Imaging

Cardiac imaging in infectious endocarditis

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Infectious endocarditis remains both a diagnostic and a treatment challenge. A positive outcome depends on a rapid diagnosis, accurate risk stratification, and a thorough follow-up. Imaging plays a key role in each of these steps and echocardiography remains the cornerstone of the methods in use. The technique of both transthoracic echocardiography and transesophageal echocardiography has been markedly improved across the last decades and most recently three-dimensional real-time echocardiography has been introduced in the management of endocarditis patients.

Echocardiography depicts structural changes and abnormalities in the heart, but it does not uncover the underlying pathophysiological processes at the cellular or molecular level. This problem is addressed with introduction of new molecular imaging methods as 18F-fluorodesoxyglucose (18F-FDG) PET-CT and single photon emission computed tomography fused with conventional CT (SPECT/CT). Of these methods, 18F-FDG PET-CT carries the best promise for a future role in endocarditis. But there are distinct limitations with both SPECT/CT and 18F-FDG PET-CT which should not be neglected. MRI and spiral CT are methods primarily used in the search for extra cardiac infectious foci. A flowchart for the use of imaging in both left-sided and right-sided endocarditis is suggested.

Keywords
Endocarditis • Multimodal imaging • Valve disease

Introduction

The diagnosis of infectious endocarditis (IE) relies on a coherent evaluation based on clinical information, blood cultures, clinical chemical laboratory data, and the result of echocardiography and supplementary imaging techniques. Imaging also plays a decisive role in pre-operative evaluation, during heart valve operations and in the evaluation of the often severe complications to the disease. Additionally, imaging is used at the end of treatment and during the follow up to reveal any long-term consequences either on the heart or in other organs.

The purpose of the present review is to give an overview of the advantages and limitations of the different imaging techniques used in IE, some of which have appeared in the field of infectious diseases within the last few years. We further aim to present a workflow for diagnostic strategy indicating the possible use of the different imaging modalities.

Echocardiography

Echocardiography plays a key role in the assessment of infective endocarditis (IE). The ‘Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis’ of the European Society of Cardiology and the ‘Recommendations for the practice of echocardiography in infective endocarditis’ of the European Association for Echocardiography recently underlined the value and limitations of echocardiography in IE, and gave recommendations for the optimal use of both transthoracic (TTE) and transesophageal (TOE) echocardiography in IE. Echocardiography is useful both for the diagnosis of endocarditis, the assessment of the severity of the disease, the prediction of short-term and long-term prognosis, the prediction of embolic risk, the management of its complications, and the follow-up of patients under therapy.

Native valve infective endocarditis

Echocardiography for diagnosis of endocarditis

The major echocardiographic criteria for IE are vegetation and abscess. Echocardiography is the reference method for the diagnosis of vegetation (Figures 1 and 2). The sensitivity for the diagnosis of vegetation is ~75% for TTE and 85–90% for TEE. In addition, both TTE and TEE are useful to assess the size, the mobility and the evolution of the vegetation under antibiotic therapy. However, atypical findings are frequent, and echocardiography may be falsely negative in ~15% of IE, particularly in cases of pre-existent severe lesions (mitral valve prolapse, degenerative lesions, and prosthetic valves). For this reason, repeat TTE/TEE examination must be
performed 7/10 days after the first examination when the clinical level of suspicion is still high (Figure 3). Conversely, it is sometimes difficult to differentiate between vegetations and thrombi, cusp prolapse, cardiac tumours, myxomatous changes, Lambli’s excrescences, strands, or non-infective vegetations.6

Abscesses represent the second most typical findings suggesting infective endocarditis (Figure 2), and may be complicated by pseudo-aneurysm or fistulization.7,8 The sensitivity of TTE is ~50%, that of TEE 90%. Diagnosis of an abscess may be difficult in case of small abscess, when echocardiography is performed very early in the course of the disease and in patients with abscess localized around calcification in the posterior mitral annulus.9

Other echocardiographic features suggestive of IE include valve destruction and prolapse, aneurysm, and/or perforation of a valve (Figure 4).

