All patients underwent both TEE before TLE and ICE that was performed right before TLE and prosecuted during the procedure for monitoring possible complications. The authors also included a control group of patients referred to TLE for lead malfunction. ICE allowed higher sensitivity for vegetations (100% vs. 73% in patients with definite endocarditis), with no reported loss in specificity (all controls resulted negative for both techniques). The main advantages of ICE have been described in patients with intracardiac masses located in sites whose visualization at TEE is reduced, such as vegetations attached to the right ventricular lead, crossing the tricuspid valve. This is mostly due to the suboptimal visualization of the right ventricle with TEE, given the greater distance between the probe and this chamber, placed anteriorly [20]. Moreover, ICE allows detection of vegetations also in unusual sites like innominate vein [21]. The lower risk of shadowing artifacts from leads and other prosthetic materials also has a role [13], enabling the possibility to detect concentric masses around leads [8]. The main factor limiting a wider adoption of this methodic is the relatively high cost of the disposable devices and the need for the invasive nature of the procedure. For this reason, while it is clearly a helpful tool for monitoring patient during TLE, the indication for ICE in the diagnostic process of CIEDI have still to be defined.

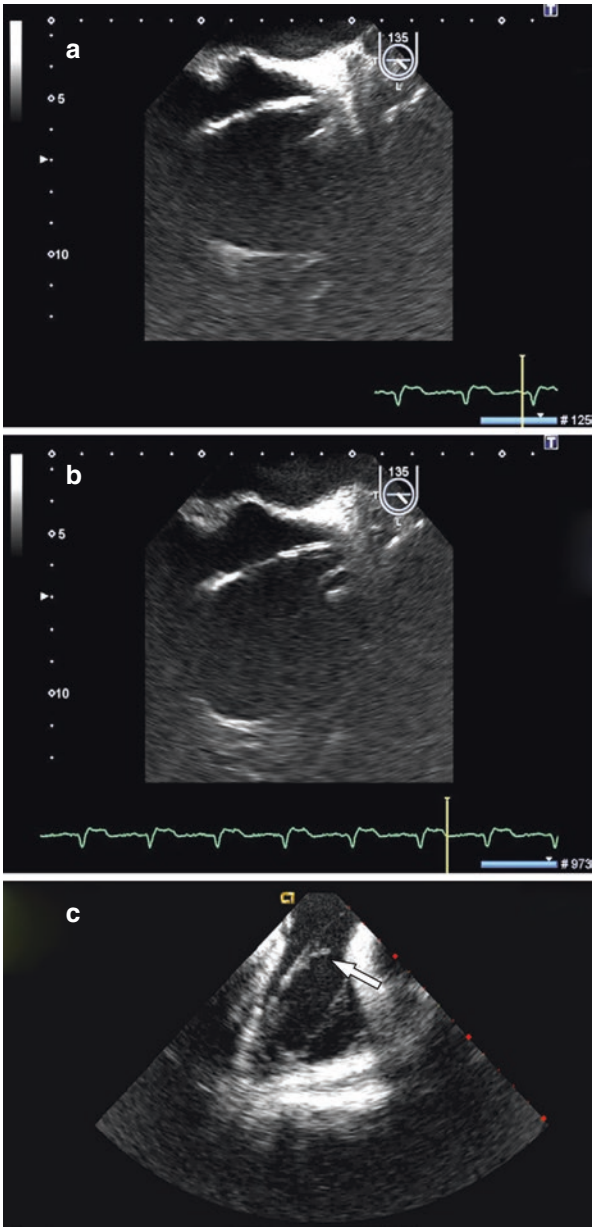

Fig. 5.6 Intracardiac echocardiography. Figures (**a**) and (**b**) show a transesophageal echocardiogram (TEE) of a patient with a suspect of CIED infection with no evidence of cardiac vegetations. The intracardiac echocardiography (**c**) shows a vegetation attached to the CIED lead, not visualized with TEE. (Reproduced from Narducci et al. [13] with permission)

5.2.4 Peri-/Postoperative Role of Echocardiography

As previously mentioned, echocardiogram plays also a role during TLE and for postoperative follow-up, to rule out possible complications [22]. In case of general anesthesia TEE is performed during TLE for a quick detection of vascular tears

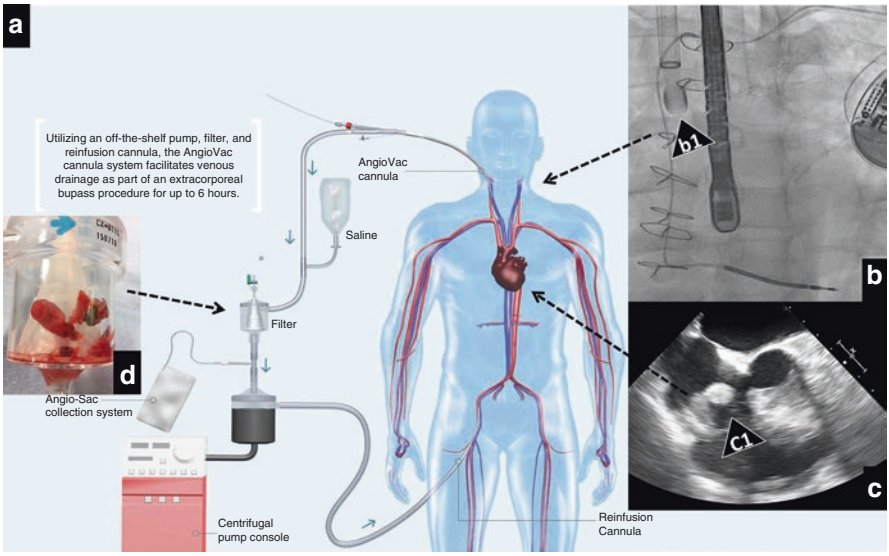

Fig. 5.7 Representation of the AngioVac system. AngioVac system (Panel **a**) (the image in the background is reproduced from Ram et al. [23] with permission). The AngioVac cannula (b1), inserted through the jugular vein under X-ray guidance (Panel **b**), drains the target vegetation (c1) under TEE guidance (Panel **c**), which is collected in the filter (Panel **d**). A reinfusion cannula is also inserted in the femoral vein to allow blood reinfusion

(with limited sensitivity), pericardial effusion, and embolization of vegetations. ICE, when available, represents an added value for improving detection of these findings but also for characterizing vascular obstruction and stenosis and the presence of fibrosis [8]. Moreover, ICE does not require general anesthesia to be used for monitoring during TLE, and this should be carefully considered when planning the procedure. A particular case is represented by candidates to percutaneous aspiration of vegetations. The AngioVac system is approved by The US Food and Drug Administration (FDA) "to remove fresh, soft thrombi or emboli during extracorporeal bypass for up to 6 h." It consists of a 22F suction cannula and is combined with a veno-venous bypass circuit and a reinfusion cannula through a filter canister, which traps any undesired material such as thrombus, before being reinfused into the patient via a reinfusion cannula (Fig. 5.7) [23]. Obviously to properly perform aspiration the procedure has to be performed under combined X-ray and echocardiography guide (TEE or ICE).

