Aortic valve imaging

Towards new standards in prosthetic valve endocarditis

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Cover: ECG-gated computed tomography three-chamber view of the heart in a patient with prosthetic valve endocarditis. The image shows large pseudoaneurysms anterior and posterior to the mechanical valve. The pseudoaneurysms drain into the left ventricular outflow tract.

Aortic valve imaging – Towards new standards in prosthetic valve endocarditis

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To my loved ones Henrik and Valter

Abstract

Background: Aortic prosthetic valve endocarditis (PVE) is a disease with high mortality, and diagnosis is difficult. Transesophageal echocardiography (TEE) has been the mainstay imaging modality in the diagnostic workup, but TEE has diagnostic shortcomings. Thus, new imaging methods might improve the diagnostic workup of PVE.

Aims: I) To investigate the agreement in findings between electrocardiogram (ECG)-gated computed tomography (CT) and TEE in patients with aortic PVE. II) To identify a clinically useful cutoff value for aortic wall thickness to detect PVE. III) To compare ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake around prosthetic aortic valves in patients with and without PVE and to determine the diagnostic performance of ^{18}F-FDG PET/CT in the diagnosis of PVE. IV) To investigate the value of ECG-gated CT in the surgical decision-making and preoperative evaluation in patients with aortic PVE.

Methods: In paper I, ECG-gated CT and TEE were compared in a prospective series of 27 patients with aortic PVE. In paper II, the aortic wall thickness on chest CT in patients with a prosthetic aortic valve with PVE (n = 43) and without PVE (n = 260) was compared. In paper III, ^{18}F-FDG uptake on PET/CT in patients with a prosthetic aortic valve with PVE (n = 8) and without PVE (n = 19) was compared. In paper IV, 68 aortic prosthetic valves with PVE were prospectively evaluated with ECG-gated CT and TEE. The impact of both modalities on surgical decision-making was studied, and the coronary arteries were evaluated with ECG-gated CT.

Results: In paper I, the strength of agreement [kappa (95 % CI)] between ECG-gated CT and TEE was 0.83 (0.62–1.0) for wall thickening, 0.68 (0.40–0.97) for the presence of abscess/pseudoanuerysm, 0.75 (0.48–1.0) for valve dehiscence and 0.55 (0.26–0.88) for vegetation. In paper II, receiver operating characteristic (ROC) analysis yielded an area under the curve of 0.89 for aortic wall thickness in the detection of PVE beyond three months postoperatively. With a cutoff value of 5 mm, the sensitivity was 67% and the specificity was 95%. In paper III, visual analysis of ^{18}F-FDG PET/CT exhibited a sensitivity of 75% and a specificity of 84% for the diagnosis of PVE. ROC analysis of the Standardized Uptake Value ratio yielded an area under the curve of 0.90. In paper IV, 58 of 68 PVE cases had indications for surgery based on imaging findings. In eight of these cases (14%), there was an indication for surgery based on CT but not on TEE findings (all with pseudoaneurysms). In 11 cases (19%), there was an indication for surgery based on TEE but not on CT findings. In 31 of 32 patients with indication for preoperative coronary angiography, ECG-gated CT coronary angiography was diagnostic.

Conclusions: ECG-gated CT provides additional information over TEE regarding paravalvular extension of infection, which influences surgical decision-making. ECG-gated CT can in most cases replace invasive coronary angiography in the preoperative evaluation. Increased aortic wall thickness on CT (> 5mm) beyond three months postoperatively is a sign of PVE with high specificity. The level of ^{18}F-FDG uptake in the aortic valve area on ^{18}F-FDG PET/CT shows good diagnostic performance in the diagnosis of PVE.

Keywords: prosthetic valve endocarditis, aortic valve endocarditis, ECG-gated CT, cardiac CT, ^{18}F-FDG PET/CT

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List of publications

This thesis is based on the following papers that are referred to in the text by their Roman numerals.

I. Fagman E, Perrotta S, Bech-Hanssen O, Flinck A, Lamm C, Olaison L, Svensson G

ECG-gated computed tomography: a new role for patients with suspected aortic prosthetic valve endocarditis

Eur Radiol. 2012 Nov; 22(11): 2407-14

II. Fagman E, Bech-Hanssen O, Flinck A, Lamm C, Svensson G

Increased aortic wall thickness on CT as a sign of prosthetic valve endocarditis

Acta Radiol. 2016 Feb 6. DOI: 10.1177/0284185116628336

III. Fagman E, van Essen M, Fredén Lindqvist J, Snygg-Martin U, Bech-Hanssen O, Svensson G

^{18}F-FDG PET/CT in the diagnosis of prosthetic valve endocarditis

Int J Cardiovasc Imaging. 2016 Apr; 32(4): 679-86

IV. Fagman E, Flinck A, Snygg-Martin U, Olaison L, Bech-Hanssen O, Svensson G

Surgical decision-making in aortic prosthetic valve endocarditis: the influence of ECG-gated computed tomography

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Table of contents

Abbreviations

AVR	aortic valve replacement
CT	computed tomography
FDG	fluorodeoxyglucose
IE	infective endocarditis
MDCT	multidetector computed tomography
MRI	magnetic resonance imaging
NVE	native valve endocarditis
PET	positron emission tomography
PVE	prosthetic valve endocarditis
ROC	receiver operating characteristic
SPECT	single-photon emission computed tomography
SUV	standardized uptake value
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography
TAVI	transcatheter aortic valve implantation

Introduction

Ancient Egyptian medical practices are some of the oldest that have been documented and were highly advanced for their time. Several Egyptian medical papyri have been preserved, and one of the oldest is The Ebers Papyrus that dates to around 1500 BC. The papyrus describes, maybe for the first time in the history of mankind, that the heart is the center of the blood supply, with vessels attached for every part of the body [1]. The Greek physicians Hippocrates and Erasistratos both studied at the temple of Amenhotep in Egypt, and they acknowledged that the practices of Egyptian medicine had contributed to their own knowledge. Erasistratos was the first to describe the valves of the heart around the 3rd century BC, although he did not fully understand their function [2]. In the 16th century AD, Leonardo da Vinci seems to have understood the function of the cardiac cycle and the pulse, and he explained the hemodynamic mechanism of valve opening and closure [3].

A description of vegetations on the heart valves as a sign of infection was first made by the French physician Lazare Rivière in the 17th century [4]. At autopsy, he described how "rounded carbuncles…which resembled a cluster of hazelnuts…filled up the opening of the aorta" [4]. The condition was named endocarditis by another French physician, Jean-Baptiste Bouillaud, in the beginning of the 19th century [5]. The first comprehensive description of endocarditis was presented by William Osler, founding professor of Johns Hopkins Hospital, in the Gulstonian lectures in 1885 [6]. His lectures drew attention to the disease, but there was no effective treatment.

The possibility to cure endocarditis first came in the 1940s with the introduction of penicillin [7]. Antibiotics improved the prognosis but could not cure all patients. Twenty years later, in the 1960s, the other cornerstone in the treatment of endocarditis was introduced – surgery with valve replacement [8]. This further improved the prognosis for endocarditis patients [9]. However, soon after the introduction of aortic valve replacement came the first reports of infection in a prosthetic heart valve – prosthetic valve endocarditis (PVE) [10]. This condition proved to be more difficult both to diagnose and to treat than native valve endocarditis [11]. With surgery as a therapeutic option, there was a greater need for an imaging method that could create a visual representation of the native or prosthetic valve and could determine the presence and extension of infection.

The visual representation of the interior of the body became possible after the discovery of x-rays in 1895 by Willhelm Conrad Röntgen [12]. There were early studies of the heart with x-rays, but it was not possible to visualize the aortic valve [12]. Sonar systems were developed for submarines during the Second World War, and in the 1960s the same technique was applied to diagnostic imaging with the introduction of medical ultrasound [13]. Ultrasound of the heart (echocardiography) was introduced in clinical use in the 1970s, and for the first time it was possible to visualize vegetations on the heart valves [14]. With the introduction of transesophageal echocardiography (TEE) in the 1980s, the ability to detect signs of endocarditis improved [15,16]. However, when a prosthetic heart valve is present, the diagnosis of endocarditis remains difficult [17]. TEE still has diagnostic shortcomings, and TEE has been reported to be false negative in 14–20% of PVE cases [18-20].

Technical improvements have opened up for new diagnostic modalities with the potential to improve the diagnostic workup of patients with aortic PVE, and this is the subject of this thesis.

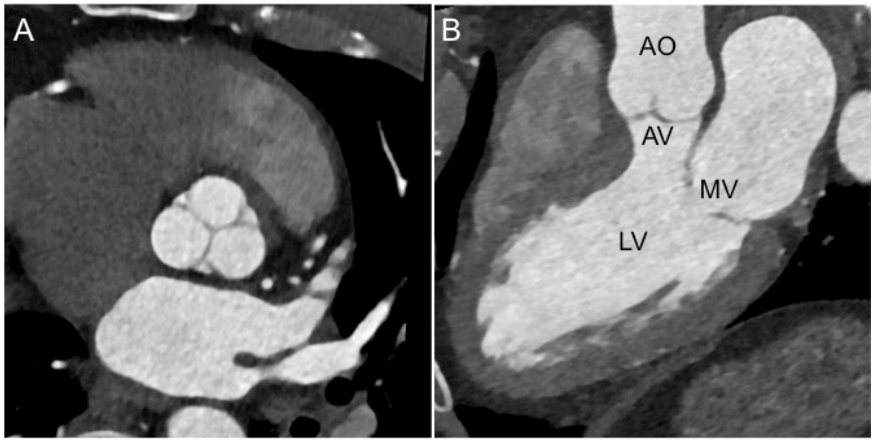

Figure 1. ECG-gated CT images of a normal aortic valve. A. Transaxial image of the aortic root in diastole shows three symmetric valve leaflets that are closed. B. Three-chamber view of the left ventricle. AO: aorta, AV: aortic valve, MV: mitral valve, LV: left ventricle.