Figure 3 summarizes the respective indications of TTE and TEE in IE as proposed by the ESC recommendations. An exception are patients with Staphylococcus aureus bacteraemia where the risk of IE
is so high that routine echocardiography is justified irrespective of the primary focus of entry.\textsuperscript{1,10}

Echocardiography must be performed rapidly, as soon as IE is suspected. However, the sensitivity and specificity of TTE and TEE are diminished when applied indiscriminately, particularly in the patients with low likelihood of IE. Appropriate use of echocardiography using simple clinical criteria improves diagnostic yield.\textsuperscript{1} The list of the clinical situations in which IE must be suspected—and thus early echocardiography must be performed—has been clearly established in the ESC guidelines.\textsuperscript{1}

### Echocardiography for prognostic assessment, risk stratification, and surgical decision

Echocardiography also plays an important role both in the short-term and long-term prognostic assessment of patients with IE,\textsuperscript{11,12} and thus plays a crucial role both for the decision to operate or not and for the choice of the optimal timing of surgery.\textsuperscript{13} Indications for surgery in IE may be subdivided in three categories—haemodynamic, infectious, and embolic indications.\textsuperscript{1}

**Haemodynamic indications**

Heart failure represents the main indication for surgery in IE. Echocardiography must be performed on an urgent setting as soon as symptoms or signs of heart failure are detected.\textsuperscript{1} Recent European guidelines recommend early surgery to be performed in patients with acute regurgitation and HF, as well as in patients with obstructive vegetations.\textsuperscript{1} Echocardiography is useful in both situations, allowing a detailed assessment of valve lesions, a quantification of valve regurgitation, and the evaluation of the haemodynamic tolerance of the regurgitation (cardiac output, pulmonary arterial pressures, left and
right ventricular function). Some echocardiographic features suggest the need for urgent surgery including premature mitral valve closure (in aortic IE), massive regurgitation, and extensive destructive valvular lesions (Figure 2).1,2

**Infectious indications**
Locally uncontrolled infection, including abscess, false aneurysm, fistula, and enlarging vegetation, represents the second main indication for urgent surgery. Echocardiography plays a key role in the assessment of these severe complications. Surgery must be performed on an urgent basis in such patients or even on an emergency basis when perivalvular lesions are associated with severe heart failure. Enlarging vegetations under therapy also indicates urgent surgery, justifying repeat TTE/TEE in the follow-up of patients with IE.

**Embolic indications**
Embolic events are a frequent and severe complication of IE, occurring in 20–50% of patients, and the risk of new embolic event, occurring after initiation of antibiotic therapy is 6–21%.1 Echocardiography plays a major role in the assessment of embolic risk, although this prediction remains difficult in the individual patient.12,14–16 The size and the mobility of the vegetations are the best predictors of embolism, although several factors have been associated with an increased risk of embolism, including the localization of the vegetation on the mitral valve, the increasing or decreasing size of the vegetation under antibiotic therapy, the type of micro-organism, previous embolism, multivalvular endocarditis, and biological markers. Consequently, careful measurement of the maximal vegetation size at time of diagnosis and during the follow-up is strongly recommended as part of the risk stratification, using both TTE and TEE.2 A recent randomized trial demonstrated that early surgery in patients with large vegetations significantly reduced the risk of death and embolic events when compared with conventional therapy.7

The ESC guidelines1 recommends surgical therapy in case of large (>10 mm) vegetation following one or more embolic episodes, and when the large vegetation is associated with other predictors of complicated course (heart failure, persistent infection under therapy, abscess, and prosthetic endocarditis), indicating an earlier surgical decision. The decision to operate early in isolated very large vegetation (>15 mm) is more difficult. Surgery may be preferred when a valve repair seems possible, particularly in mitral valve IE. But the most important point is that the surgery, if needed, must be performed on an urgent basis.

**Echocardiography during and after surgery**
Intra-operative transoesophageal echocardiography is mandatory in all the patients with IE undergoing cardiac surgery.2 It is of utmost importance for the final assessment of valvular and perivalvular lesion, just before surgery and is particularly useful to assess the immediate result of conservative surgery and in cases of complex perivalvular repair. Finally, echocardiography must be used for the follow-up of patients with IE under antibiotic therapy and after surgery. After hospital discharge, the ESC guidelines1 recommend performing serial examinations at 1, 3, 6, and 12 months during the first year following completion of therapy.