Notably, in patients who underwent TLE, aseptic residual tubular and mobile masses following the route of the extracted CIED lead have been found by echocardiogram (Figs. 5.8 and 5.9). One of the first reports of these was from Le Dolley who defined these images as "ghosts" [24]. The reported incidence for "ghosts" after TLE was 8% and authors observed a correlation between a diagnosis of CIED-related endocarditis and the detection of ghosts, which have never been observed in noninfected patients who underwent TLE. The proposed mechanism leading to

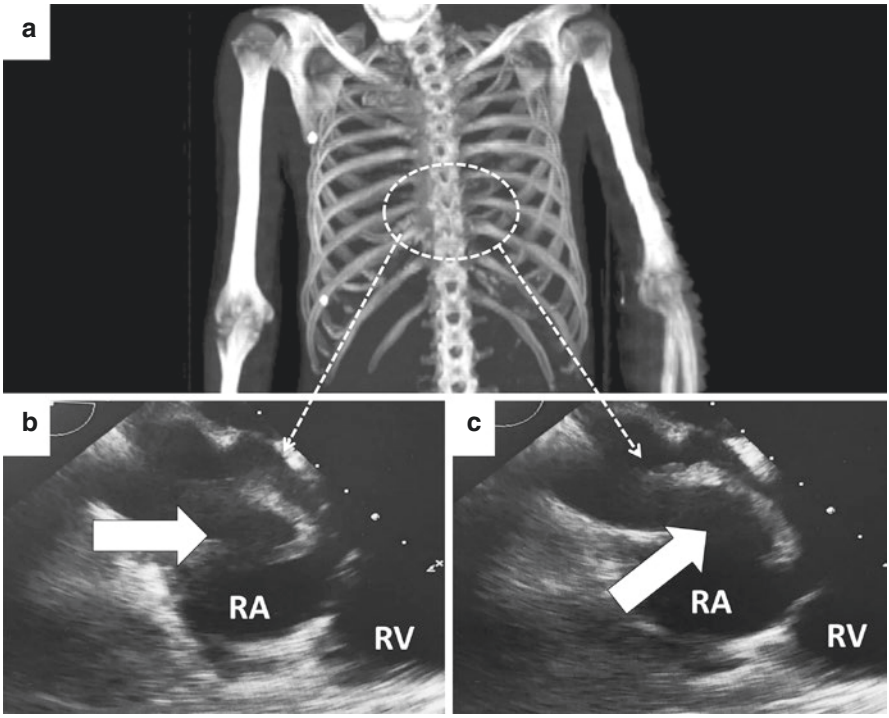

Fig. 5.8 "Ghost" found at echocardiogram. After complete extraction of all hardware (Panel **a**) the transesophageal echocardiogram shows a tubular mass fluctuating inside the right atrium, called "ghost" (Panels **b**, **c**; white arrows). *RA* right atrium, *RV* right ventricle

ghost formation after device extraction is the persistence, in patients with infection, of the fibrous sheath that surrounds the lead, with a possible overlap of vegetations. These findings should not be overlooked since the presence of "ghosts" has been associated with an over threefold increase in post-TLE mortality [25, 26].

5.3 Computed Tomography

The role of computed tomography in the diagnostic workup and risk stratification for endocarditis is a topic of growing interest during last years. When performed with ECG gating, computed tomographic angiography (CTA) demonstrated high performances for detection of morphological alterations and structural damage induced by the endocarditic process, like abscess, fluid collections, and vegetations [3, 27–29]. Technological progress allows very high levels of spatial resolution (<0.5 mm) and the ability to discriminate fast moving objects like hypermobile vegetations attached to valvular leaflets, with the possibility of tridimensional reconstruction of anatomical structures [28]. CTA findings may be helpful when performed in a patient with suspect endocarditis, but also have an added value even

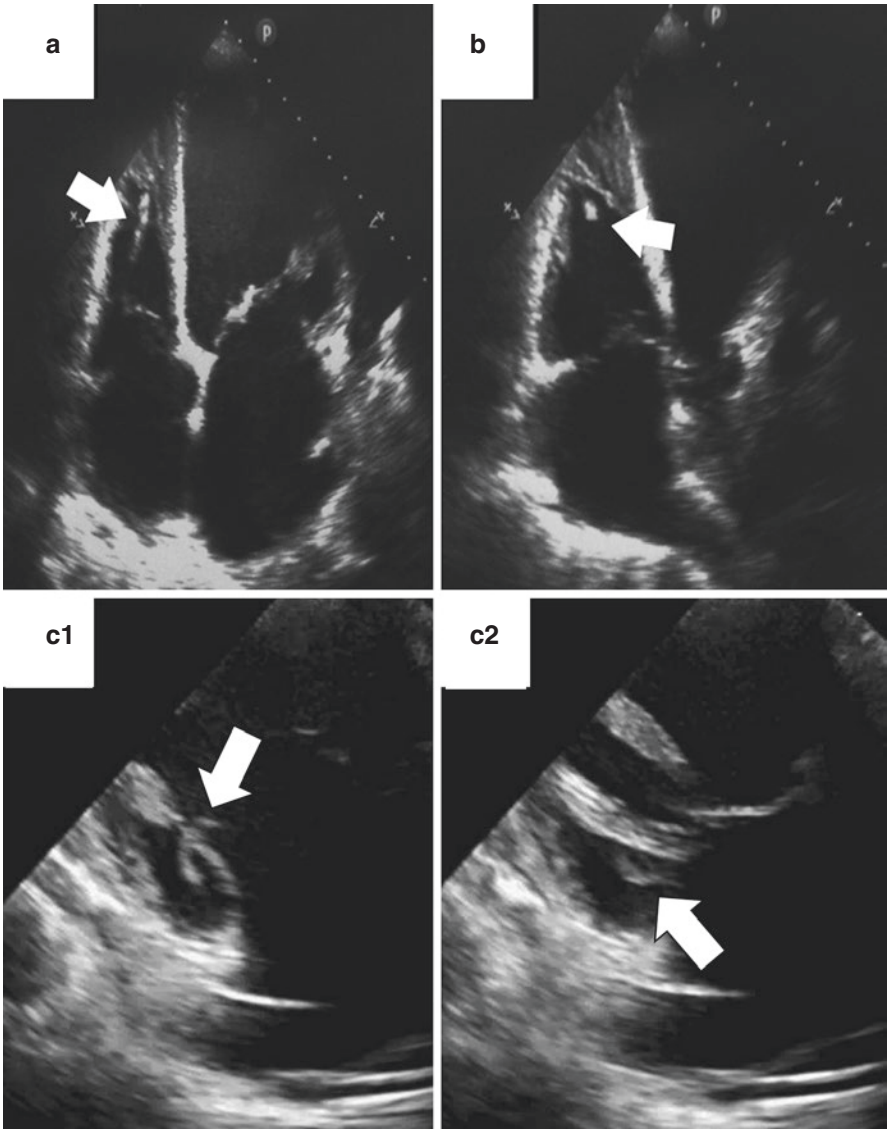

Fig. 5.9 Migration of a "ghost." Figure (**a**) is obtained from the transthoracic echocardiogram of a patient after the removal of an infected electronic device. A "ghost" is present (pointed by the arrow). Image (**b**) was recorded afterward from the same patient, showing the result of a spontaneous embolization of the "ghost" just below the tricuspid valve (**C1**, **C2**)

for those with an already established diagnosis, since it allows to detect most of endocarditic complications. CTA can detect cardiac vegetation and measure their size, thus stratifying the embolic risk, and if correctly set it is able to visualize valvular leaflet fissuration [28]. In addition, CTA has proven to be useful to assess the