The aortic valve

The aortic valve is positioned between the left ventricle and the aorta. It is composed of three symmetric leaflets that open when the heart contracts in systole and close when the heart relaxes in diastole (Fig. 1). Aortic valve dysfunction occurs when the leaflets do not open fully in systole (aortic stenosis) or do not close completely in diastole (aortic regurgitation). Aortic stenosis is the most common cardiac valve disease [21]. It is an active disease process that is related to atherosclerosis and leads to progressive calcifications and reduced motion of the leaflets [22,23]. The reduced opening area of the valve induces hemodynamic changes that eventually cause symptoms. Typical initial symptoms are dyspnea on exertion and decreased exercise tolerance [24]. Once symptoms occur, the prognosis is poor and the only effective treatment is surgery with aortic valve replacement (AVR) [24]. The prevalence of aortic stenosis is strongly correlated to age with a reported prevalence of 0.2% in the age group 50–60 years increasing to as high as 10% in persons >80 years [25].

Aortic regurgitation is less common than stenosis, and moderate/severe regurgitation has a reported prevalence of 0.5% [26]. The most common cause of aortic regurgitation in developed countries is bicuspid aortic valve (a congenital condition where the aortic valve consists of two leaflets instead of three) [26]. In severe symptomatic aortic regurgitation, treatment is surgical [24].

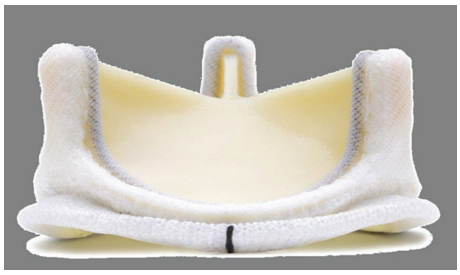

Figure 2. Biological prosthetic valve. (Courtesy of Edwards Lifesciences)

Figure 3. Mechanical prosthetic valve. (Courtesy of St. Jude Medical)

Surgical treatment of aortic valve disease

The era of surgical treatment of aortic valve disease started with the development of cardiopulmonary bypass (the heart-lung machine) in the 1950s, which made it possible to operate on a non-beating heart [27]. The first mechanical prosthetic valve was implanted in 1960, and the first bioprosthesis in 1965 [28,29]. Since then, the technique has evolved rapidly and surgical AVR is now a routine procedure for treatment of aortic valve dysfunction. AVR is performed with cardiopulmonary bypass and during surgery the heart-lung machine temporarily replaces the pumping action of the heart and the function of the lungs with oxygenation of the blood. The aorta is x-clamped and opened, and the diseased aortic valve is removed and replaced with a substitute, most often a prosthetic valve. The prosthetic valve is sewn into the annulus of the removed native valve.

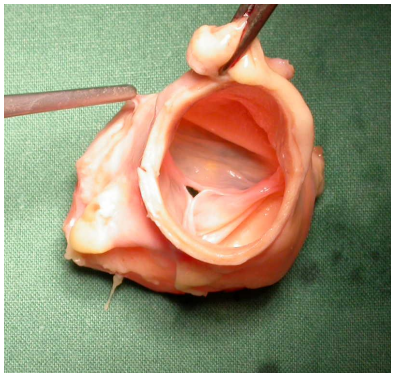

Figure 4. Aortic homograft.

The most common valve types are bioprosthetic and mechanical prosthetic valves (Figs. 2 and 3). AVR can also be performed with a homograft or with the Ross procedure. A homograft (allograft) is an aortic valve that has been removed from a human donor (deceased or a heart transplant recipient) and frozen under sterile conditions (Fig. 4). A homograft may be used when part of the aortic root is destroyed by infection [30]. In the Ross procedure, the aortic valve is replaced with the patient's own pulmonary valve, and the pulmonary valve is replaced by a homograft (a pulmonary valve from a human donor) (Fig. 5). Candidates for the Ross procedure are children, young adults, and women of child-bearing age [31]. There are also different types of valve-sparing surgeries that can be used in the case of aortic regurgitation and dilated aortic root [32].

The choice of valve type is controversial. In patients with aortic stenosis, current guidelines suggest the choice of a bioprosthesis in patients >65 years and a mechanical valve in patients <60 years [33]. Mechanical valves are durable but require lifelong anticoagulation, which puts the patient at risk of bleeding complications [33]. Bioprosthetic valves have the advantage of better rheologic properties and do not require anticoagulation, but they have a limited durability [33]. The use of bioprosthetic valves has increased in the last decade due to improved durability, and currently a majority of the patients receive a bioprosthetic valve [34]. For patients with comorbidities and who are at too high a risk to undergo cardiac surgery, a new method of replacing the aortic valve in the case of aortic stenosis was developed in the early 2000s – transcatheter aortic valve implantation (TAVI) [35]. This valve is placed in the correct position with a catheter introduced through an artery, usually the femoral artery. There are both self-expandable and balloon-expandable valves. The stenotic native valve is not removed but is destroyed when the new valve expands. TAVI has been shown to be a safe alternative to surgical AVR in high-risk patients [36].

With increased life expectancy in the population, the mean age of patients receiving a prosthetic valve has increased and the annual volume of aortic valve replacements (both surgical and transcatheter) has increased [34]. All types of valve surgery are associated with a risk of prosthetic valve endocarditis (PVE).

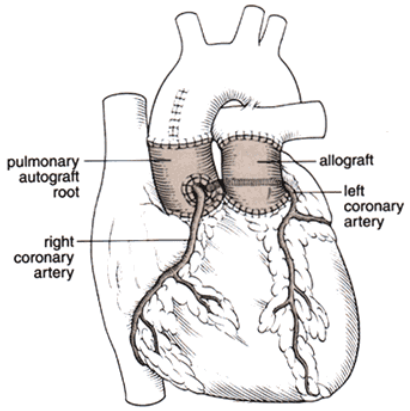

Figure 5. The Ross procedure. The aortic valve and aortic root are replaced with a pulmonary autograft (the patient's own pulmonary valve), and the pulmonary valve is replaced by a homograft.

Prosthetic valve endocarditis

Epidemiology

All four valves of the heart, both native and prosthetic, can be affected by infective endocarditis (IE) [17]. Left-sided endocarditis (aortic and mitral valve) is much more common than right-sided endocarditis (pulmonary and tricuspid valve) and accounts for 90–95% of all IE cases [17]. PVE, the most severe form of endocarditis, affects the aortic valve in 66–69% of all PVE cases [37,38].

The reported overall incidence of IE worldwide is about 3–10 cases per 100,000 people, and in Sweden the incidence is about 6 cases per 100,000 people [39,40]. The age of patients with IE has increased substantially over the last 30 years, and in Sweden the mean age of patients with native valve endocarditis (NVE) is 67 years compared to 70 years in PVE patients [41]. With the increasing prevalence of prosthetic heart valves and intra-cardiac devices in the population, the incidence of PVE is rising and PVE accounts for 20–30% of endocarditis cases today [42,43]. The presence of a prosthetic valve increases the risk of endocarditis 50 times compared with the general population. The reported incidence of PVE worldwide is 0.3–1.2%, and in Sweden it is 0.4% [24,39]. Reports on PVE after TAVI is limited, but a recently published multicenter registry study reported an incidence of 0.67% [44].

Etiology and pathophysiology

IE is an infection of the inner layer of the heart, the endocardium. The healthy endothelium is resistant to bacteria, but when the endothelium is damaged a platelet-fibrin thrombus forms that makes it easier for bacteria to adhere to the surface [45]. Endothelial damage and bacteremia (the presence of bacteria in the blood) are the two most important factors in the pathophysiology of IE [11]. Endothelial damage can be caused by congenital or degenerative valve changes, inflammation, or injury from catheters and electrodes [11]. Bacteremia with oral pathogens is seen during invasive procedures such as dental extraction, but transient bacteremia is also common with everyday activities such as chewing and tooth brushing [11].

The underlying heart conditions of IE have changed in recent years, especially in developed countries. Rheumatic disease, which used to be a common cause and still is in developing countries, is rarely seen in the Western world [11,24]. IE is now more often associated with degenerative valve changes, intravenous drug abuse, prosthetic heart valves, and intra-cardiac devices [11,46]. The introduction of foreign material, e.g. a prosthetic valve, into the body results in an

increased risk of infection at the implant site. Bacteria or other microorganisms can be introduced perioperatively at the implant site or can be blood-borne during later episodes of bacteremia [47].

Microbiology

Both community-acquired and health care-associated *Staphylococcus aureus* bacteremia is increasing worldwide [46,48], and today *S. aureus* is reported as the most common cause of IE in many studies [49,50] and accounts for around 30% of all episodes [43,46]. Other common pathogens are oral streptococci from the viridans group, enterococci, and coagulase-negative staphylococci [40,46]. The causative pathogens differ in NVE and PVE with coagulase-negative staphylococci, gram-negative bacteria and fungi being more common in PVE [17]. The etiological spectrum also varies between early and late PVE; in late PVE the bacterial etiology resembles what is seen in NVE [38,47]. Staphylococcal endocarditis is associated with an increased risk of in-hospital death, whereas endocarditis caused by viridans streptococci is associated with a lower risk [46].

Symptoms

Clinical presentation of IE can be non-specific, and the diagnosis is often missed or is initially uncertain. The most common presenting symptom is fever, which is seen in more than 90% of the patients [11]. Fever in combination with risk factors such as prosthetic valve, intracardiac device, valvular disease, congenital heart disease, or intravenous drug abuse should lead to the suspicion of endocarditis. Presenting symptoms in IE can also be caused by a complication such as a cerebral or systemic embolic event, which is seen in 20–40% of the patients [40,46,51]. Other symptoms are immunological phenomena such as splinter hemorrhages under the nails, retinal hemorrhages (Roth spots) and glomerulonephritis [11]. An atypical presentation with non-specific symptoms and the absence of fever is more common in elderly patients and also in PVE [52]. In the postoperative period after valve replacement, fever is also common in the absence of PVE, which leads to a diagnostic dilemma in such a situation [17].

Diagnostic workup

IE is a diagnosis based on multiple objective findings that also takes into account specific risk factors associated with the disease. Positive blood cultures and signs

of endocardial involvement on echocardiography are cornerstones of the diagnosis. In 1994, Durack et al presented criteria for the diagnosis of endocarditis that are referred to as the Duke criteria [53]. Based on blood cultures and echocardiographic and clinical signs, the diagnosis was classified as definite, possible or rejected endocarditis. The criteria were criticized because a large proportion of patients received the diagnosis "possible endocarditis" [54], and this led to a modification of the Duke criteria in 2000 [55]. The modified criteria have been used ever since (Table 1).