**Prosthetic valve infective endocarditis**
The diagnosis of endocarditis is more difficult in the presence of a prosthetic valve when compared with a native valve. Transoesophageal echocardiography is mandatory in the assessment of prosthetic valve infective endocarditis (PVE),1,2 because of its better sensitivity and specificity for the detection of vegetations, abscesses, and perivalvular lesions in patients with prosthetic valves. However, the value of both TTE and TEE is lower in PVE when compared with NVE.16 The Duke criteria have been shown to be less helpful in prosthetic endocarditis because of their lower sensitivity in this setting.19–21 Other imaging techniques, such as PET-CT may be useful in doubtful cases. An algorithm for the evaluation of patients with suspected PVE, including echocardiography and PET-CT, is suggested (Figure 5).

**Right-sided infective endocarditis**
Right-sided infective endocarditis (RIE) is most often seen in patients with central venous catheters, congenital heart disease, cardiac devices, or intravenous drug abuse (IVDA).22,23 Because of the lower pressure and lower flow velocities vegetations on the right side grow faster and are larger than on the left side. Vegetations can be found in any place on the endocardium, but are typically located on the atrial side of the tricuspidal valve or on cardiac device leads less frequently on the pulmonary valve. Echocardiography is the key imaging technique in suspected RIE. Transthoracic echocardiography provides valuable information because right-sided structures are located anteriorly and close to the TTE transducer. However, in some patients anatomic interference may limit the use of TTE. In addition to standard views, including subxiphoidal recording, modified views are necessary to get a clear overview of the right ventricle inflow and outflow tracts, the Eustachian valve and the posterior leaflet of the tricuspid valve.22 Importantly, some mobile normal structures on the right side, i.e. the Chiari network or a large mobile Eustachian valve, can mimic vegetations.24,25 Right atrial thrombus and old non-infected vegetations from previous disease may also cause diagnostic confusion. In the right atrium, crista terminalis should be recognized, as well as the moderator band in the right ventricle. The sensitivity of TTE and TEE was compared in 47 patients with right-sided cardiac lesions.26 Transoesophageal echocardiography provided a significantly higher diagnostic yield than did TTE. In another contemporary study in young IVDA patients, the sensitivity of TTE and TEE was similar.23

**Central venous catheter blood stream infections**
These patients are older and have a high number of co-morbidities. Very little data are available, but in a retrospective study including both RIE and LIE, TTE was much less sensitive than TEE, missing the IE diagnosis in 42% of the patients.27

**Cardiac device infection**
Cardiac device infection (CDI) represents a group of patients with specific diagnostic and treatment challenges of their own. The number of device implantations has increased two- to three-fold across the last 10–15 years.28,29 Unfortunately, the rate of CDI has increased in parallel. Almost 40–50% of the patients have additional valve infection, and these patients carry a specific enhanced mortality
risk. Echocardiography is most important for diagnosing CDI. Since it can be difficult to visualize all parts of the leads with TTE, especially areas close to the vena cava superior (VCS) where vegetations are often located, TEE is mandatory. In patients with CDI, the sensitivity of TEE is much superior to that of TTE, 70–90% vs. 20–30%. However, the frequency of CDI may be overestimated with both TTE and TEE since lead aggregations very similar to vegetations can be found in up to 20% of PM patients without infection. This underscores the importance of taking the pre-diagnostic likelihood of CDI into account in the evaluation of echocardiographic imaging results.

After the removal of an infected device system so-called ‘ghost’ sheets may be demonstrated by TTE or TEE (Figure 6). These are echogenic, sleeve-like structures visualized in the right atrium often attached to the rim of VCS. The presence of ‘ghost’ sheets indicates a more severe outcome.

In highly selected patients where the results of TTE and TEE are uncertain, or a TEE cannot be performed, intracardiac echocardiography (ICE) can be an option (Figure 7). Although the image resolution of ICE is superior to TEE, it is an invasive procedure and at present only two-dimensional (2D) imaging is possible. An algorithm for the evaluation of patients with suspected CDI is suggested (Figure 8).