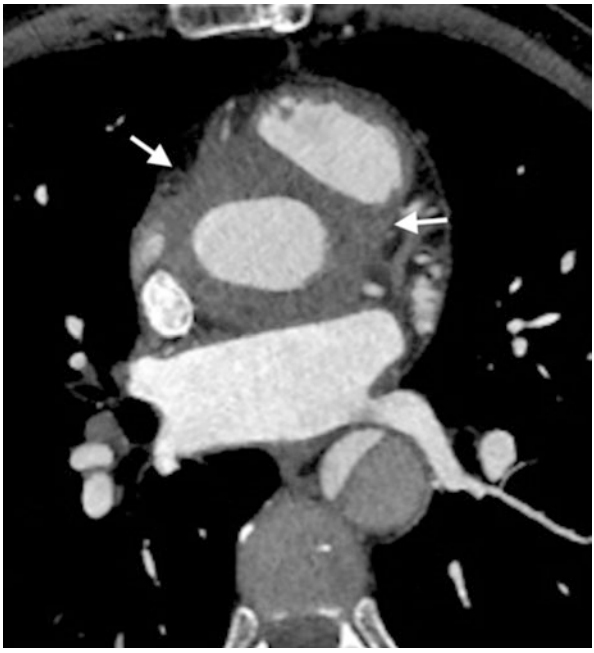

Fig. 5.10 Cardiac CT scan in endocarditis. ECG-gated computed tomography shows a para-aortic inflammatory fluid collection in a patient with endocarditis. (Reproduced from Hryniewieck et al. [30] with permission)

involvement of the perivalvular tissues by the infective process, showing high accuracy for the detection of perivalvular abscesses, pseudoaneurysms and valve dehiscence (Fig. 5.10) [30]. This information is of paramount importance since these complications represent one of the most frequent indications for cardiac surgery in patients with endocarditis [4, 31]. A comparison [32] between CTA and surgical findings reported very high rate of sensitivity and specificity for CTA in detecting paravalvular complications.

A limitation of CTA is the lower quality of images obtained in patients with irregular heart rhythms or tachycardia (a common condition in patients affected by endocarditis), that could obstacle the ECG-gating leading to the formation of artifacts. Another limitation of CTA is represented by the limited accuracy for small vegetations and small valvular perforation [28]. Moreover, metal artifacts could be present in patients who are carrier of intracardiac prosthetic material like CIED leads, which may further reduce the accuracy of CTA [27]. This is a well-known issue raised by previous studies on CIED carriers performing CTA scan showing a very high rate of reported "asymptomatic perforation" of cardiovascular structures [33]. However, the relatively low incidence of severe cardiovascular complications during TLE in current practice [34] seems to challenge these findings. Recently, first studies combining CTA with ^{18}F-FDG PET/CT have been published [35]. The key point of this new technique (PET/CTA) adding to the functional whole-body findings of ^{18}F-FDG PET/CT with a highly accurate chest CTA with ECG gating. The main goal is to obviate to the limited capacity of anatomical reconstruction for cardiac structures of the low-dose, not ECG-gated CT usually combined with PET scan, which cannot

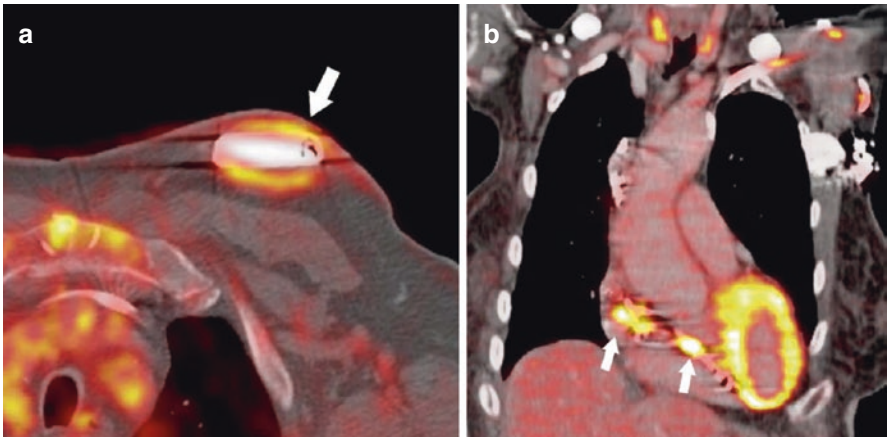

Fig. 5.11 PET/CTA. PET/CTA combines the high spatial resolution of ECG-gated computed tomography with the metabolic data provided by ^{18}F-FDG-PET. Image (**a**) shows an increased uptake of radiotracer around the CIED generator. Image (**b**): PET/CTA allowed to detect the involvement of CIED lead in a patient with infective endocarditis. (Reproduced from Pizzi et al. [35] with permission)

visualize images like valvular leaflets or vegetations [36] (Fig. 5.11) [35]. Evidence regarding the usefulness and the cost-effectiveness of this methodic is lacking, and it is not included in guidelines yet [3]. Pizzi et al. [35] reported higher sensitivity and specificity of PET/CTA compared to standard PET/CT for diagnosis of CIED and prosthetic valve-related endocarditis. Notably in that study, given the higher resolution of PET/CTA for cardiac anatomy, this technique allowed to detect a larger number of complications of endocarditis, more than PET/CT alone and also more than TEE. This is a striking fact since lots of the reported complications detected with PET/CTA (coronary artery involvement, pseudoaneurysms, fistulas) could have a surgical indication. As stated by authors further studies are needed to assess the role of this technique.

5.4 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) plays a little role in the management of patients with CIED infection. The detection of vegetations is limited by the low spatial resolution of MRI [37] and the evidence supporting the usefulness of this technique to detect endocarditis lesions comes from case reports and studies with a limited number of patients [38–40]. MRI could help in assessing perivalvular extension of endocarditis and the extent of valve regurgitation [37]. An added value of MRI is the high performance of this method in detecting secondary localizations of endocarditis in targeted sites. In particular, MRI offers high sensitivity for detection of brain embolism [41, 42].

However, focusing on CIED infections, it should be underlined that we lack of data regarding the usefulness of MRI in this context. The main determinants of this lack of evidence are represented by the aforementioned limitations of MRI and the impossibility to perform this imaging technique in a large number of carriers of older, non-MRI compatible CIED [43]. Given the larger diffusion of MRI-compatible devices nowadays, it cannot be excluded that the role of MRI for CIED infections may be further investigated in the future.