Table 1: Modified Duke criteria for the diagnosis of infective endocarditis

Major criteria

-blood culture positive for endocarditis

- typical microorganisms consistent with IE from two separate blood cultures or
- microorganisms consistent with IE from persistently positive blood cultures or
- single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer >1:800

-evidence of endocardial involvement

- echocardiography positive for IE
- new valvular regurgitation

Minor criteria

-predisposition predisposing heart condition, drug use

-fever temperature >38°C

-vascular phenomena major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions

-immunologic phenomena glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor

-microbiological evidence positive blood culture but does not meet a major criterion or serological evidence of active infection with an organism consistent with IE

Definite endocarditis	**Possible endocarditis**
-2 major criteria or -1 major and 3 minor or -5 minor	-1 major and 1 minor or -3 minor

IE = infective endocarditis. Adapted from Li et al [55].

In NVE, the criteria have a reported sensitivity of 70–80% [17]. However, in the presence of a prosthetic valve, the modified Duke criteria have a lower sensitivi-

ty, mainly due to the lower diagnostic accuracy of echocardiography in PVE [17]. In the modified Duke criteria, specific echocardiographic findings are major criteria in the diagnosis of endocarditis [56]. The first-line imaging method is transthoracic echocardiography (TTE), but TEE is a more sensitive method and is recommended in all patients with a prosthetic heart valve or intracardiac device and in patients with suspicion of NVE when TTE is negative [17].

Three echocardiographic findings constitute major criteria in the diagnosis of endocarditis: vegetation, abscess/pseudoaneurysm, and new dehiscence of a prosthetic valve. Vegetations are masses containing bacteria, platelets, and fibrin that adhere to the valve leaflets, and this is the most common finding in NVE [46]. In PVE, the infection more often affects the valve ring and extends into the aortic wall and the perivalvular myocardium. Abscess cavities might form adjacent to the valve ring, and when an abscess cavity drains into the aorta or the left ventricle a pseudoaneurysm is formed [57]. Tissue destruction can lead to partial detachment of the prosthetic valve ring from the aortic wall resulting in valve dehiscence with perivalvular regurgitation of blood. Perivalvular extension of infection has been reported in 14–39% of NVE cases [46,58,59] and in 30–60% of PVE cases [38,58,59]. The data on PVE in TAVI patients are limited, but in a multicenter registry study of 53 TAVI PVE cases, vegetation was the most common imaging finding (77%) and perivalvular abscess/pseudoaneurysm formation was seen in 18% of the patients [44].

The sensitivity of TEE for detection of endocarditis is lower in PVE than in NVE [60], and TEE has been reported to be false negative in 14–20% of PVE cases [18-20].

Treatment

Microbial eradication with antimicrobial drugs and surgical removal of all infected material are the two major components in the treatment of IE. Medical therapy with antimicrobial drugs is used in all cases. In PVE patients, a treatment period of a minimum of six weeks is recommended [17]. In many cases, surgical treatment is also required to eradicate the infection and to replace a dysfunctional valve. Indications for surgery follow the same principles in NVE and PVE. The main indications for surgery are heart failure, uncontrolled infection, and the prevention of embolic events [17]. The decision for surgery should be individualized and discussed in a multidisciplinary team considering both comorbidities and risks associated with surgery and the prospect of recovery without surgery [17].

In PVE patients, uncontrolled infection is in most cases caused by perivalvular extension of the infection, which is associated with poor prognosis and high likelihood of a need for surgery (Fig. 6) [11]. Around 50% of patients with PVE undergo surgical therapy [38,61]. The type of surgery performed is individually tailored and depends on the extension of infection. The most common indication for surgery in PVE patients is perivalvular extension of infection and in this case the use of a homograft is favorable [62]. The infected valve and all necrotic and infected tissue around the valve are removed, and a homograft is implanted. When the infection is limited to the valve leaflets with no perivalvular destruction, a bioprosthesis or a mechanical valve can be used. In Gothenburg, 64% of aortic PVE patients over the last 20 years received a homograft [63].

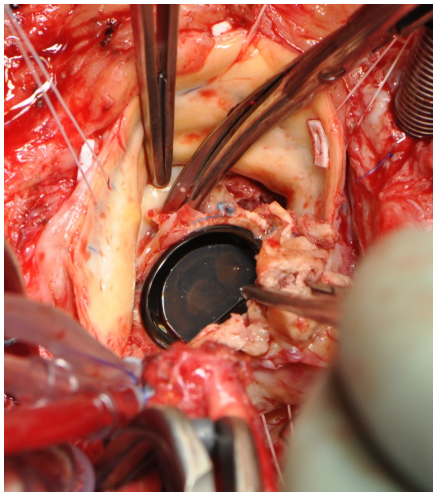

Figure 6. Surgery for PVE in a patient with a mechanical prosthetic valve. The aorta was transected, and the valve was exposed. The prosthetic valve was dehisced in 2/3 of the circumference and was excised only in the area seen to the left in the figure.

Prognosis

PVE is the most severe form of endocarditis with a reported in-hospital mortality of 20–40% [17,38,64]. The corresponding figures for NVE are 15–30% [17]. Heart failure, perivalvular complications, and *S. aureus* infection are factors associated with increased risk of death, and when all three factors are present the risk reaches 79% [65].

Imaging of the heart valves

Imaging of the heart is challenging because the structures are small and they move continuously during the cardiac cycle. This means that both high spatial and temporal resolution are required to visualize the heart and heart valves. In most cases, echocardiography is the first choice when valve disease is suspected. Cardiac computed tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) may provide additional information regarding valve pathology and metabolic activity.

Echocardiography

History

High-frequency ultrasonic systems were developed late in the Second World War by the US Navy to navigate submarines. Shortly after the war, the American physician John Wild had the idea to use ultrasound for detecting changes of texture in living tissues, and the era of medical ultrasound began [66]. One of the first reports of using ultrasound to study heart movements came from the physician Inge Edler and the electrotechnician Hellmuth Hertz in Lund, Sweden, in 1954 [67]. The use of ultrasound for examination of the heart was named echocardiography, and the method has been in widespread clinical use since the 1970s. With the transducer placed on the thoracic cage, the method is called TTE. In the 1980s, TEE was introduced in which the examination is performed with the transducer placed in the esophagus [68]. With this method, the transducer comes closer to the dorsal side of the heart, and TEE is superior to TTE in depicting the heart valves, aorta, and atria (Fig. 7). In the same decade, color flow Doppler imaging was developed as a technique to detect valvular regurgitation [69]. The most recent improvement in echocardiography technique is three-dimensional echocardiography [70], which can provide 3D images of the heart valves.

At Sahlgrenska University Hospital, echocardiography has been in use since the late 1970s, and currently around 10,000 clinical echocardiography examinations are performed annually at the Department of Clinical Physiology.

Technical aspects

The sound waves used in clinical ultrasound have a frequency of 1–20 MHz, which are not audible to the human ear [71]. Pulses of ultrasound waves are sent

into the body tissue from a transducer placed on the chest wall or in the esophagus. Different tissues reflect the sound to a varying degree, and the reflected sound echoes are recorded by the transducer and displayed as an image. The temporal resolution of echocardiography is excellent and goes down to 20 ms, which means that 50 images per second are displayed. Doppler echocardiography uses the Doppler effect to determine whether blood is moving towards or away from the transducer [72]. Both the direction and the speed of the blood flow can be studied, and this method is particularly useful for studying valve function.

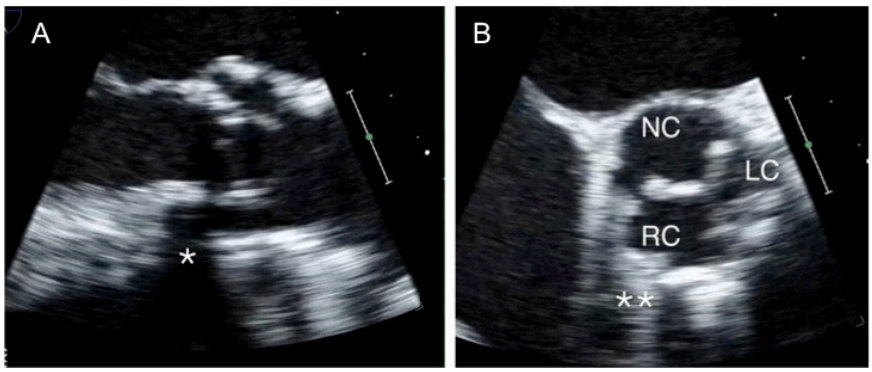

Figure 7. TEE images of a normal biological prosthetic valve. A. Long axis projection in systole. The asterisk marks acoustic shadowing from the prosthetic valve. B. Short axis projection in diastole. The asterisks indicate artifacts adjacent to the right coronary cusp. NC: non-coronary cusp, LC: left coronary cusp, RC: right coronary cusp.

Risks and costs

TTE is a safe and non-invasive imaging method, and ultrasound has no known risks or complications to the patient. When TEE is performed, a probe is introduced into the esophagus, which means a small risk of injury to the esophagus, bronchospasm, or cardiac arrhythmias [73]. The reported complication rate for TEE is 0.18% [73]. A TTE examination currently costs around 3500 SEK at Sahlgrenska University Hospital, and a TEE examination costs around 4200 SEK.

Clinical use

Medical ultrasound is used in imaging of all parts of the body. Major areas of use are abdominal (liver, gall bladder and kidneys), gynecological, vascular, and cardiac imaging. Echocardiography is an easily accessible cardiac imaging method that is performed on most patients where cardiac disease is suspected.

Heart valve imaging with echocardiography

Echocardiography is the first-line imaging method in the workup of patients with valvular heart disease [24]. It depicts both the morphology and the motion of the cardiac valves and can in most cases determine the etiology of valvular heart disease. It is also used for the monitoring and follow-up of patients with known valvular heart disease [24]. TEE is recommended in patients with suspicion of cardiac source of embolism, for evaluation of the aortic and mitral valve, and for prosthetic heart valve evaluation [74]. In patients with suspicion of endocarditis, TEE is recommended in most cases and is mandatory in the presence of a prosthetic heart valve [17].

