Invited review

Cardiac computed tomography in the contemporary evaluation of infective endocarditis

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ABSTRACT

Increasing data have accumulated on the role of Cardiac Computed Tomography (CCT) in infective endocarditis (IE) with high accuracy for large vegetations, perivalvular complications and for exclusion of coronary artery disease to avoid invasive angiography. CCT can further help to clarify the etiology of infective prosthetic valve dysfunction (e.g. malposition, abscess, leak, vegetation or mass). Structural interventions have increased the relevance of CCT in valvular heart disease and have amplified its use. CCT may be ideally integrated into a multimodality approach that incorporates a central role of transesophageal echocardiography (TEE) with 18-FDG PET and/or cardiac magnetic resonance in individually selected cases, guided by the Heart Team. The coronavirus-19 (COVID-19) pandemic has resulted in renewed attention to CCT as a safe alternative or adjunct to TEE in selected patients. This review article provides a comprehensive, contemporary review on CCT in IE to include scan optimization, characteristics of common IE findings on CCT, published data on the diagnostic accuracy of CCT, multimodality imaging comparison, limitations and future technical advancements.

1. Introduction

Infective endocarditis (IE) is a complex entity caused by damage to the valvular endothelium that causes platelet and fibrin deposition leading to vegetations; accurate imaging is essential to improve prognosis. Traditionally IE has been evaluated by echocardiography (trans-thoracic (TTE) and transesophageal (TEE)) as the first line diagnostic testing modality. 1 However, important data on the diagnostic accuracy of cardiac computed tomography (CCT) have accumulated during recent years. 2–5 Structural interventions have increased the relevance of CCT in valvular heart disease and have amplified its use. 6–8 The non-invasive nature of CCT and the minimal person-to-person contact have also renewed interest in CCT amidst the coronavirus disease 2019 (COVID-19) pandemic as a means to reduce the risk to healthcare workers (HCW) of high risks of exposure with TEE as an aerosol generating procedure. 9

This review article provides a comprehensive, contemporary review on CCT in IE to include scan optimization, characteristics of common IE findings on CCT, published data on the diagnostic accuracy of CCT, multimodality imaging comparison, limitations and future technical advancements.

2. CCT imaging principles, scan optimization and clinical indications in infective endocarditis

2.1. CCT imaging principles and scan optimization

CCT is a robust modality for cardiac anatomy evaluation given the sub-millimeter (~0.5 mm) “isotropic” resolution that is superior when compared to other imaging modalities. 10 As a full 3D cardiac dataset, the use of post-processing multiplanar reconstruction (MPR) techniques enables structures to be interrogated from any angle allowing for accurate assessment of pathologic location (anterior, posterior, medial, lateral). This allows, for example, an anterior vegetation or abscess to be better...
visualized when compared to transesophageal echocardiography (TEE), whereas far-field structures (anterior aortic annulus, tricuspid valve) may suffer from acoustic shadowing. Additionally, calcium can be much more clearly differentiated from tissue on CCT in comparison to echocardiography. With the high spatial resolution of CCT, paravalvular abscesses may be clearly seen due to excellent tissue-contrast differentiation highlighting heterogeneous regions. An important benefit of CCT angiography is for coronary artery evaluation in patients requiring surgery, potentially avoiding invasive cardiac catheterization. This may be of important benefit to avoid interaction of invasive catheters with an infected valve that could lead to vegetation embolization or associated abscess tissue. Although higher radiation dose is received with retrospective ECG-gated acquisition (3–7 mSv) in comparison to prospective ECG-gated acquisition, retrospective is the preferred method in IE to assess for vegetations, valve mobility and dehiscence.