5.5 White Blood Cell Single-Photon Emission Computed Tomography/Computed Tomography

Radiolabeled white blood cell single-photon emission computed tomography/computed tomography (WBC SPECT/CT) is a nuclear medicine imaging technique that has been proposed for improving the diagnostic workup for CIEDI. Autologous leukocytes are collected and labeled in vitro with a radioisotope, either ^{111}In-oxine or ^{99}mTc-hexamethylpropyleneamine oxime (HMPAO). Labeled white blood cells are then reinjected through the bloodstream, spreading and accumulating preferentially in sites where inflammation and leukocyte migration is present [44]. Then images are acquired with a gamma camera from multiple angulations and fused with those produced by a low-dose computed tomography acquired at the same time; acquisition is performed usually 4 h after injection of radiolabeled leukocytes (Fig. 5.12) [45]. ^{111}In-oxine was the first isotope to be utilized and has progressively

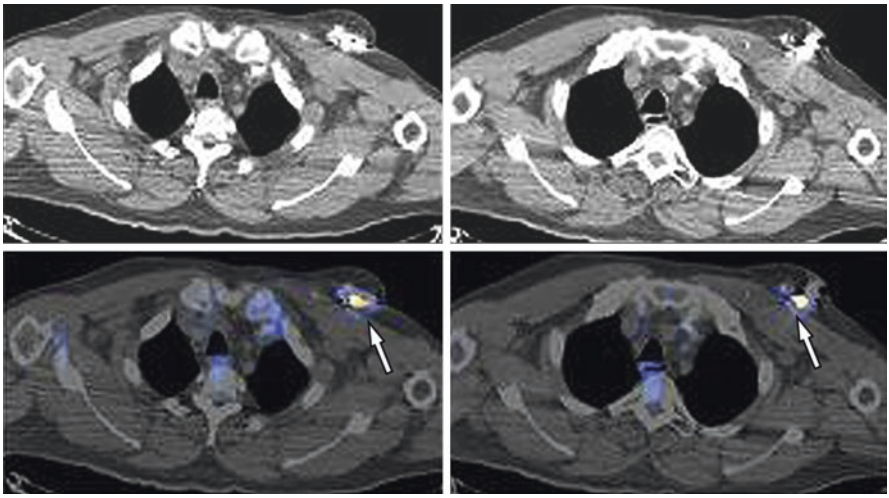

Fig. 5.12 Labeled white blood cell SPET/CT for CIEDI. Tecnetium-99 hexamethylpropyleneamine oxime-labeled autologous white blood cell (99mTc-HMPAO-WBC) scintigraphy in a patient with a suspect of CIED infection, which shows a localized pocket involvement at SPECT/CT fusion imaging (lower images; upper images show CT scan alone of the same patient). (Reproduced from Erba et al. [45] with permission)

been substituted by ^{99}mTc-HMPAO in view of the lower half-life and consequently radiation burden for the latter.

The sensitivity of WBC SPECT/CT is strictly dependent on the migration rate of labeled cells, which is influenced by the residual activity of marked leukocytes after the in vitro labeling process, the production of inflammatory mediators, the pathogenicity, and the concentration of microorganisms. Overall, WBC SPECT/CT presents low sensitivity but high specificity for infection [27]. This fact was confirmed by Rouzet et al. [46] in a small size study (39 patients) comparing WBC SPECT/CT with ^{18}F-FDG PET/CT for diagnostic accuracy for prosthetic valve endocarditis. ^{18}F-FDG PET/CT showed higher sensitivity (93% vs. 64%) but lower specificity (71% vs. 100%) compared to WBC SPECT/CT. Authors suggested that WBC SPECT/CT could be helpful after an inconclusive PET (in case of suspect of false positive) or in the immediate period after CIED implantation/cardiac surgery (when ^{18}F-FDG PET/CT utility is lowered by the high metabolism associated with the reparation process). Regarding the performance of WBC SPECT/CT for CIEDI, only one study with at least ten patients was performed [47]. Compared to a gold standard based on an integrated diagnosis with clinical and echocardiographic parameters and a 12-month follow-up, authors reported a high diagnostic accuracy for WBC SPECT/CT (94% sensitivity, 100% specificity).

5.6 Positron Emission Tomography

Being started to be adopted for clinical use during the 1990s [48], positron emission tomography (PET) with fluorodeoxyglucose marked by fluorine-18 (^{18}F-FDG) is a relatively novel imaging technique, able to provide information about the functional state of organs and tissue. PET scan reveals the pattern of utilization of glucose among body's tissues, giving to operators information about the presence of an increased metabolic activity among a particular body district, usually indicating neoplastic, inflammatory, or regenerative processes (Fig. 5.13).

5.6.1 Technical Aspects

^{18}F-FDG represents by far the most widely used tracer for PET. Fluorine-18 presents a half-life (given by radioactive decay) of 110 min and labels a molecule of fluorodeoxyglucose, an analog of glucose with similar metabolism [48]. Radioactive tracer thus is administered to the patient 45–60 min before acquiring PET scan, with an injection in blood circulation. During this period, marked fluorodeoxyglucose spreads throughout the body, being preferentially uptaken by tissues with higher glucose consumption. When transported inside cells it is metabolized to FDG-6-phosphate, a metabolite which (as opposite of normal glucose) cannot be further processed and remains trapped in cells [49]. ^{18}F-FDG accumulation is higher for neoplastic tissues, as a consequence of the higher expression of glucose transporter proteins due to increased anaerobic metabolism [50]. Moreover, some tissues

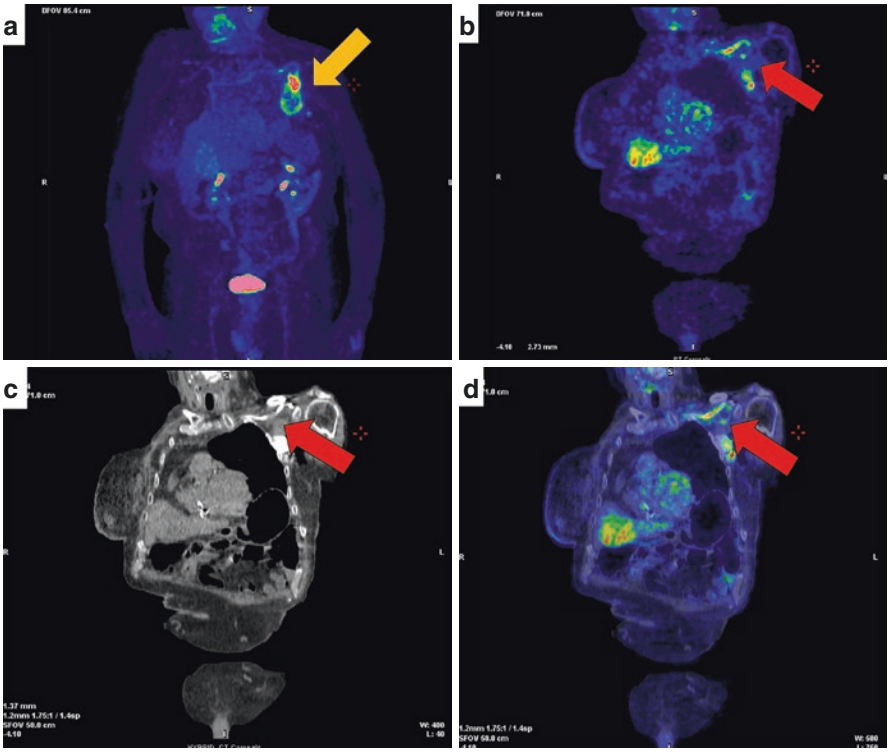

Fig. 5.13 PET/CT scan for the diagnosis of CIEDI. ^{18}F-FDG PET/CT performed in a patient with CIEDI. This scan clearly shows the increased FDG uptake at the pocket site (orange arrow in PET-only anteroposterior image, Panel **a**). The involvement of the CIED lead is evidenced after proper rotation in a trans-axial image, as evidenced by the red arrow (Panel **b**=PET-only image; Panel **c**=CT scan; Panel **d** = fusion PET/CT)

present a high rate of glucose uptake even in normal conditions, due to their intrinsically high metabolic demand, like brain, myocardium, brown adipose tissue, and urinary and gastrointestinal tract [51]. Finally, body sites where an increased concentration of cells is present, like inflammatory cell infiltration, infection site, or regenerative processes after a surgical intervention, also present an increased ^{18}F-FDG accumulation [48]. PET scan is clearly a whole body examination, usually not including the brain. The entire process (since radiotracer administration) requires usually less than 2 h [27], which represents a substantial advantage when compared to WBC SPECT/CT which takes several hours. ^{18}F-FDG undergoes beta decay with emission of positrons. After a very short distance, the issued positron meets an electron in the patient's tissue, thus developing the annihilation of both particles with release of a pair of 511-KeV photons which travel in opposite direction [48]. PET scanner detects this gamma radiation and it is able to compose the image, showing the distribution of radiolabeled FDG in the patient's body. After a first visual examination of PET images, semiquantitative evaluation is performed to establish the

maximal standardized uptake value (SUV_{max}). One of the most common pitfalls for ^{18}F-FDG PET scan is represented by the risk of false positives. ^{18}F-FDG PET is not specific for infections and/or cancers, as previously mentioned. To increase discrimination between pathologic and physiologic accumulation of the tracer, all patients should observe a fasting period of several hours, in order to reduce the concentration of insulin which contributes to alter results [48].