Cardiac Computed Tomography

History

A CT scanner consists of an x-ray tube that rotates around the patient, and images are taken from different angles and are combined in the computer to produce cross-sectional images of the body. The first generation of CT scanners was introduced in 1972 [75], an invention that earned Godfrey Hounsfield and Allan Cormack the Nobel Prize in Medicine in 1979. The scanner was used for brain imaging only, and the examination was time-consuming because the scanning of one cross-sectional image took about five minutes. The first report of cardiac imaging with CT is from 1981 [76]. The CT scanner used had a rotation time of two seconds, yielding a temporal resolution of one second, and motion-free images could not be acquired.

In the 1980s, the electron-beam CT scanner was introduced, and this scanner was constructed for cardiac imaging where both the detector and the source were stationary. The first electron-beam CT scanners had an improved temporal resolution of 100 ms. In combination with the introduction of electrocardiogram (ECG)-gating of the scan (see below), motion-free images of the heart in diastole could be acquired [77]. However, the spatial resolution remained a problem. In

1989, slip-ring technology was introduced with the first helical CT scanner, an invention that improved the spatial resolution [78]. In helical scanning (also named spiral CT), the patient moves continuously through the scanner while the gantry rotates. The technique was further improved with the introduction of multiple detector rows in the 1990s, known as multidetector CT (MDCT) [79], which allows simultaneous acquisition of multiple slices per gantry rotation. Since the 1990s, this technique has been rapidly evolving with an ever-increasing number of detector rows (currently up to 320) and faster rotation times. In the latest generation of CT scanners, the temporal resolution is as low as 66 ms with a spatial resolution of 0.24 mm. These technical advances, in combination with software development, have made high-resolution and motion-free imaging of the heart possible.

At Sahlgrenska University Hospital, the first 64-slice CT scanner was installed in 2005 and had a temporal resolution of 175 ms and a spatial resolution of 0.625 mm and was suitable for cardiac imaging. This was the first scanner used for cardiac CT studies in this thesis.

Technical aspects

Other names used in the literature for cardiac CT are ECG-gated CT of the heart and MDCT of the heart. The basic principle of cardiac CT is synchronization of data acquisition to the patient's ECG. The key to successful imaging is a slow and regular heart rhythm, and, if possible, a beta-blocker is administered before the examination to lower the heart rate. The examination is performed with intravenous contrast administration to enhance the vessels and cardiac chambers.

There are two basic acquisition principles, *retrospective* and *prospective* ECG-gating. In *retrospective* ECG-gating, CT scanning is performed in a helical mode with continuous data collection during the entire cardiac cycle. Afterwards, the ECG record is used to select data that have been acquired during the same phase of the cardiac cycle, and image stacks can be reconstructed at any cardiac phase. For example, the cardiac cycle can be split into 10 equal phases, which means that 10 image stacks of the heart will be reconstructed. These image stacks can be used to create moving images (cine films) of the heart.

In *prospective* ECG-gating, CT scanning is performed in axial mode (the table is at a fixed position while the gantry rotates) at a pre-defined phase of the cardiac cycle. To acquire motion-free images of the heart, imaging is usually best performed in diastole. Because the duration of diastole is long with slow heart rates and decreases with faster heart rates, a slow heart rate is preferable. The drawback of prospective ECG-gating is that cardiac function cannot be as-

sessed because images are created in a single phase of the cardiac cycle. The advantage is a lower radiation dose.

The technique of prospective ECG-gating has improved, and this method is currently the first choice for imaging of the coronary arteries because of the lower radiation dose. When the heart rhythm is high or variable, retrospective gating should be used. Retrospective gating is also the method of choice for valve imaging because it gives the possibility to study the movement of the valve with cine films.

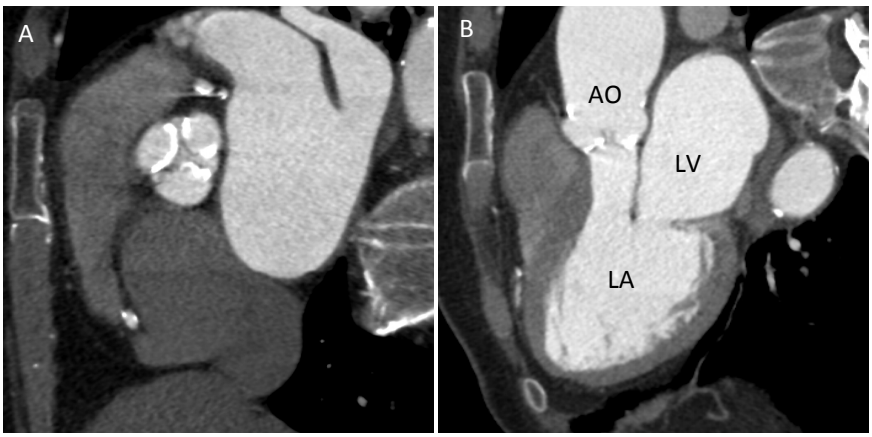

Figure 8. ECG-gated CT of a stenotic aortic valve performed prior to TAVI. The images are used to measure the dimensions of the aortic valve annulus and its relation to the coronary arteries. The information is then used for planning the TAVI procedure and selecting the right size of the valve prosthesis. A. Transaxial image of the aortic valve shows calcified valve leaflets. Cine imaging showed reduced opening area of the valve. B. Three-chamber view of the left ventricle. A post-stenotic dilatation of the ascending aorta is seen. AO: aorta, LV: left ventricle, LA: left atrium.

Risks and costs

Cardiac CT is an x-ray technique, which means that the patient is exposed to ionizing radiation. Radiation doses from cardiac CT are getting lower with new generations of scanners, and the latest scanners can perform a cardiac CT scan with a dose of around 1 millisievert (mSv) under optimal conditions [80]. Retrospective ECG-gating, which is the method used when the cardiac valves are studied, still means higher radiation doses [81]. The mean radiation dose for the

cardiac CT examinations performed in this thesis was around 10 mSv, which is ten times the yearly natural background radiation in Sweden.

Another risk with cardiac CT is the administration of intravenous contrast medium. In patients with impaired renal function, the contrast medium implies a risk for contrast-induced nephropathy and should be used with caution [82]. The contrast medium can also cause allergic reactions including anaphylaxis [83]. An ECG-gated cardiac CT examination currently costs around 5700 SEK at Sahlgrenska University Hospital.

Clinical use

The main use of cardiac CT is imaging of the coronary arteries. The negative predictive value of cardiac CT is very high, which means that the method can be used to rule out coronary artery stenosis [84]. Current European guidelines state that cardiac CT can be used to rule out stable coronary artery disease in patients with intermediate pre-test probability [85]. Other common clinical applications include evaluation of the anatomy of the pulmonary veins before pulmonary vein ablation, assessment of congenital heart disease, and assessment of the pericardium [86].

Heart valve imaging with cardiac CT

Valve imaging with cardiac CT started in the beginning of the 21st century with the description of aortic valve morphology in patients with aortic stenosis [87]. Since then, the method has become a clinical standard for the evaluation of valve morphology and aortic root dimensions prior to TAVI (Fig. 8) [88]. Other clinical applications include imaging of congenital valve disease [89] and valve tumors [90]. In patients with a prosthetic heart valve, cardiac CT has been used to detect thrombosis and pannus formation on the valve leaflets [91] and to depict valve degeneration [92]. In 2009, Feuchtner et al studied valvular abnormalities in patients with IE on cardiac CT and compared the findings with TEE and surgery [93]. The results were promising and suggested that cardiac CT might have a role in the workup of patients with IE. A few case reports have demonstrated that CT might also have a role in diagnosing PVE in patients with a TAVI valve, but no larger studies have been published on this group of patients [94,95].

^{18}F-FDG PET/CT

History

PET/CT is the youngest of the imaging methods discussed in this thesis. The method was developed in the 1990s, and the first commercial PET/CT scanner was introduced in 2001 [96]. At Sahlgrenska University Hospital, the first PET/CT scanner was installed in 2008. To date, the radiopharmaceuticals used are produced in Lund and transported in a taxi to Gothenburg. A cyclotron will be installed at Sahlgrenska University Hospital in 2016, and the production of radiopharmaceuticals for clinical use will start in 2017.

Technical aspects

PET/CT is a combined anatomical and functional imaging method where a CT scanner and a PET scanner are combined in a single gantry. The PET scanner detects gamma rays that are emitted from a positron-emitting radionuclide that is injected intravenously into the patient. The CT scanner provides anatomical information, and when the two separately recorded images are fused an image containing both anatomical and functional information is produced (Fig. 9).

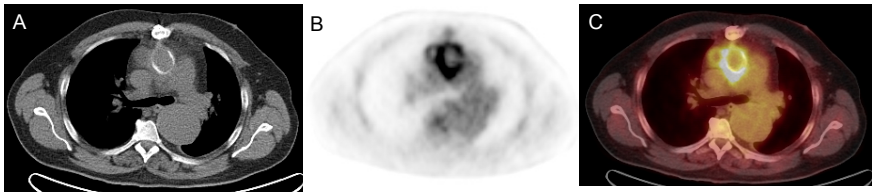

Figure 9. ^{18}F-FDG PET/CT in a patient with an infected composite graft in the ascending aorta. Transaxial images through the mid-thorax at the level of the bifurcation of the pulmonary artery. The images show increased ^{18}F-FDG uptake around the graft indicating infection. A. Low dose CT. B. ^{18}F-FDG PET. C. Fused ^{18}F-FDG PET/CT.

The most common radiopharmaceutical used in PET/CT imaging is the glucose analogue ^{18}F-FDG. The radionuclide ^{18}F is synthetized in a cyclotron and then incorporated in the glucose molecule yielding ^{18}F-FDG. When injected into the body, this radiopharmaceutical distributes according to the tissue cell uptake of glucose. FDG cannot be further metabolized in the cells. After the injection, the patient rests for an hour while the glucose analogue distributes throughout the

body. Muscle activity should be minimized during this period because active muscles metabolize glucose, which can cause artifacts. After 60 minutes of rest, the scanning is performed, which takes about 15 minutes.