Retrospective ECG-gated acquisition should be performed with scan coverage of the entire heart as per SCCT guidelines. A sufficient IV contrast volume rate should be administered to provide differentiation between contrast-enhanced blood pool and surrounding structures. A coronary artery volume contrast flow rate (5–6 ml/s) is advisable for the best visualization of small abscesses and pseudoaneurysms, while tailoring to local scanner characteristics. If evaluating only the left or right side of the heart, triggering or timed-bolus should be protocolled for the specified region. However, in the usual circumstances, both left and right sided opacification would be ideal to evaluate all cardiac valves and surfaces. This may require a longer contrast bolus to increase time of opacification. A triphasic contrast protocol, which can mitigate streak artifact and prolong contrast time, is recommended when opacifying the right heart. Multiphase CCT acquisition, reconstructed at 5–10% increments, is ideal to maximize temporal distinction of vegetations, pseudoaneurysms, and paravalvular abscesses across the cardiac cycle (See Fig. 1). For the assessment of aneurysms and pseudoaneurysms, the use of pre- and post-contrast images may further allow for identification of an intramural hematoma showing a low attenuation coefficient (60–70 HU) in the aortic wall in non-contrast images. For optimal prosthetic valve visualization a medium smooth tissue reconstruction kernel is typically utilized.

2.2. Clinical indications for CCT in IE

CCT doesn’t have the high temporal resolution that 2D-Echocardiography has, and potentially could miss small highly mobile vegetations, however it can identify large vegetations and although less common, abscesses in patients with suspected native valve IE. If a cardio-embolic event in the coronaries is suspected in the context of IE, CCT can help in diagnosing and identifying it. For patients with suspected IE that may have a relative contraindication for TEE, such as esophageal pathology or concerns for contagion as with COVID, CCT may be considered as an alternative. For patients with IE undergoing surgical valve replacement, CCT could help identify presence of obstructive CAD that may benefit from surgical revascularization. As for surgical planning for aortic IE, CCT may help defining the size, anatomy and calcification of the aortic valve, root and ascending aorta for surgical planning. In right-sided endocarditis, CT may reveal concomitant pulmonary disease, including abscesses and infarcts. For prosthetic valves it can be used to detect abscesses/pseudoaneurysms with a diagnostic accuracy similar to TEE, and is superior in the detecting the extent and consequences of any perivalvular extension, including the anatomy of pseudoaneurysms, abscesses and fistulae as it will be discussed further.

3. CCT findings and characterization of infective endocarditis

Important imaging findings in IE may be categorized into valvular (vegetations, valve perforations) and perivalvular (abscesses, pseudoaneurysms, prosthesis dehiscence, and fistulas) abnormalities. Vegetations may be seen on any of the valves or any other structure in the heart (Fig. 1) and often exhibit mobility which can be appreciated through multiphase CCT imaging. Valve perforations may be difficult to

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**Fig. 1. Aortic, Mitral and Tricuspid vegetations on cardiac computed tomography.** A and B. 75-year man with Streptococcus pneumoniae aortic endocarditis with severe aortic regurgitation underwent CF to assess coronary arteries prior to surgical intervention. An irregularly shaped 1.3 cm × 1.3 cm mobile vegetation (A) was identified downstream to the valve with (B) non-coronary cusp ballooning and leaflet perforation. C and D. 39-year-old woman with a pelvic malignancy. A (D) transthoracic echocardiogram showed classic findings of “marantic endocarditis” or also known as non-bacterial thrombotic endocarditis. (C) CCT confirms findings of “marantic endocarditis” with vegetations attached to both mitral valve leaflet tips. E and F. Round-shaped mass-like mobile vegetation attached to the posterior side of septal tricuspid valve leaflet. Pedunculated lesion of >1 cm size indicates risk of embolization. (E) Multiphase reformat during systole shows the mass on posterior surface (arrow) floating into the downstream chamber, the right atrium. (F) 3D volume-rendered reformat during diastole shows anterior mass movement over tricuspid valve orifice towards the right ventricle. G and H. (G) Normal coronary arteries in Case (A, B) that allowed the patient to avoid invasive angiography. H. Coronary embolism suspected to have arisen from mitral valve lesions in Case (C, D) causing abrupt cut-off (arrow) of the left anterior descending artery with color map of resting perfusion abnormality (as shown in blue) in the apex of the left ventricle. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
visualize on CCT, especially when small in size due to limited temporal resolution. Volume-rendering techniques may be helpful as a supplementary technique to evaluate for perforation, but volume dropout is common and these must be interpreted carefully and informed by the 2-dimensional slices.14