Whenever it is necessary to investigate the heart, as in the suspect of CIEDI, further precautions should be followed. Despite the preferential use of lipids as the primary substrate, myocardial cells have also a high glucose uptake which can conceal a lead vegetation/abscess. Thus, a fasting period >12 h preceded by one, or more, meal at high percentage of lipids and with strict limitation of carbohydrates should be considered since it can improve PET diagnostic accuracy by suppressing the native myocardial glucose uptake [52]. Unfractionated heparin has also been proposed to further reduce the physiological myocardial glucose uptake, but supportive data are more limited [53].

A known drawback of standard PET scan is the limited spatial resolution of this technique [51]. For this reason PET scan is usually combined with low-dose computed tomography (^{18}F-FDG PET/CT). This allows to correlate anatomical reconstruction and CT pathological findings with PET functional imaging, improving the sensitivity and specificity of PET scan alone [51]. An additional improvement of combining CT scan is the possibility to correct PET scan on the base of density of patient's tissues, thus providing more precise data. However, it has to be considered the possibility of generating new artifacts caused by overcorrection of attenuation for materials with high density (such as CIED leads), resulting in a false-positive increased ^{18}F-FDG uptake [27]. To preclude this, both attenuation-corrected and non-attenuation-corrected acquisitions should be evaluated when a focal positivity is observed in ^{18}F-FDG PET/CT [27].

5.6.2 ^{18}F-FDG PET/CT for Diagnosis of Infection

Every inflammatory process (either aseptic or infective) presents several characteristics favoring local FDG accumulation: (a) initially there is an increase of local perfusion combined with an increase of vascular permeability; (b) later there is a recruitment and migration of white blood cells promoted by chemotaxis; (c) finally, white blood cells, microbiological agents, and concomitant reparative process induce a higher FDG consumption [54]. All these factors contribute to the efficacy of ^{18}F-FDG PET/CT for supporting diagnosis of several challenging infectious/inflammatory processes, like fever of unknown origin [55], vasculitis [56, 57], sarcoidosis [58], and musculoskeletal infections [59]. As previously discussed, the diagnosis of infections involving the heart (i.e., CIEDI, endocarditis, prosthetic valve infection, mechanical circulatory support device infection) is particularly challenging, given the nonspecificity of symptoms and the presence of various limitations of the available diagnostic techniques. In addition, achieving an early

diagnosis of endocarditis is a mandatory task, since delay of treatment is usually associated with severe outcomes [1].

^{18}F-FDG PET/CT showed good performances in terms of sensitivity and specificity for detection of the endocarditic process. A recent meta-analysis by Mahmood et al. [60] reviewed 13 studies (for a total of 537 patients) investigating the usefulness of ^{18}F-FDG PET/CT in the contest of infective endocarditis in native or prosthetic cardiac valves and infected CIED. Authors examined all the available studies large enough to assess ^{18}F-FDG PET/CT sensitivity and specificity for diagnosis of possible infective endocarditis. The pooled sensitivity of ^{18}F-FDG PET/CT for diagnosis of endocarditis resulted 76.8% (95% CI 71.8–81.4%) and specificity 77.9% (95% CI 71.9–83.2) [60]. An ancillary but interesting fact reported by authors was a higher sensitivity found by studies with a more strict dietary control for suppression of myocardial glucose uptake before PET administration.

Consistent results were reported in a systematic review [29] where ^{18}F-FDG PET/CT reported good ability for detecting endocarditis in patients with prosthetic valves (73–100% sensitivity, 71–100% specificity, and 67–100%), whereas authors concluded that we lack data to assess performance of this methodic for detecting native valve endocarditis. Sensitivity and specificity rate increased when CT angiography was added [29].

5.6.3 Role of ^{18}F-FDG PET/CT for the Diagnosis of CIED Infection

The first report of detection of CIEDI by ^{18}F-FDG PET can probably be dated to 2006 [61]. Since then, several studies have been published on this topic, given the progressively increase of evidence supporting the usefulness of this methodic in this challenging disease both in the diagnostic and treatment process. However, we lack of large studies on ^{18}F-FDG PET/CT scan mainly because of organization issues (all available studies enrolled less than 100 patients). Table 5.2 [35, 62–71] reports the principal studies on this topic. Evidence regarding the performance of ^{18}F-FDG PET/CT for CIEDI infection comes primarily from meta-analysis and systematic reviews. The systematic review published by Gomes et al. (2016) [29] considered nine studies, mainly prospective and all of them assessing the usefulness of ^{18}F-FDG PET/CT for detecting CIEDI and finding potential extracardiac complications in patients with a suspect of CIEDI with/without endocarditis, diagnosed according to modified Duke criteria [2]. The reported sensitivity and specificity for diagnosis of CIEDI resulted high (80–89% sensitivity, 86–100% specificity, 94–100% positive and 85–88% negative predictive values). The diagnostic value was high for both lead involvement detection (24–100% sensitivity, 79–100% specificity, 66–100% positive and 73–100% negative predictive values) and pocket infection (87–91% sensitivity, 93–100% specificity, 97% positive and 81% negative predictive values). Interestingly, one of the included studies [68] compared the effectiveness of ^{18}F-FDG PET/CT performed with the standard delay of 1 h after radiotracer injection with a longer delay of 3 h; authors reported higher accuracy for 3-h delayed PET. In a more recent meta-analysis published in 2017 Juneau et al. [72] included 11 studies

Table 5.2 Main studies (more than 20 patients) assessing ^{18}F-FDG PET/CT diagnostic performance in CIED infection