**Three-dimensional echocardiography**

The potential to assess the complete spectrum of pathologies with traditional TTE and TEE is limited to the two-dimensional orientation and is further impaired in case of valve calcification and in prosthetic valves. Live three-dimensional echocardiography (RT3D) allow a rapid ‘online’ image acquisition that is well suited for the assessment of cardiac morphology and structure (Figures 1 and 4). Three-dimensional echocardiography is particular useful for the assessment of paravalvular abscess, paravalvular regurgitation, valve perforation, and dehiscence. Another major advantage of RT3D compared both with TTE and TEE is the ability to acquire ‘en face’ views of valves and presentation in a ‘surgical view’ during heart valve operations. At present, 3D echocardiography should be regarded as a supplement to standard 2D and its major limitation, a low frame rate, should be recognized since it may impair detection of smaller vegetations.

**Multislice computed tomography**

With the most recent development of multislice CT scanners, a CT scan of the heart can be performed with acquisition time of a single
to a few heart beats, and with high spatial and temporal resolution. A complete examination of thorax takes a few minutes at the exposure of only 2–3 mSV of radiation. In NVE and PVE, IE patients’ results of multislice CT are comparable in detecting valvular abnormalities to intra-operative findings, and with no significant difference to TEE. Transesophageal echocardiography is superior in detecting small vegetations and valve perforations. But CT seems to have an advantage in patients with more extensive calcification of the valves, in the assessment of the perivalvular extent of the disease such as abscess and pseudo-aneurysm or in PVE where acoustic shadowing can decrease the sensitivity of TEE. In difficult to diagnose cases different imaging modalities are therefore often complementary (Figure 9). A key use of CT in patients with IE is the non-invasive assessment of the coronary arteries prior to surgery, particularly in patients at low risk of coronary artery disease and in patients with extensive aortic valve IE where coronary angiography is associated with risk of systemic embolism of vegetations and aortic wall perforation. In the same CT study, a cerebral or abdominal CT scan can be obtained in order to detect silent embolism. Multislice CT is well suited for monitoring extra cardiac manifestations/complications to IE and all the patients with symptoms pointing towards a systemic dissemination should be carefully examined, whereas routine CT-screening is not yet recommended. Multislice CT is limited by the use of iodine contrast and the method is therefore not applicable in patients with more severely decreased renal function, in patients with unstable hemodynamics and with iodine allergy.

**Magnetic resonance imaging**

Magnetic resonance imaging (MRI) is a non-ionizing imaging technique which primarily is used in IE patients to diagnose clinical and subclinical cerebral embolic events. These are manifested as ischemic or hemorrhagic stroke, more rarely as mycotic aneurysm or cerebral abscess. By systematic use of MRI, cerebral lesions have been demonstrated in as many as 82% of IE patients, and subclinical cerebrovascular events have been found in 30–40% of IE patients.

**Figure 7** Intracardiac echocardiography image of pacemaker lead infection in the right atrium (with permission of Dr J. Hedegaard and Dr E. Korup, Aalborg University Hospital, DK). RA, right atrium; white arrow, pace lead; yellow arrow, vegetation on pace lead.

**Figure 8** Proposed algorithm for evaluating patients with suspected cardiac device infection.
Although detection of cerebral complications in IE may influence the clinical decisions, routine MRI screening is not recommended. Vertebral osteomyelitis is another frequent complication in IE. Magnetic resonance imaging permits an accurate diagnosis showing neurological involvement when it is present. Magnetic resonance imaging is limited by lower spatial resolution and availability and is more time consuming compared with multislice CT. Owing to magnetic field interference MRI cannot be used in patients with certain cardiac implantable electronic devices (CIEDs).

**Molecular imaging**

**18F-FDG PET-CT**

The use of 18F-fluorodesoxyglucose (18F-FDG) PET-CT allows the detection of enhanced glucose metabolism within organs. The method is widely used in cancer diseases for diagnosing and staging. More recently, the method has been proved useful in diagnosing and monitoring inflammatory and infectious conditions. A few reports, mostly in PVE, have shown promising results of 18F-FDG PET-CT imaging in IE. Adding an abnormal FDG uptake around a prosthetic valve as a new major criterion increases the sensitivity of the modified Duke criteria at admission from 70 to 97%. In NVE, the use of 18F-FDG PET-CT may be limited. Although abscess formation and perivalvular extension of the infection has been demonstrated with 18F-FDG PET-CT, the method has mostly been used to confirm the IE diagnosis. In patients with pyrexia of unknown origin, 18F-FDG PET-CT has also been useful to reveal IE despite negative TEE. In patients with cardiac device infection (Figure 11) diagnostic sensitivity and specificity of 89 and 86%, respectively, are reported. These important data need to be verified in larger series since treatment of definitive cardiac device infection implies generator and lead extraction, a procedure associated with major complications in 1–2% of the operations and with a 0.8% mortality. 18F-FDG PET-CT is also useful in detection of peripheral embolic and metastatic infectious events. Finally, 18F-FDG PET-CT may play a potential role in discovering neoplastic lesions as infectious origin in IE, i.e. colon tumours in Streptococcus gallolyticus endocarditis.