Perivalvular complications of IE are typically well-visualized on CCT. Perivalvular extension of IE has been noted in up to 35% of patient undergoing operation for IE and abscess is a risk factor for adverse outcomes including operative death.15 The perivalvular complications of pseudoaneurysm, dehiscence, and fistula can be co-existent with or the result of perivalvular abscess. Abscess typically appears as a low CT attenuation with liquid density (20–50 HU) or heterogeneous collection adjacent to the valve, depending on the degree and extent of necrosis (Figs. 2 and 3; Video 1). Abscess may – or may not – present with an outer hyperenhancing rim (abscess “capsule”), which indicates active inflammation. A hyperintense rim is more suspicious of an acute abscess than an exclusive liquid collection, especially after surgery or in patients without clinical signs of IE. Hyperenhancement is best seen at a delayed scan of either 70 s, or very late after 2–3 min.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.jcct.2021.02.001.

In particular, the aortic root is usually surrounded by periaortic fatty tissue (<0 up to ~100 HU). The loss of the periaortic lipid layer, and an increase of HU above 0 into positive ranges (1–30 HU), should always raise the concern of periaortic abscesses. Abscess typically appears as a low CT attenuation with liquid density (20–50 HU) or heterogeneous collection adjacent to the valve, depending on the degree and extent of necrosis (Figs. 2 and 3; Video 1). Abscess may – or may not – present with an outer hyperenhancing rim (abscess “capsule”), which indicates active inflammation. A hyperintense rim is more suspicious of an acute abscess than an exclusive liquid collection, especially after surgery or in patients without clinical signs of IE. Hyperenhancement is best seen at a delayed scan of either 70 s, or very late after 2–3 min.

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Multi-phase CCT can further elucidate the pulsatile nature of pseudoaneurysms throughout the cardiac cycle. As the abscess or pseudoaneurysm extends, fistulation into other cavities may occur. Whereas flow cannot be directly visualized, contrast flow into areas of prosthetic dehiscence and fistula formation can be seen. Contrast-based findings can be elucidated and further characterized through several techniques, including maximum-intensity projection and volume-rendering. As findings such as leaflet perforation and fistula may not exist in a single plane, expanding the field of view beyond a single slice may be helpful (Fig. 5). CCT findings may help in deciding whether surgical treatment is indicated or not based on size of vegetation, qualitative mobility (>1 cm and mobile likely favors surgery), presence and extent of perianular or periprosthetic complications may help define if management will lean more towards surgical or conservative approaches.

4. CCT role in coronary and extra cardiac embolic evaluation

A distinct advantage of CCT angiography is the high diagnostic accuracy to reliably exclude obstructive coronary artery disease in patients with lower pre-test probability of CAD and in younger individuals to avoid unnecessary invasive angiography.17 In a study by Sims et al. in patients who underwent both CCT and invasive coronary angiography, over 80% had no change in management based on invasive angiography. In some instances, particularly aortic valve vegetation, CCT may allow for dual visualization of vegetation and coronary anatomy in a single scan for patients with IE may need prompt surgical treatment with prosthetic valve infection, invasion beyond valve leaflet and at risk recurrent systemic embolization due to large mobile vegetations, or persistent sepsis.18 In patients with prior valve replacement or coronary bypass CCT may further provide important information on the status of surgical adhesions that may complicate the procedure.19 In addition, a CT based evaluation may allow for assessment of septic emboli in a single scan. In the study by Kim et al. focused on cardiac evaluation, in 4 out of 75 patients (5.3%) extracardiac emboli (1 pulmonary, 3 splenic) were identified. As for mycotic aneurysms, CCT allows for visualization of the wall of the aorta and surrounding structures to appreciate prominence of inflammatory soft tissue surrounding aorta and fat stranding,20 which