Risks and costs

^{18}F-FDG PET/CT, like cardiac CT, means that the patient is exposed to ionizing radiation. When ^{18}F-FDG PET/CT is performed, radiation comes both from the injected radioactive tracer that is distributed throughout the body and from the low-dose CT scan. The current total radiation dose for a PET/CT scan at Sahlgrenska University Hospital is around 8 mSv, including 5 mSv from the radioactive tracer [for a 70 kg person (4 MBq/kg)] and 3 mSv from the low-dose CT scan. An ^{18}F-FDG PET/CT examination costs around 18,000 SEK.

Clinical use

^{18}F-FDG is taken up by cells that are using glucose for their metabolism, which yields a high activity in tissues with high glucose uptake such as the brain, heart, and liver. Most malignant tumors also have a high glucose uptake, and the current main clinical application for ^{18}F-FDG PET/CT is oncological imaging. ^{18}F-FDG PET/CT is used in the diagnosis, staging, and evaluation of treatment response of many cancer forms such as lung cancer, head and neck cancer, lymphoma, and malignant melanoma and in the workup of cancer of unknown origin [97-100].

^{18}F-FDG PET/CT in the imaging of infection

Cells involved in the inflammatory process have a high glucose uptake, and there is an increasing interest in using ^{18}F-FDG PET/CT to identify infectious processes [101,102]. ^{18}F-FDG PET/CT has been used in the diagnosis of osteomyelitis [103] and spondylodiscitis [104] and in cases of fever with unknown origin [105]. Initially, doubts were raised about the ability to detect infectious processes close to the heart due to the physiological FDG uptake in the cardiac muscle [106]. This can be overcome with a low carbohydrate and high fat diet – which elevates the level of free fatty acids in the blood and introduces fat-dominated metabolism – followed by an 18-hour fasting period prior to the examination. The procedure reduces the physiological accumulation of ^{18}F-FDG in the myocardium [107].

The first reports of ^{18}F-FDG PET/CT imaging in endocarditis considered detection of metastatic infection/septic emboli [106]. The first study on ^{18}F-FDG PET/CT in the diagnosis of endocarditis came in 2013 [108]. This study showed a sensitivity of 39% and a specificity of 93% for the diagnosis of endocarditis [108]. All but two valves studied were native. The first study on prosthetic valves came the same year and found a sensitivity of 73% and a specificity of 80% for the diagnosis of PVE [109]. The authors suggested that ^{18}F-FDG PET/CT could be added to the diagnostic criteria for PVE, thus reducing the number of "possible" PVE cases [109].

Aims

General aim

The aim of this thesis was to investigate the value of ECG-gated CT and ^{18}F-FDG PET/CT in the diagnostic workup of aortic PVE.

Specific aims

I. To investigate the agreement in findings between ECG- gated CT and TEE in patients with aortic PVE.

II. To identify a clinically useful cutoff value for aortic wall thickness to detect PVE.

III. To compare ^{18}F-FDG uptake around prosthetic aortic valves in patients with and without PVE and to determine the diagnostic performance of ^{18}F-FDG PET/CT in the diagnosis of PVE.

IV. To investigate the value of ECG-gated CT in the surgical decision-making and preoperative evaluation in patients with aortic PVE.

Patients and Methods

Paper I and paper IV present results from a prospective study where the Regional Ethics Review Board gave ethical approval and informed consent was obtained from all patients.
Paper II and paper III are retrospective studies where the Regional Ethics Review Board waived the need for informed consent.

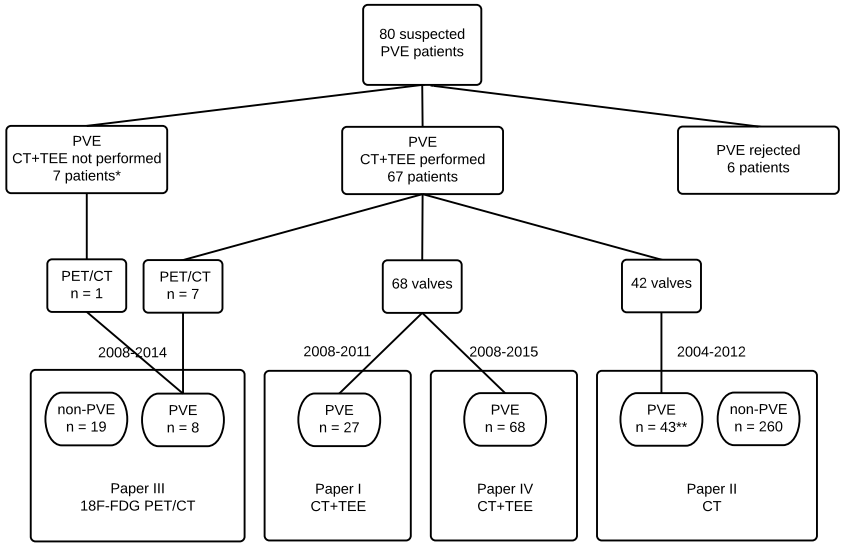

Figure 10. Flowchart of included patients in all four papers. *CT not performed (n = 4), TEE not performed (n = 1), neither CT nor TEE performed (n = 1), case missed in study inclusion (n = 1); **one CT examination was performed before 2008.

Patients

Recruitment of PVE patients for all four papers is shown in Fig. 10.

Paper I

Twenty-seven consecutive patients with PVE underwent ECG-gated CT and TEE, and the results were compared. Imaging was compared with surgical findings.

Paper II

CT studies performed on a CT scanner with at least 16 slices on patients with a prosthetic aortic valve were retrospectively analyzed. The aortic wall thickness in patients with definite PVE (n = 43) was compared to the aortic wall thickness in patients without PVE (n = 260).

Paper III

^{18}F-FDG-uptake on ^{18}F-FDG PET/CT around prosthetic aortic valves in patients with PVE (n = 8) and without PVE (n = 19) was compared. ^{18}F-FDG PET/CT examinations in the PVE group were performed between 2013 and 2014 in clinical practice when results from routine clinical workup were inconclusive regarding the diagnosis or the extension of the infection. The controls had undergone an ^{18}F-FDG PET/CT examination between 2008 and 2014, and the indication for the examination was suspicion of malignancy or staging/treatment control of malignancy.

Paper IV

Sixty-eight prosthetic valves in 67 patients with aortic PVE were prospectively evaluated with ECG-gated CT and TEE. Indication for surgery based on imaging findings from ECG-gated CT and TEE was evaluated. Imaging findings considered as indications for surgery were 1) abscess/pseudoaneurysm formation, 2) prosthetic valve dehiscence, 3) valve destruction with valvular regurgitation, and 4) large vegetations (>1.5 cm). The coronary arteries were evaluated with ECG-gated CT. Clinical data including surgical reports and mortality data, were collected.

Imaging protocols and analysis

ECG-gated CT protocol (papers I and IV)

The protocol for ECG-gated CT in the prospective study has been described in detail in paper I. The examination started with a scan of the thorax without contrast medium. This scan was used to plan the contrast-enhanced ECG-gated CT scan but also to identify surgical material in the aortic root that could be mistaken for contrast (Fig. 11). The contrast-enhanced ECG-gated scan was performed with a retrospective technique to enable cine imaging of the valve.

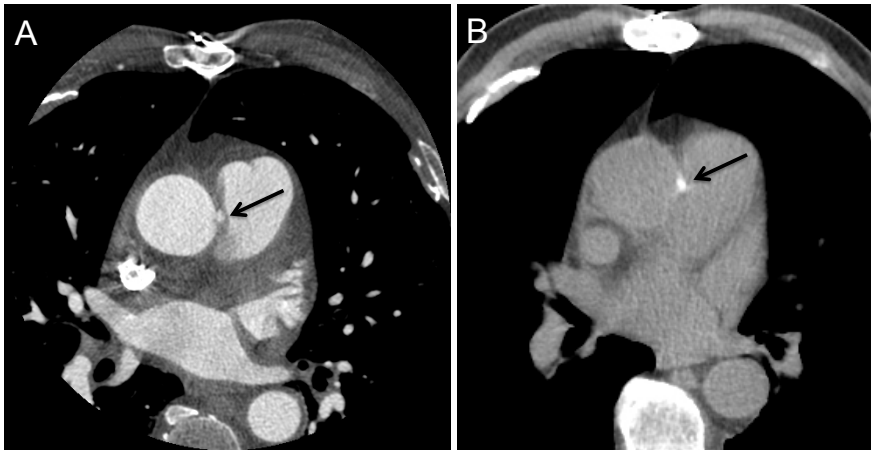

Figure 11. A. Contrast-enhanced ECG-gated CT scan shows a rounded structure (arrow) between the aorta and the pulmonary artery with attenuation similar to the contrast-enhanced blood. A small pseudoaneurysm may be suspected. B. The CT scan performed before contrast administration shows that the structure represents surgical material (arrow).

^{18}F-FDG PET/CT protocol (paper III)

The preparation for the PET/CT examination was different in the group with suspected PVE compared to the control group. Patients in the control group followed the standard preparation and fasted for 6 hours prior to PET/CT. In patients with suspected PVE, reduction of the physiological uptake of ^{18}F-FDG in the myocardium is desirable. To achieve this, the patients were requested to have a meal rich in fat and low in carbohydrates and then to fast for at least 18 hours

prior to the examination [107]. The PET/CT scan was performed when the patient had rested for 60 minutes after ^{18}F-FDG-injection in both groups. In patients with suspected PVE, only the thorax was scanned, and in the control group the scan area varied depending on the indication for the examination.

Image analysis – paper I and IV

In paper I and IV, image analyses of the ECG-gated CT and TEE examinations were performed by physicians blinded to the results of the other examination but with knowledge of the clinical history of the patient. The findings studied are summarized in Table 2, and CT findings are exemplified in Fig. 12. Imaging findings suggesting endocarditis were based on guidelines [11].