Study	Year	Design	N.	Patient selection	Diagnostic gold standard	PET sensitivity-specificity (95% CI)[a]
Bensimhon et al. [63]	2011	Prospective, single center	21	Suspect of CIEDI	Culturing after device extraction or 6-month clinical follow-up	0.85 (0.55–0.98)1.00 (0.72–1.00)
Sarrazin et al. [70]	2012	Prospective, single center	42	Suspect of CIEDI	Culturing after device extraction or clinical follow-up	1.00 (0.89–1.00)0.90 (0.58–0.99)
Cautela et al. [64]	2013	Prospective, single center	21	Patients referred for CIEDI	Clinical, microbiological, and imaging criteria	0.70 (0.46–0.88)1.00 (0.03–1.00)
Graziosi et al. [67]	2014	Prospective, single center	27	Suspect of CIED-related endocarditis	Lead cultures after CIED extraction, clinical/instrumental reevaluation after at least 6 months	0.67 (0.35–0.90)0.87 (0.59–0.98)
Leccisotti et al. [68]	2014	Prospective, single center	27	Patients referred for device extraction	Culturing of extracted device	0.86 (0.65–0.97)1.00 (0.48–1.00)
Ahmed et al. [62]	2015	Prospective, single center	46	Suspect of CIEDI	Culturing after device extraction and/or clinical follow-up	1.00 (0.88–1.00)0.94 (0.71–1.00)
Pizzi et al. [35]	2015	Prospective, single center	28	Suspect of CIEDI	Multidisciplinary team and clinical/instrumental follow-up of at least 3 months	0.87 (0.62–0.98)1.00 (0.73–1.00)
Tlili et al. [71]	2015	Retrospective, single center	40	Suspect of CIEDI	Culturing data of explanted devices or clinical follow-up for at least 1 year	0.83 (0.58–0.96)0.96 (0.77–0.99)
Memmott et al. [69]	2016	Retrospective, single center	37	Suspect of CIEDI	Culturing data of explanted devices or clinical follow-up for at least 6 months	0.88 (0.69–0.97)1.00 (0.77–1.00)
Granados et al. [66]	2016	Retrospective, single center	29	Suspect of CIEDI/CIED-related endocarditis	Multidisciplinary team (clinical, echocardiographic, and microbiological findings)	1.00 (0.75–1.00)1.00 (0.79–1.00)
Diemberger et al. [65]	2019	Prospective, single center	105	Patients with a diagnosis of CIED	Multidisciplinary team (clinical, laboratoristic, culturing, and imaging data)	0.91 (0.84–0.96) N.A. (all with a definite diagnosis of CIEDI)

N, population size; *CIED*, cardiac electronic implantable device

[a]Sensitivity and specificity refer to original article when reported or reassessed on calculation based on reported data

(all single center, mostly prospective) enrolling a total of 331 patients with suspected CIEDI with/without endocarditis. The reported pooled sensitivity of ^{18}F-FDG PET/CT for the detection of CIEDI was 87% (95% CI, 82%–91%) and pooled specificity resulted 94% (95% CI, 88%–98%). Even if this results are consistent with the already mentioned data by Gomes et al. [29], it must be underlined that authors included also one study enrolling patients with infected left ventricular assist device. Regarding the diagnostic value of ^{18}F-FDG PET/CT for CIED-related endocarditis, the analysis of six studies resulted in a pooled sensitivity of 65% (95% CI, 53%–76%) and a pooled specificity of 88% (95% CI, 77%–94%). This result is quite lower than what has been reported for CIEDI (lead/pocket involvement). The more plausible explanation is the requirement for a good myocardial glucose uptake suppression to properly assess cardiac involvement in CIEDI, and many of the evaluated studies were not specifically designed to uniformly provide a similar patient preparation [72]. Two other factors have to be considered since they have been reported to affect sensitivity: (a) type/duration of antibiotic treatment before ^{18}F-FDG PET/CT scan and (b) presence of advanced heart failure with impossibility to modify heart metabolism [65]. A second meta-analysis on this topic was produced by Mahmood et al. [73] with 14 studies including 492 patients with a possible CIEDI undergoing ^{18}F-FDG PET/CT scan. The pooled sensitivity was 85% (95% CI, 80%–89%) and pooled specificity 90% (95% CI, 84%–94%). The subgroup analysis, performed including studies with a cohort of sufficient size, demonstrated again a high performance of ^{18}F-FDG PET/CT for detecting pocket infection (sensitivity 96%, 95% CI 86–99%; specificity 97%, 95% CI 86–99%) and a lower accuracy for lead infection (sensitivity 76%, 95% CI 65–85%; specificity 83%, 95% CI 72–90%). Notably, a higher sensitivity was reported in studies in which the protocol for preparation to PET (fasting, low carbohydrate diet, or heparin utilization) was clearly established [73].

Although not conclusive, available data suggest that ^{18}F-FDG PET/CT is a reliable methodic for diagnosis of CIEDI and CIED-related endocarditis. ^{18}F-FDG PET/CT has key advantages compared to the other imaging techniques available. Main strengths reported for ^{18}F-FDG PET/CT are confirmation of CIEDI when clinical presentation and/or other examinations are inconclusive, early diagnosis of endocarditis, and detection of extracardiac infectious foci (Fig. 5.14) [65].

5.6.3.1 Confirmation of a Diagnosis of CIEDI-Related Infection in Challenging Cases

^{18}F-FDG PET/CT scan may help confirming a suspect of CIEDI with/without related endocarditis in patients when other techniques are inconclusive, and it should be considered in all these patients. Since in absence of a lead and cardiac involvement the echocardiogram is usually negative, ^{18}F-FDG PET/CT may be useful to discriminate patients with true pocket infection. Ahmed et al. [62] compared a population of 46 patients with a suspect of CIED pocket infection with 40 controls without story of infection (patients who are CIED carriers undergoing ^{18}F-FDG PET/CT scan for other reasons such as cancer surveillance). Patients with suspect pocket infection were divided in two groups: definite pocket infection (erosion or

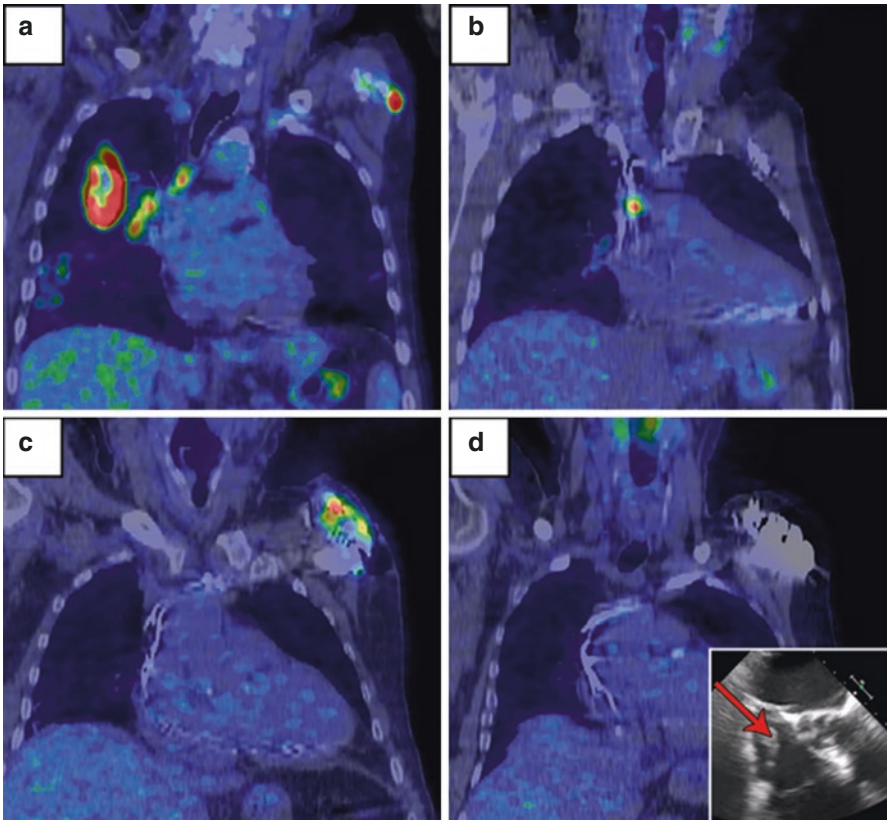

Fig. 5.14 ^{18}F-FDG PET/CT scan with different patterns in patients with CIEDI. Different presentations of patients affected by CIED infection at ^{18}F-FDG PET/CT scan. (**a**): pocket and lead involvement. (**b**): infection on the lead, negative pocket. (**c**): local infection (isolated pocket involvement). (**d**): false negative (negative PET in a patient with known endocarditis, as evidenced by echocardiogram). (Reproduced from Diemberger et al. [65] with permission)