Fig. 2. Mitral valve abscess and annulus pseudoaneurysm. An elderly male was referred for evaluation of transcatheter mitral intervention in the setting of new dyspnea. A. TTE imaging shows significant mitral regurgitation explaining patient symptoms. B and C. CCTA performed as part of transcatheter intervention workup shows a contrast filled space at the P3 scallop with calcification in the leaflet (red arrows), most consistent with healed leaflet abscess. Based on these findings, patient was referred for surgery. D. 58-year-old man presenting to the emergency department with fever and elevated C-Reactive Protein of 21 mg/dl. Transthoracic echocardiogram (TTE) during initial screening was normal. CTA showed posterior mitral annulus paravalvar pseudoaneurysm. 2-Chamber view by multiplanar reformat: White arrow pointing at left circumflex coronary artery adjacent to the cavity. E: 3D volume rendered image with the left circumflex circumventing the pseudoaneurysm. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
may be visualized with magnetic resonance angiography, but not with invasive angiography.

5. Diagnostic performance of CCT vs transesophageal echocardiography

5.1. Native valves

In native valves, the most important assessment is to determine whether there is presence or absence of vegetations, the integrity of the valve and although rare if there is development of a para-valvular abscess, for which CCT provides very good spatial and temporal resolution to detect. Prior data have shown excellent diagnostic performance of CCT and high intermodality agreement with TEE. In a prospective study of 37 patients the initial seminal study by Feuchtner et al. demonstrated excellent diagnostic accuracy of 64-slice dual-source CCTA for detection of vegetations, abscess, and pseudoaneurysms with sensitivity, specificity, PPV and NPV of >95% compared to surgical findings. On a per-valve basis, CCTA and TEE accuracy for detection of vegetations and abscess/pseudoaneurysm showed no statistical difference, although this comparison was limited by small numbers. CCT missed five small vegetations, one was missed due to CT artifacts. Three were small mitral valve vegetations (<4 mm in size) and one was a tricuspid valve vegetation that was missed due to low right ventricular contrast enhancement and artifacts due to a pacemaker. TEE missed 2 vegetations on a mechanical valve which were seen on CCT, due to metal artifacts. Subsequent studies have confirmed the overall similar ability of CCTA and TEE for general IE diagnosis, with the caveat of superior ability of CCT to diagnose...
paravalvular abscess and pseudoaneurysm, and of TEE to diagnose smaller vegetations (<10 mm) and valve perforations (Table). A recent meta-analysis included 8 studies comparing diagnostic performance of CCT and TEE for identifying IE valvular complications validating it with surgical findings. They found CCT with a higher sensitivity to diagnose pseudoaneurysm or abscess (CCT: 78% vs. TEE: 69%). For vegetations, valve perforations and paravalvular leakage the sensitivities were higher for TEE. Another recent meta-analysis showed that CCT, when compared to TEE, performs better in identifying prosthetic valve pathology in the peri-prosthetic tissue, such as prosthetic dehiscence or paravalvular abscesses.

Regarding visualization of prosthetic dehiscence, CCT has been shown in several studies to have excellent specificity and/or positive predictive value in comparison to surgical findings, with modest sensitivity compared to TEE. When referenced to intraoperative direct inspection, Hryniewiecki et al. demonstrated that a combination of echocardiography and CCT provided superior sensitivity for all valvular and perivalvular IE findings compared to either modality alone, strongly supporting a multimodality approach. However, especially in the immediate post-surgical setting, liquid collections are common and do not indicate abscess. After a time period of 2–3 months after surgery, an 18-FDG PET/CT might be able to diagnose (or rule out) findings suspicious or periprosthetic abscess. Table 1 summarizes the relevant literature for the accuracy of CCT for the evaluation of IE in native and prosthetic valves. When considering CCT and TEE for IE, it is important to mention the only study looking at how CCT and TEE findings relate to in-hospital and follow-up mortality in patients undergoing surgery for IE by Ming Wang et al. TEE findings of pseudoaneurysm or abscess were the only prognostic findings that predicted in-hospital mortality, however CCT findings of pseudoaneurysm, abscess or fistula were the only predictors of mortality during follow up.