Table 2: Imaging findings indicating PVE

Finding	Imaging characteristics
Vegetation	Oscillating or non-oscillating mass attached to the valve
Abscess	Low-echogenic/attenuating perivalvular cavity that does not communicate with the aorta or the left ventricle
Pseudoaneurysm	Perivalvular cavity communicating with the aorta or left ventricle
Valve dehiscence	New perivalvular regurgitation with or without a rocking motion of the prosthesis
Increased aortic wall thickness	Aortic wall thickness of >5 mm measured perpendicular to the wall where the aorta is apposed to the left atrium

Image analysis – paper II

The wall thickness of the aortic root was measured in a standardized procedure in the dorsal aspect of the aortic root where the aorta is apposed to the left atrium (Fig. 12B). To assess inter-observer variability, a second radiologist independently analyzed 40 studies. To assess intra-observer variability, 40 studies were re-analyzed by the first radiologist 6 months after the first evaluation.

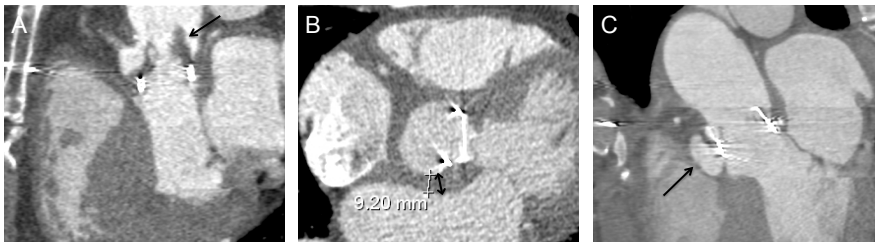

Figure 12. ECG-gated CT images with findings indicating PVE. A: Vegetation (arrow) on a biological prosthesis. B: Increased aortic wall thickness measured between the aorta and the left atrium perpendicular to the wall (arrow). C: Pseudoaneurysm (arrow) communicating with the left ventricular outflow tract.

Image analysis – paper III (^{18}F-FDG PET/CT)

Before analysis, all examinations were anonymized and cropped to include only the thorax. Two nuclear medicine physicians independently performed both visual analysis and semi-quantitative analysis. On visual analysis, a positive result was defined as focal areas of increased uptake of ^{18}F-FDG in the prosthetic valve area, and the uptake was confirmed on non-attenuation-corrected images. Semi-quantitative analysis was performed by measuring the maximal standardized uptake value (SUV_{max}) in the valve region. To adjust for background uptake, the valve SUV_{max} was divided by SUV_{max} in the descending aorta to give SUV_{ratio}.

Statistical analysis

Kappa statistics (paper I)

In the prospective study presented in paper I and IV, only patients with high suspicion of PVE were studied. Because the majority of the patients received the final diagnosis of PVE and the diagnosis was based partly on findings from the study examinations, we did not consider calculation of sensitivity and specificity to be meaningful. Instead, our choice in paper I was to present the results in crosstabs and to calculate the Cohen's kappa as a measurement of agreement between CT and TEE. With this statistical approach, neither of the methods is considered the gold standard, and the method instead describes the strength of agreement between the two methods. A kappa value of 0.41–0.60 is considered moderate agreement, 0.61–0.80 good agreement, and 0.81–1.0 very good agreement. The drawback of this method is that it does not describe the additive value of the new method (CT) compared to the old method (TEE).

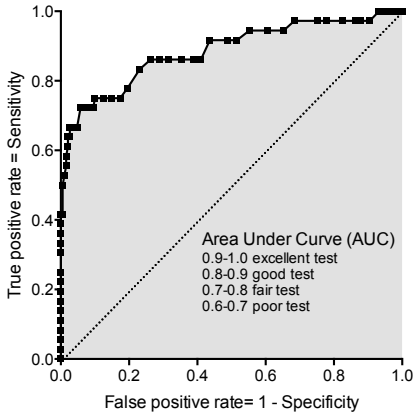

Figure 13. Example of a ROC curve. Each point on the curve represents a cutoff value. The area under the ROC curve quantifies the ability of the test to discriminate between individuals with and without disease. Increasing the cutoff value means moving to the left on the ROC curve, which increases specificity at the cost of lower sensitivity.

ROC analysis (paper II and III)

In paper II, the aortic wall thickness in PVE patients and controls was compared. In paper III, SUV_{max} and SUV_{ratio} in PVE patients and controls were compared. The Mann–Whitney U-test was used to compare groups. However, a significant difference between the two groups does not necessarily mean that the diagnostic test is useful. To determine the diagnostic performance for detection of PVE, receiver operating characteristic (ROC) analysis was performed [110]. A ROC curve is produced by plotting the true positive rate (sensitivity) against the false positive rate (1 – specificity) for all cutoff values (Fig. 13). The area under the curve is a measure of how well the test can distinguish between the two groups (PVE/non-PVE), where an area of 1 represents a perfect test. The curve can also be used to select the optimal cutoff value for the diagnostic test. An optimal cut-off value should be situated near the upper left corner of the ROC curve.

Likelihood ratios (paper II and III)

The ROC analysis is used to select a cutoff value with the desired balance between sensitivity and specificity. Once the cutoff value has been selected, likelihood ratios can be calculated. The likelihood ratios describe how the probability of having disease changes if the test is positive or negative [111]. The positive and negative likelihood ratios (LR(+) and LR(–)) are calculated as: LR(+) = sensitivity / (1 – specificity) and LR(–) = (1 – sensitivity)/specificity. A positive likelihood ratio >10 or a negative likelihood ratio <0.1 corresponds to a large increase or decrease in the likelihood of disease, respectively (this is a very informative test). The post-test odds for a patient to have the disease can be calculated by multiplying the pre-test odds by the likelihood ratio.

Results

Paper I

Twenty-seven consecutive patients with aortic PVE were investigated with ECG-gated CT and TEE. All 27 patients had definite PVE according to the modified Duke criteria [55]. TEE suggested the presence of PVE in all 27 patients, and ECG-gated CT suggested the presence of PVE in 25 of these patients. A comparison between the two methods with kappa statistics is shown in Fig. 14.

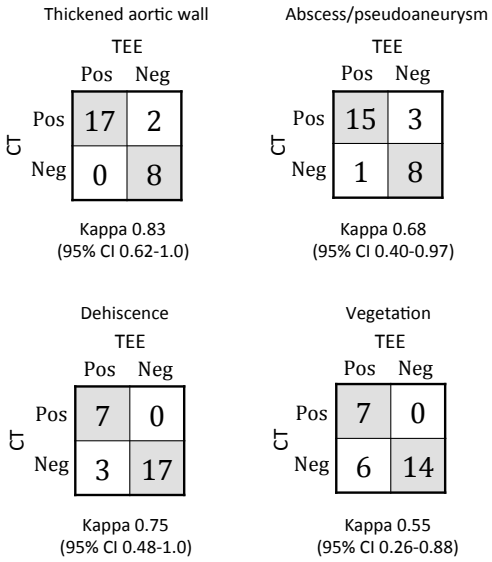

Figure 14. The distribution of positive and negative findings on CT and TEE. The quantification of agreement was performed using kappa statistics.

Sixteen out of 27 patients underwent surgery, and the strength of agreement was good between surgery and ECG-gated CT (kappa = 0.66) and TEE (kappa = 0.79). When the findings from ECG-gated CT and TEE were combined, the strength of agreement with surgery was very good (kappa = 0.88) (Fig. 15).

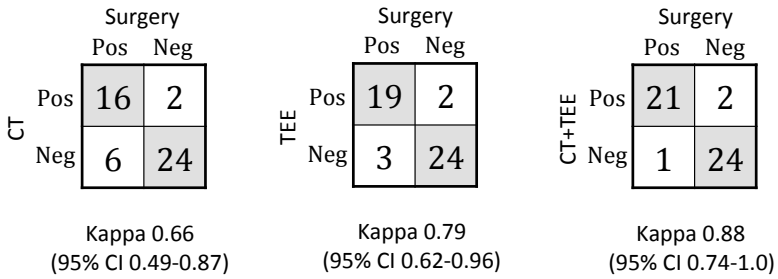

Figure 15. Crosstabs show the distribution of positive and negative findings for ECG-gated CT (left), TEE (middle) and the combination of TEE and ECG-gated CT (right) versus surgery. Positive findings are vegetation, abscess/pseudoaneurysm and dehiscence. The quantification of agreement was performed using kappa statistics.

Paper II

The study included 260 CT studies in patients (n = 185) without PVE and 43 CT studies in patients (n = 43) with definite PVE. In non-PVE patients, the wall thickness was increased in the early postoperative period with large dispersion (Fig. 16). After three months, the wall thickness had decreased and stabilized, and the 95th percentile was at 5 mm.

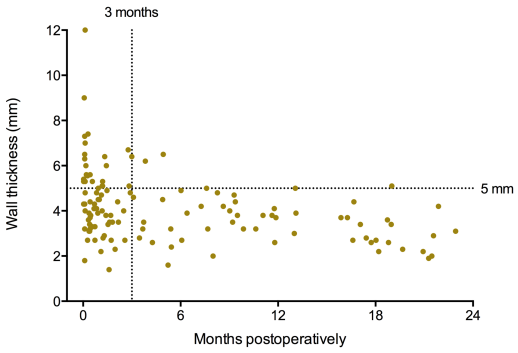

Figure 16. Aortic wall thickness in non-PVE patients for the first two years postoperatively. The wall thickness is increased in the early postoperative period.

The aortic wall thickness in PVE patients (<3 months = 6.6 ± 2.4 mm, >3 months = 6.9 ± 3.6 mm) was significantly increased compared to non-PVE patients (<3 months = 4.5 ± 1.7 mm, >3 months = 3.2 ± 1.0 mm) both when compared for the first three months postoperatively and beyond three months postoperatively ($p = 0.012$ and $p < 0.001$, respectively).
The ROC analysis of wall thickness for the diagnosis of PVE beyond three months postoperatively showed an area under the curve of 0.89 (95% CI 0.81–0.96) (Fig. 17). With a cutoff value of 5 mm, the sensitivity was 67%, the specificity was 95%, the positive likelihood ratio was 14.1, and the negative likelihood ratio was 0.35.