dehiscence of the generator pocket, purulent discharge) or "possible" pocket infection (mild erythema or pain). ^{18}F-FDG PET/CT was administered to all patients, being positive in 17/20 of the patients with definite infection and negative in all controls. Strikingly, 13 of the 26 patients with only mild symptoms presented a positive ^{18}F-FDG PET/CT scan and the diagnosis of infection was subsequently confirmed for 11/13 (84.6%) of them. Authors concluded that ^{18}F-FDG PET/CT is a useful examination to classify and stratify the risk of these patients and it should be considered in all patients presenting with mild signs and symptoms like pocket erythema. After a standardized [3] diagnostic workup evidence for presence of CIED infection may be still limited and echocardiogram can difficulty discriminate the nature of a mass adherent to CIED leads [19] and some area cannot be explored due to presence of prosthetic material [29]. In these cases, if the clinical suspicious persists, ^{18}F-FDG PET/CT is an added value for the diagnosis of intravascular

CIEDI. Some authors also proposed to include ^{18}F-FDG PET/CT findings as a major criteria in modified Duke criteria, in order to increase the accuracy in diagnosis of CIED-related endocarditis. Pizzi et al. [35] in a prospective study enrolling 92 patients with CIED or prosthetic cardiac valves admitted for suspicious infective endocarditis, all undergoing ^{18}F-FDG PET/CT scan, compared standard modified Duke criteria (assessed at the admission) with Duke criteria including ^{18}F-FDG PET/CT findings as imaging criteria. According to results, ^{18}F-FDG PET/CT drastically improved the accuracy of the diagnosis of CIED infection. Reported sensitivity (compared to a final, multidisciplinary diagnosis of endocarditis made after a follow-up of 3 months, which was assumed as gold standard) was 90.7% (95% CI 79.7–96.9) for Duke criteria including PET versus 52% (95% CI 37.8–65.7) of standard modified Duke criteria. Sensitivity was slightly inferior for Duke criteria with PET (89.5%, 95% CI 75.2–97.1, versus 94.7, 95% CI 82.3–99.4). A potential concern regarding this data is the cost-effectiveness [66], since ^{18}F-FDG PET/CT scan was performed in all patients at admission, even those with rejected endocarditis at standard modified Duke criteria. Granados et al. [66] instead administered ^{18}F-FDG PET/CT to 80 consecutive patients with a diagnosis of possible endocarditis obtained with Duke criteria. After inclusion of ^{18}F-FDG PET/CT 90% of the patients were reclassified to both rejected or definite endocarditis (18 cases). Consistent findings have been also found in a more recent study [65] with 105 patients referred for TLE, where the adoption of ^{18}F-FDG PET/CT allowed to reclassify 23.8% of patients with 11 new diagnosis of endocarditis.

5.6.3.2 Early Diagnosis of Endocarditis

The functional nature of ^{18}F-FDG PET/CT, whose performances are related to metabolic process and may detect the presence of infection since from the first phases of the pathological process, allows the possibility to perform a diagnosis of CIED earlier than any other techniques, before the onset of morphological alterations and anatomical damage [27]. This point is of crucial importance since a delay in diagnosing CIED infection can result in a progression of the infective process, related to a worse outcome and to a higher risk of relapse [74].

5.6.3.3 Detection of Extracardiac Localizations of Infection

Extracardiac infections are a well-known complication of infective endocarditis, adding a further burden of mortality and morbidity to primary infection. CIED infection can spread either by direct embolization of vegetations (usually to lungs) or by hematogenous seeding, causing more frequently septic arthritis, osteomyelitis, and spondylitis [75]. Pulmonary embolization, especially in patients with larger vegetations, is a major concern and it is related with a higher mortality at 6 months (hazard ratio 3.76; 95% CI 1.25 to 11.30) [16]. They have been reported in 38.4% of patients with CIED-related endocarditis [11]. Spinal abscess represents another common secondary localization of CIED infection [75, 76]. The detection of secondary infectious site is often challenging, because they are often asymptomatic [11] or because related symptoms may be not specific and be masked by the primary infection.

MRI is often adopted as the preferred imaging technique for detection of spondylodiscitis [77] but it presents several limitations both in terms of feasibility (many patients with CIEDI have abandoned or damaged leads, which until now pose a contraindication for MRI [43]) and quality of obtained images (due to artifacts from implanted hardware [78]).

The main consequence of this is the risk of delaying or completely missing the diagnosis of septic embolism, despite the possibility of relevant consequences and the impossibility of adjusting antimicrobial therapy duration. Recently, the role of ^{18}F-FDG PET/CT for the detection of hidden infective localization of CIED infection has started being investigated, given the promising results in finding extracardiac complications of infective endocarditis (^{18}F-FDG PET/CT positive for extracardiac infection in a quarter of patients) [79, 80]. Furthermore, ^{18}F-FDG PET/CT allows to scan the whole body at once, providing the possibility to detect infection complications at distance from the primary site. No large study specific for this topic exists, comparing ^{18}F-FDG PET/CT with other imaging techniques, and all available studies exhibit a limited number of patients. In a 2016 prospective study by Amraoui et al. [76] ^{18}F-FDG PET/CT was administered to 35 patients before the execution of TLE, aiming to identify metastatic foci. They reported septic emboli in 29% of patients (seven spondylodiscitis, two septic pulmonary emboli, and one infected aortobifemoral vascular prosthesis). None of the cases of spondylodiscitis have been diagnosed prior to PET administration (patients resulted asymptomatic or other imaging exams resulted inconclusive). Thus, authors underlined the important contribution of ^{18}F-FDG PET/CT, which allowed to modify patient therapy according to scan results for all patients positive for secondary foci, either by prolonging antimicrobial therapy duration or administering nonpharmacological treatments.

A more recent, prospective, study [65] with a larger cohort size of 105 patients, aiming for investigating the prognostic value of the extension of CIED infection at ^{18}F-FDG PET/CT scan, reported that PET scan allowed to perform a first detection of septic emboli in 11.4% of patients. These findings allowed to adjust patient treatment and to optimize the timing of CIED reimplantation. Moreover, although not representing the main focus of imaging for CIED infection, ^{18}F-FDG PET/CT also allows to detect other pathological conditions, unrelated to CIED infection like neoplastic processes [73, 76], which may have a prognostic significance and may lead to a change of strategy in terms of treatment and assessment for reimplantation. Notably, systemic infections caused by some microbial agents have been related with presence of occult cancer [81]. Although not completely exhaustive, available data thus report a good performance of ^{18}F-FDG PET/CT in detecting occult metastatic infections and suggest that routine administration of ^{18}F-FDG PET/CT could improve patient management, at least in patients with proven endocarditis [29].