6. Multimodality comparison to PET/CT and cardiac magnetic resonance

PET/CT has been used to detect valvular and Cardiovascular Implantable Electronic Devices (CIED) infections. The data regarding the use of 18F-FDG PET as an adjunctive diagnostic tool to diagnosis infective endocarditis and CIED related infections are comprised mostly of small observational studies. There have been a few large meta-analyses evaluating the data collectively; however, there were no standardized PET/CT criteria for diagnosis of infectious endocarditis, as many of them incorporated qualitative or semiquantitative evidence of the PET/CT in the clinical Duke criteria, which was already influenced by echocardiographic findings. A meta-analysis of 6 studies involving 246 patients investigating the diagnostic value of 18F-FDG PET for patients with infectious endocarditis found a pooled sensitivity and specificity of 61% and 88%, respectively. Notably, 5 of the 6 studies used the Modified Duke Criteria as the reference standard, while only 1 used bacteriological data from CIED infections. In another meta-analysis of 13 studies involving 537 patients, the pooled sensitivity and specificity of 18F-FDG PET for diagnosis of IE was 76.8% and 77.9%, respectively. (Figs. 6 and 7 demonstrate 18F-FDG PET imaging for IE evaluation). Disadvantages of 18F-FDG PET are inability to image cardiac motion, inability to visualize valvular vegetations and requirement of dietary preparation, which may delay diagnosis when compared to CCT. Another disadvantage of 18F-FDG PET is a lower spatial resolution of 5 mm in most scanners as compared to cardiac CT.

However, 18F-FDG PET is an accurate modality for the detection of prosthetic valve endocarditis (PVE), especially for periprosthetic abscess or infection. The most accurate approach, however, is the multimodality interpretation: Both TEE, cardiac ECG-gated and PET/CT findings should

Fig. 5. Aortic Root to Left Atrial Fistula in the Setting of Multiple Surgeries for IE. A 35-year-old female with a history of multiple surgeries presented with dyspnea. A. CCTA axial images suggested aortic root to left atrial fistula (red arrow) and an LVOT pseudoaneurysm is seen. Short-axis (B) and long-axis (C) MIP images elucidate the fistula tract further given its serpiginous path (red arrows). D. Correlative TEE color Doppler biplane image demonstrates a color Doppler jet originating from the aortic root and exiting into the left atrium. As this fistula was small, hemodynamic consequences were minimal. Abbreviations: Ao = aorta; AV = aortic valve; CCTA = cardiac computed tomography angiography; LA = left atrium; LV = left ventricle; LVOT = left ventricular outflow tract; MIP = maximum-intensity projection; PSA = pseudoaneurysm; TEE = transesophageal echocardiogram. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
be interpreted head-to-head in adjunction, in order to rule-in or rule out a diagnosis (see Central Illustration, Fig. 8). Serial follow-up of unclear but suspicious lesions, after antibiotic treatment, is a valuable strategy in clinical practice, which is usually recommended after 6–8 weeks up to 3 months (depending on lesion type). The sensitivity and specificity of 18F-FDG PET in native valve IE is limited, as it is more robust in prosthetic valve IE. 18F-FDG PET should be utilized preferably in the context of case series and a few case reports. However, the robust accuracy of CMR in valvular regurgitation quantification might be helpful in certain cases in which further assessment is needed. CMR lacks the submillimeter spatial resolution of CCT to assess the perivalvular region when prosthetic valves are present, and the signal void generated by some prostheses may impair the assessment of prosthetic valve function. The data on usefulness of CMR in IE is limited, it may identify complications related to IE and might help in clarifying severity of valvular regurgitation from IE in cases where that information could make a difference in clinical management.