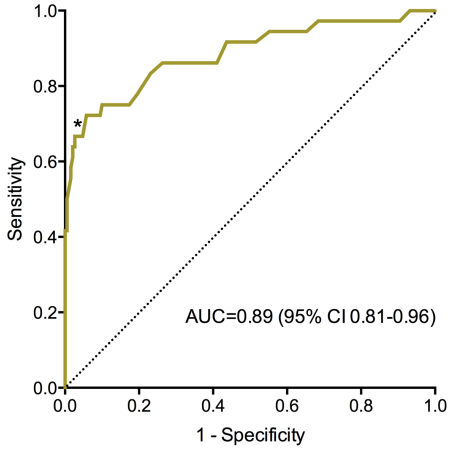

Figure 17. ROC curve of the performance of aortic wall thickness in the diagnosis of PVE. The asterisk marks the coordinate for a 5 mm cutoff.

Paper III

Eight ^{18}F-FDG PET/CT examinations in patients with suspected PVE were compared to 19 ^{18}F-FDG PET/CT examinations in control patients without PVE. On visual analysis, the sensitivity was 75%, the specificity was 84 %, the positive likelihood ratio was 4.8 and the negative likelihood ratio was 0.3 for the detection of PVE. Prosthetic valve SUV_{max} was significantly higher in PVE patients [5.8 (IQR 3.5–6.5)] than in non-PVE patients [3.2 (IQR 2.8–3.8)] ($p < 0.001$) (Fig. 18A). The prosthetic valve to background SUV_{ratio} was also significantly higher in PVE patients [2.4 (IQR 1.7–3.0)] compared to non-PVE patients [1.5 (IQR 1.3–1.6)] ($p < 0.001$) (Fig. 18B).

ROC analysis of prosthetic valve SUV_{max} and SUV_{ratio} for the diagnosis of PVE yielded an area under the curve of 0.90 (95% CI 0.77–1.0) and 0.90 (95 % CI 0.74–1.0), respectively (Fig. 19).

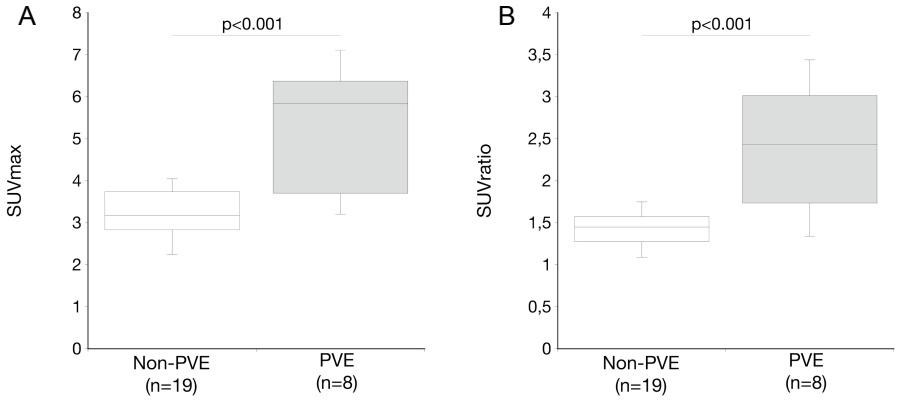

Figure 18. Boxplot of SUV_{max} (A) and SUV_{ratio} (B) in non-PVE and PVE cases. Both SUV_{max} and SUV_{ratio} were significantly higher in PVE cases.

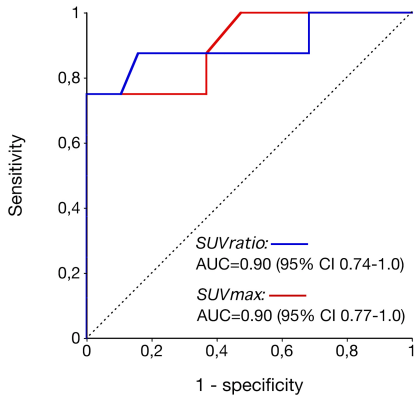

Figure 19. ROC curves for the performance of SUV_{max} and SUV_{ratio} in the diagnosis of PVE.

Paper IV

Sixty-eight PVE cases that had undergone both ECG-gated CT and TEE were included in the study. In total, 58 out of 68 patients had indications for surgery. The numbers of cases with indications for surgery based on CT and TEE findings are shown in Fig. 20. In eight cases (14%), there was indication for surgery based on CT but not on TEE findings, and in all of these cases CT detected pseudoaneurysms that were not seen with TEE. On the other hand, there were 11 cases (19%) where there was indication for surgery based on TEE but not on CT findings (large vegetation n = 1; valve destruction n = 1, valve dehiscence n = 4; non-drained abscess n = 5).

Of 36 patients who underwent surgery, 32 had indications for preoperative coronary angiography according to guidelines [33]. In 31 out of these 32 patients, ECG-gated CT coronary angiography was diagnostic. In one patient, ECG-gated CT coronary angiography was inconclusive, and invasive coronary angiography was performed.

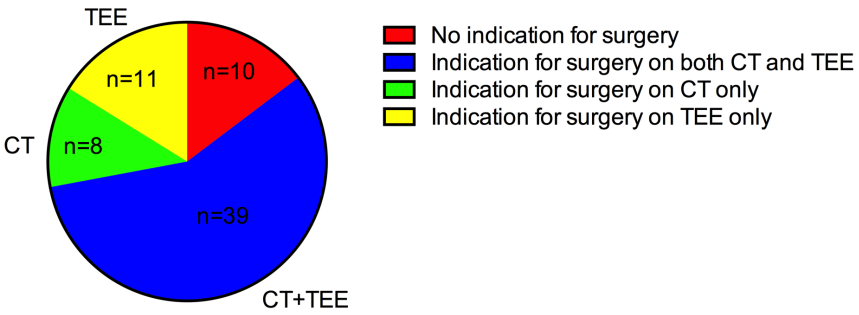

Figure 20. Indication for surgery based on imaging findings in 68 PVE cases.

Discussion

PVE is a disease with high mortality and it is important that the diagnosis is made as soon as possible because initiation of therapy (antibiotics and in many cases surgery) is crucial for the prognosis [11]. The diagnosis of PVE is based on the modified Duke criteria, where positive blood cultures and imaging findings are the two major criteria [55]. Imaging is routinely performed with TTE and TEE. TEE is the recommended imaging method in the presence of a prosthetic valve and it has higher sensitivity than TTE [11]. However, both methods have diagnostic shortcomings. TTE has been reported to be positive in only 15–36% of PVE patients and TEE in 80–86% [18-20]. These diagnostic difficulties suggest the need for additional imaging modalities to improve the diagnostic workup of PVE patients. By adding information from new imaging modalities, more patients with PVE might be detected and the diagnosis can be made earlier and with a higher degree of reliability. Early diagnosis may improve the prognosis [56].

Imaging in PVE patients is also used to determine the extension of infection, which influences the decision of therapy (conservative/surgical) [17]. The identification of patients in need of surgery is important because surgery improves the prognosis [112]. The timing of surgery can also influence the outcome, and early surgery is preferred in patients with complicated endocarditis [113]. Local uncontrolled infection, defined as extension of infection into the perivalvular tissue with perivalvular abscess cavities, pseudoaneurysms, and/or prosthetic valve dehiscence, is an indication for surgery [17]. In a study comparing TEE findings with surgery, abscess formation was missed by TEE in 36% of PVE cases, and prosthetic valve dehiscence was missed in 29% [114]. Hence, there is a need for other imaging modalities also to determine the extension of infection, which may influence surgical decision-making.

ECG-gated CT in the diagnosis of PVE

The results from paper I indicate that ECG-gated CT is comparable to TEE in the diagnostic performance of patients with PVE. ECG-gated CT detected signs of PVE in 25 out of 27 patients, whereas TEE was positive in all 27 patients. This result is consistent with that in a study by Feuchtner et al where CT was

positive in 28 out of 29 endocarditis patients with positive TEE (a majority of the valves were native) [93]. However, our results suggested that the profiles of the two imaging methods might be different and complementary:
1) TEE detected more vegetations than CT. Small vegetations have also been reported to be missed by CT in studies by Feuchtner and Gahide et al, where a majority of the valves were native [93,115]. This fact is likely to be related to the higher temporal resolution of TEE compared to CT. Because the valves move rapidly when opening and closing, TEE has a greater ability to depict small moving vegetations that might be blurred on CT images with lower temporal resolution.
2) TEE was superior to CT in detecting signs of valve dehiscence. Previous reports on CT and valve dehiscence are scarce. The study by Feuchtner et al had only one case of valve dehiscence, and this was detected by both CT and TEE [93]. In a study by Pizzi et al, which only included PVE patients, CT detected four out of eight cases of valve dehiscence [116]. TEE has the advantage over CT in that Doppler imaging can be used to detect perivalvular blood flow as a sign of dehiscence [117]. In our experience, CT can show a rocking motion of the prosthesis during the cardiac cycle in cases of a large dehiscence, but it has difficulties in detecting small perivalvular leaks.
3) CT detected more pseudoaneurysms than TEE. This finding is in accordance with the study by Feuchtner et al where most valves were native and with a study by Habets et al on prosthetic heart valves [93,118]. CT provides good image quality around the entire circumference of the prosthetic valve. With TEE, however, echo shadowing from the valve prosthesis is a problem, and certain parts of the circumference might be obscured. Because the right coronary cusp is positioned opposite to the TEE transducer, this region is most commonly affected by echo shadowing [119]. This fact is supported by findings in paper IV where six of 11 pseudoaneurysms detected with CT but not TEE were positioned adjacent to the right coronary cusp.

In addition to the imaging signs described above that are all included in the diagnostic criteria of PVE, we studied the thickness of the aortic root wall. Increased aortic root wall thickness on TEE as a sign of PVE has been described in some previous publications [114,120] and is used in our clinical practice with TEE. However, no studies have been published that evaluate the accuracy of this sign. We and others have hypothesized that abscess formation, which is a dynamic process, starts with inflammation that leads to increased wall thickness in the aortic root [17]. We included this sign of PVE in paper I and found that increased wall thickness was a common finding in PVE patients both on CT and TEE. This led to the hypothesis that increased aortic wall thickness can be used as a sign of PVE on CT, and this hypothesis was tested in paper II.