5.6.3.4 Prognostic Value of PET Findings

Several authors reported a worse survival rate for patients affected by systemic CIED infection than those with an infection limited to the site of the CIED pocket [82, 83]. Considering the ability of ^{18}F-FDG PET/CT to assess the localization and the extension of the infectious process and to discriminate a local versus a diffuse

infection, the possible role of ^{18}F-FDG PET/CT findings in predicting the outcome of patients with CIEDI has been investigated. A recent study by Diemberger et al. [65] enrolled 105 patients with an already established (by clinical criteria) diagnosis of CIEDI and referred for TLE, all of them undergoing ^{18}F-FDG PET/CT scan before procedure. Comparison was made between patients with pocket infection alone and those with systemic involvement at ^{18}F-FDG PET/CT scan (infection of endovascular trait of leads, cardiac valves, secondary localization). A trend toward a better survival for patients with local infection was reported, but it didn't reach statistical significance. However, the most relevant finding of this study was that a CIED pocket with a negative ^{18}F-FDG PET/CT scan and absence of signs of infection (*Cold Closed Pocket*, found in 24/105 patients) was a strong independent predictor of mortality (hazard ratio 2.84, 95% CI 1.37–5.89). Authors suggested that the PET scan negative for pocket infection, the longer period since last CIED implant/replacement, and the higher percentage of positive blood cultures in patients with *Cold Closed Pocket* may be related with a metastatic nature of the CIEDI in these patients, started elsewhere. This is a topic of interest, given that the actual strategies to reduce the risk of CIEDI are mainly focusing on surgical procedures.

5.6.3.5 Limitations of ^{18}F-FDG PET/CT: False Negatives and False Positives

Despite the good performance of ^{18}F-FDG PET/CT in terms of sensitivity and specificity, both false negative and false positive have been reported. Graziosi et al. [67], investigating the role of PET for the diagnosis of CIED-related endocarditis, reported 17 negative PET scans, four of them false negatives. Diemberger et al. [65] reported also nine false-negative PET in a sample of 105 patients. As underlined by authors, patients with false-negative ^{18}F-FDG PET/CT scan were usually treated with prolonged antimicrobial therapy, already started before PET administration. Long-lasting antibiotic therapy is a known cause of false-negative ^{18}F-FDG PET/CT scan [29]. A possible workaround to fix this is performing ^{18}F-FDG PET/CT early during the management of a patient with a suspicious of CIEDI, possibly before starting an antimicrobial therapy if allowed by patient's clinical conditions and PET availability, in order to maximize ^{18}F-FDG PET/CT sensitivity. Additional causes of false negatives are the possibility of little size vegetations, falling below the spatial resolution of ^{18}F-FDG PET/CT (4–5 mm) [29], and the insufficient suppression of myocardial glucose uptake (by inadequate dietary preparation of the patient before the administration of PET) which can mask the presence infection (Table 5.3) [84]. False-positive results are mostly caused by increased FDG uptake during noninfective processes, such as inflammatory diseases or cancer or inadequate glucose uptake suppression. An increased FDG uptake is often observed during first period after CIED implantation [73] and this should also be kept in mind before performing PET. Another cause of false positivity of ^{18}F-FDG PET/CT is artifact by overcorrection of attenuation in proximity of high density materials like CIED leads; for this reason a visual comparison between imaging obtained with attenuation correction and non-corrected images should always be performed.

5.6.3.6 Considerations About ^{18}F-FDG PET/CT Role in CIEDI Management

The growing interest on ^{18}F-FDG PET/CT role in diagnosis of CIEDI is motivated by the high diagnostic yield of this imaging technique. ^{18}F-FDG PET/CT provides high sensitivity and specificity and should have a role in the management of a CIEDI. Actually, ^{18}F-FDG PET/CT still has not an established role in guidelines of European Society of Cardiology regarding CIEDI [3], dated 2015, and available evidences suggest that this examination should deserve a more prominent role. Notably since reimplantation strategy is strongly affected by systemic involvement of CIEDI (for additional information see Chap. 7), it should be carefully considered to perform ^{18}F-FDG PET/CT also in patients with a defined diagnosis of CIEDI since about one quarter of the patients can be reclassified according to modified Duke criteria if ^{18}F-FDG PET/CT is systematically performed [65]. However, cost-effectiveness (no data are actually available on this topic) and the risk of false positive/negative still remains a concern (Table 5.4).

Table 5.3 Recommendations for the patients' preparation before administration of ^{18}F-FDG PET for cardiac structures

The patient should follow a low carbohydrate diet for 24 h prior to the PET/CT administration or at least a low-carbohydrate meal before starting the recommended fasting period before the study (6 h).
Patients must avoid strenuous exercise for at least 6 h before the FDG PET/CT study, and preferably for 24 h, in order to minimize the glucose uptake of skeletal muscles.
The patient should be able to lie still for the entire duration of the PET/CT scan (30–60 min).
If the patient has a blood glucose concentration higher than 11 mmol/L (200 mg/dL), the FDG PET/CT scan should be rescheduled or the patient excluded.
In patients affected by diabetes mellitus, FDG PET/CT study should be preferably performed in the late morning.

Recommendations from European Association of Nuclear Medicines Guidelines [84]

Table 5.4 Strengths and limitations of the discussed imaging techniques for CIED infection

Imaging techniques	Strengths	Limitations
Transthoracic echocardiogram (TTE)	• Easily available and low-cost technique • Identification and measurement of lead endocarditic vegetations • Detection of endocarditis-related complications (i.e., tricuspid valve regurgitation, other valve involvement)	• Limited to heart CIEDI involvement • Lower sensitivity (in general), especially if performed too early • Limited discrimination of cardiac masses • Accuracy limited by artifacts from prosthetic material
Transesophageal echocardiogram (TEE)	• Low costs • Higher sensitivity for vegetations • Better visualization vs. TTE • Detection of valvular and perivalvular extension of CIEDI • Gold standard for diagnosis of endocarditis • Allows perioperative monitoring	• Suboptimal visualization of some sites (right ventricle, extracardiac vessels) • Lower sensitivity if performed too early • Limited discrimination of cardiac masses • Accuracy limited by artifacts from prosthetic material

(continued)

Table 5.4 (continued)

Imaging techniques	Strengths	Limitations
Intracardiac echocardiography	• High sensitivity for vegetations • Better visualization of remote areas vs. TEE/TTE • Better discrimination of cardiac masses vs. TEE • Higher performance for perioperative monitoring	• High costs and limited availability • Requires an invasive access • Impractical for pure diagnostic purposes
ECG-gated computed tomography (CT)	• Very high performances in estimation of endocarditis extension (detection of paravalvular abscesses, fluid collection)	• Limited accuracy in tachycardia/rhythm disturbance • Low accuracy for detection of small vegetations • Presence of metal-induced artifacts in patients with CIED
WBC SPECT/CT	• Functional imaging • Allows detection of infection before the onset of anatomical damage • High specificity for infections, may be considered for confirmation of PET (+++ patients with recent procedure)	• Longer time required • Sensitivity inferior to PET/CT scan
^{18}F-FDG PET/CT	• Functional imaging • Allows detection of infection before the onset of anatomical damage • High sensitivity/specificity for CIEDI • Allows a whole body scan (excluding brain) to detect extracardiac complications of CIEDI • Shorter execution time compared to SPECT	• False positives in case of inadequate glucose suppression or recent cardiac surgery • False negatives in case of prolonged antimicrobial therapy • High costs and limited availability, even if progressively increasing

CIED cardiac electronic implantable device, *WBC SPECT/CT* white blood cell single-photon emission computed tomography/computed tomography, *^{18}F-FDG PET/CT* positron emission tomography (PET) with fluorodeoxyglucose marked by fluorine-18

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