However, there are a number of limitations to 18F-FDG PET-CT. Issues such as detection limit of small oscillating vegetations in face of a high general glucose metabolism and movement of the heart muscle, timing of 18F-FDG PET-CT in relation to start of antibiotic treatment, and the validity of 18F-FDG PET-CT in slowly evolving infections and in dysregulated diabetic patients have not been clarified. Owing to high glucose metabolism in brain tissue 18F-FDG PET-CT is less suitable for detection of infectious embolic events in the brain. Furthermore, in uninfected prosthetic vascular grafts in cancer patients enhanced FDG uptake similar to that in infected grafts has been observed. Finally, caution must be displayed when interpreting 18F-FDG PET-CT in patients who recently have undergone cardiac surgery. As a result of the post-operative inflammatory response 18F-FDG PET-CT may be false positive for a longer post-operative period.

**Single photon emission computed tomography /CT**

Single photon emission computed tomography (SPECT) is a nuclear medicine imaging tomography technique measuring gamma rays from injected radionuclides. Plane 2D images are obtained from multiple angles and by subsequently applying single photon emission computed tomographic algorithm images are reconstructed in 3D. By fusion of SPECT images with low-dose contrast-enhanced conventional CT images, an exact anatomical localization of the enhanced isotope concentration is provided (SPECT/CT). Technetium-99 m (99mTc), indium-111 (111In), and gallium-67 (67Ga) have been used as radioactive tracers in detection of various cardiovascular infections including IE, either labelled to leucocytes (99mTc, 111In) or citrate(67Ga). The sensitivity of SPECT/CT used in leucocyte scintigraphy depends on the accumulation of neutrophil granulocytes and sensitivity is highest in the acute phase of infection. The results of leucocyte SPECT/CT in IE patients are diverging, but a few case reports have found SPECT/CT helpful in patients with PVE and in cardiac device infection. In the only larger series, 131 consecutive patients with suspected IE without CIED were investigated with 99mTc-HMPAO leucocyte scintigraphy. The method was true positive in 46 of 51 patients finally diagnosed with IE and false negative in 5 of 51 cases in whom IE was
excluded. Septic embolism was detected in 41% of patients but both false positive and false negative findings were observed. Leucocyte SPECT/CT is more specific for detection of infectious foci than $^{18}$F-FDG PET-CT, but also much more time consuming, and $^{18}$F-FDG PET-CT has a better spatial resolution and photon detection efficiency.

**Conclusion**

Imaging plays a pivotal role in IE, both in the diagnostic phase, to evaluate dispersion of the infection, during heart valve operation and as a control of response to therapy. For the last decades echocardiography has been—and still is—the cornerstone of the imaging techniques. Transthoracic echocardiography is recommended as the first line modality in all the patients with suspicion of IE, but may only be sufficient in patients where the probability of IE is low and with a clear acoustic window, first of all in patients with RIE. Transoesophageal echocardiography is strongly recommended in all other patients, in particular with moderate or high suspicion of IE due to the higher accuracy of TEE. But echocardiography has distinct limitations and novel use of other imaging modalities are emerging. CT and MRI have limited value for diagnosing intracardiac infections, but are
supplementary for the evaluation of embolic events and anatomical characterization of metastatic infectious processes. Nuclear molecular techniques and 18F-FDG PET-CT in particular are evolving as an important supplementary method for patients with diagnostic difficulties. However, data on PET-CT are still too limited for a general recommendation as a diagnostic tool in IE. The role of SPECT/CT in IE has so far not been established. Although more data are needed it is beyond doubt that in the future multimodal imaging will play an increasing role in IE.

Conflict of interest: none declared.

References


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