7. CCT to improve safety of infective endocarditis imaging amidst COVID-19

Amidst the novel coronavirus disease (COVID-19) pandemic, it has become essential to balance the risk of virus aerosolization with HCW safety and optimal patient care. The Society of Cardiovascular Computed Tomography/American College of Cardiology (ACC) endorsed COVID-19 guidance statement suggests acute endocarditis, perivalvular extension or abscess as potential urgent CCT indications. A JACC: Cardiovascular Imaging/ACC Imaging Council collaboration statement articulates CCT with the highest rating for invasive complications of endocarditis amongst the major cardiac imaging modalities to minimize risk, reduce resource use and maximize clinical benefit. In acute phase COVID-19 patients, an ACC Imaging Council document supports the use of CCT instead of TEE in selected cases during the acute phase of COVID-19, to decrease the risk of exposure of HCW from aerosol-generating procedures and in cases where there is a suspicion of coronary embolism. However, the increased risk of kidney dysfunction due to iodine contrast agent exposure has to be considered in critically ill COVID-19 patients, and carefully balanced to the urgency of the indication.
Even with known advantages in the assessment of extravalvular IE findings, CCT has been historically underutilized for IE evaluation (14% in a recent retrospective study). The most recent American Heart Association and European Society of Cardiology Guidelines mention CCT and other modalities as ancillary methods of evaluating IE with echocardiography as the only Class 1 imaging modality. These guidelines have not been updated since 2015 to incorporate more contemporary data such as those cited in the current review. However, a recent survey published in 2020 by the European Association of Cardiovascular Imaging finds that 60% of surveyed sites are using CCT for diagnostic purposes, most often in those patients with complex prosthetic valve endocarditis and in cases when TEE is inconclusive.

Currently, there are several new technologies available or in development which may further improve IE detection by CCT. The use of dual-energy CCT to improve tissue characterization via differentiation of high and low photon energies has been studied and is currently in limited clinical use. Dual-energy CCT has been shown to reduce beam hardening and partial volume averaging artifacts. Spectral CCT takes this a step further by ascertainment of multiple energy levels. Preclinical studies have shown the ability to differentiate multiple tissue
aortic valve disease to avoid invasive angiography. In
patients with suspected prosthetic valve dysfunction, CT can help to
clarify the type of dysfunction (e.g. malposition, abscess, leak, vegetation
or mass). CCT may be ideally integrated into multimodality approach
that incorporates a central role of TEE with 18-FDG PET and/or CMR in
individually selected cases that is guided by the Heart Team with an
emphasis on high accuracy, high quality imaging while avoiding un-
necessary testing to improve the diagnosis and outcomes of patients with
IE.

9. Limitations of CCT in endocarditis evaluation

Despite the rising evidence presented in this paper, several important
limitations of CCT in endocarditis require discussion. Acute kidney injury
is a concern when giving iodinated contrast to patients with pre-existing
renal insufficiency. In general, the risk of contrast-induced nephropathy
increases with estimated glomerular filtration rate of ≤30 mL/min/1.73
m2, although the impact of intravenous contrast is debated. CCT has been
found to have limited sensitivity and accuracy in patients with small
(<10 mm) leaflet vegetations. Low temporal resolution and the absence
of direct flow assessment limit the ability of CCT to evaluate for leaflet
perforation or valvular dysfunction. There exists a selection bias in the
literature as most studies have evaluated CCT in patients undergoing
surgical valve repair or replacement in IE. Most of the data related to CCT
in IE are from small, single center retrospective studies. Therefore, the
evidence for CCT to exclude vegetations in persistently bacteremic pa-
tients with low risk TTE findings is unknown, though an emerging im-
aging approach at some centers, especially during the COVID-19
pandemic to avoid TEE. For patients with acute illness or heart failure
with elevated heart rates and those who may not be able to perform a
proper breath-hold may have lower diagnostic accuracy placing
enhanced importance on optimizing scan parameters and heart rate
control measures to achieve high diagnostic quality.

10. Conclusion

CCT has an important role in the contemporary assessment of IE, with
high accuracy for large vegetations, perivalvular complications and for
exclusion of coronary artery disease to avoid invasive angiography. In

Declaration of competing interest

Dr. Choi reports equity interest in Cleerly, Inc. Dr. Lopez-Mattei and
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