In paper II, we showed that an aortic root wall thickness >5 mm is a highly specific sign of PVE (specificity 95%). However, the sensitivity of the sign was lower (67%). A possible reason for this is that increased wall thickness represents invasion of bacteria into the aortic wall with inflammation in the tissue, but this pathological process is not present in all PVE patients. A subgroup of patients has an infection limited to the valve leaflets with valve vegetations and/or destruction as the only imaging manifestations of infection [17], and this group of patients might have a normal wall thickness in the aortic root.

Interestingly, six patients in paper IV had non-drained abscess cavities that were detected with TEE but not with CT. In all six cases, the wall thickness was increased in the same region on CT. This finding suggests that focal increased wall thickness on CT might represent a non-drained abscess cavity. This is in accordance with findings from Habets et al, who reported that in three cases of abscesses detected with TEE but not with CT, nonspecific aortic wall thickening was present on CT when images were retrospectively evaluated [118]. However, increased wall thickness can be seen on TEE in the absence of visible abscess cavities, and it is likely that increased wall thickness can also be an early sign of extension of infection into the perivalvular tissue that precedes the formation of an abscess cavity. In paper III, we describe a case with focal increased wall thickness of the aortic wall on CT and vegetations on TEE as the only imaging findings. ^{18}F-FDG PET/CT showed increased ^{18}F-FDG uptake in the region of increased wall thickness, and surgery confirmed abscess formation in this region.

In summary, increased wall thickness of the aortic root on CT is a specific sign of PVE and might be the first sign of extension of infection into the aortic wall. Adding increased wall thickness as a diagnostic criterion of PVE might improve the performance of the modified Duke criteria.

^{18}F-FDG PET/CT in the diagnosis of PVE

The concept of using ^{18}F-FDG PET/CT in the diagnosis of PVE is appealing because it has the potential to depict the actual inflammatory activity caused by the infection. This is in contrast to ECG-gated CT and TEE, both of which are purely morphological methods. The first report on PET and endocarditis concerned native valves, and the results were discouraging with a reported sensitivity of 39% and a specificity of 93% for the diagnosis of endocarditis [108]. A possible reason for the low sensitivity is that vegetation is the most common imaging finding in NVE [46]. Because of the fast movement of the valve leaflets and adherent vegetations, they can be difficult to depict with ^{18}F-FDG PET/CT, which has low temporal resolution and is routinely performed without ECG-

gating. In paper III, we studied the diagnostic performance of ^{18}F-FDG PET/CT in the diagnosis of PVE and found a higher sensitivity (78%). Our result is similar to four other studies published on ^{18}F-FDG PET/CT and PVE showing a sensitivity of 73%, 93%, 89%, and 87%, respectively [109,116,121,122]. The higher sensitivity in PVE compared to NVE is likely to be due to the higher presence of perivalvular extension of infection in PVE. The perivalvular tissue is not moving to the same extent as the valve, which means that high temporal resolution is less important.

The main contribution of paper III is that we, in contrast to previous studies, included a control group containing patients without suspicion of PVE. Previous studies were performed on patients with a high suspicion of PVE without negative controls, and the risk of false positive results was a concern [123]. We showed that ^{18}F-FDG uptake around non-infected aortic prosthetic valves was low. The specificity of ^{18}F-FDG PET/CT was 84% with visual analysis, which is similar to the specificity presented in previous studies (80%, 71%, and 92%) [109,116,121]. Our results also showed that semi-quantitative analysis of ^{18}F-FDG-uptake by measuring the SUV_{ratio} had good accuracy for the diagnosis of PVE (ROC analysis gave an area under the curve of 0.90). It is likely that the specificity of the method can be further improved by combining visual analysis and measurement of the SUV_{ratio}. For evaluation of cutoff values, further studies are needed.

ECG-gated CT and ^{18}F-FDG PET/CT in surgical decision-making

In paper IV, we studied the role of ECG-gated CT in surgical decision-making. Surgical decision-making in PVE patients is a complicated process that is influenced by both the extension and activity of the infection, the response to treatment with antibiotics, complications, the clinical status of the patient, and comorbidities [124]. Current guidelines emphasize that decision-making should be managed by a dedicated endocarditis team [17]. Imaging in the evaluation for surgery is routinely performed with TEE, and the following imaging findings are considered indications for surgery: abscess/pseudoaneurysm formation, valve dehiscence, large vegetations, and valve leaflet destruction [11]. In paper IV, we found that out of 58 PVE cases with indication for surgery based on imaging findings, 14% had indication for surgery based on CT but not TEE findings and 19% had indication for surgery based on TEE but not CT findings. The strength of CT was that it was superior to TEE in detecting perivalvular pseudoaneurysms as a sign of perivalvular extension of infection. This is in accordance with

previously published data from Habets et al who studied 28 PVE patients and found that CT resulted in a major diagnostic change in 21% of patients, mainly driven by novel detection of pseudoaneurysms by CT [118]. Our results emphasize the need for both ECG-gated CT and TEE in the preoperative evaluation because both examinations add important information.

Another advantage of ECG-gated CT in the preoperative evaluation is that it includes evaluation of the coronary arteries. Preoperative coronary angiography is recommended according to guidelines in men >40 years, post-menopausal women, and patients with at least one cardiovascular risk factor or a history of coronary artery disease [33]. In PVE patients, it is considered safe to perform coronary angiography unless there are large vegetations that might dislodge from the valve during the procedure [125]. However, coronary angiography is an invasive procedure with a reported overall complication rate of 2–4% and a mortality rate of 0.1% [126,127]. Bettencourt et al reported that invasive coronary angiography could be replaced by ECG-gated CT in 73% of patients planned for valve surgery, and Catalan et al found that ECG-gated CT was diagnostic in 81% of patients scheduled to undergo non-coronary cardiac surgery [128,129]. In paper IV, ECG-gated CT could replace invasive coronary angiography in 31 out of 32 patients (97%). A possible reason for the higher proportion of diagnostic examinations in our study is that only the nine most proximal coronary artery segments were included in the analysis, which is in contrast to the other two studies that included all 17 coronary artery segments. The reason for including only the proximal segments was that these are the segments that can be considered for bypass grafting during the surgical procedure.

Another advantage of ECG-gated CT in the preoperative evaluation is that it provides information regarding anatomy, including the course of bypass grafts in relation to the sternum and anatomical anomalies of the native coronary arteries. This information helps the surgeon to minimize the risk during surgery, and preventive surgical strategies can be adopted in high-risk patients [130]. Performing CT as part of the preoperative evaluation has been shown to reduce the risks associated with re-do cardiac surgery [131].

The usefulness of ^{18}F-FDG PET/CT in surgical decision-making has to our knowledge not been studied. Paper III focused on the diagnostic ability of ^{18}F-FDG PET/CT in the diagnosis of PVE but we did not study how ^{18}F-FDG PET/CT influenced surgical decision-making. Interestingly, in this retrospective study, 5 out of 11 ^{18}F-FDG PET/CT studies on PVE patients were performed when results from routine clinical workup were inconclusive regarding the extension of the infection. Because ^{18}F-FDG-uptake around the prosthetic valve represents inflammatory activity, it is possible that high ^{18}F-FDG uptake represents a more active infection, which could support the need for surgery. Further

studies are needed to evaluate if ^{18}F-FDG uptake in the perivalvular area can be used as an indication for surgery.

Diagnosis of PVE in the early postoperative period

The diagnosis of PVE is particularly challenging in the early postoperative period when the clinical presentation might be atypical, and fever and inflammatory syndrome can also be seen in the absence of infection [47]. TEE findings can be difficult to interpret, and the diagnosis of an abscess is more difficult in this period [117]. Edema and inflammation in the perivalvular area is a part of the healing process after surgery and cannot easily be distinguished from infection [117,132]. In paper II, increased wall thickness of the aortic root was a common finding during the first months postoperatively in non-PVE patients, and we suggest that this sign should be used only beyond three months postoperatively.

^{18}F-FDG PET/CT can also be false positive in the early postoperative period. In a study by Rouzet et al, false positive ^{18}F-FDG PET/CT was seen in six out of 39 patients with suspected PVE, and all six patients had been investigated during the first two months postoperatively [121]. In paper III, only one ^{18}F-FDG PET/CT examination in a non-PVE patient was performed in the early postoperative period, and this was correctly interpreted as negative. The time limit after which ^{18}F-FDG PET/CT can be considered safe to use in the diagnosis of PVE has not yet been studied. It is possible that a higher cutoff value for SUV_{ratio} can be used to compensate for the expected higher inflammatory activity in the early postoperative period. In the study by Rouzet et al, leukocyte single-photon emission computed tomography (SPECT) had higher specificity than ^{18}F-FDG PET/CT for the diagnosis of PVE in the early postoperative period, and this method might be of value in unclear cases [121].

Limitations

The major limitation of paper I and IV is that surgery, which could be considered the gold standard for confirmation of imaging findings, was not performed in all patients. The major limitation of paper II and III is the retrospective study design with PVE groups and control groups that were different in some respects. In paper II, the control group consisted of CT examinations performed on different scanners, and the majority of the examinations were not ECG-gated. In paper III, the control group consisted of ^{18}F-FDG PET/CT examinations performed on cancer patients with a different clinical background from the PVE patients. Another limitation is the small study populations in papers I and III.

General discussion on imaging of PVE patients

Both ECG-gated CT and ^{18}F-FDG PET/CT are imaging methods that add information to TEE in the workup of patients with suspected PVE and might be valuable complements. Besides the diagnostic value of an imaging method, availability, costs, and risks are factors to consider. Echocardiography is widely available, safe, and performed at low cost. The availability of ECG-gated CT is increasing, and it is likely to be available in most hospitals in Sweden within a few years. In addition, the radiation dose of ECG-gated CT is getting lower with modern equipment. The risk of contrast-induced nephropathy is a concern, but with the use of a low-kilovoltage protocol, the contrast dose can be minimized in patients with impaired renal function. Nevertheless, potential damage of the kidneys is a possibility. ^{18}F-FDG PET/CT is the most expensive examination of the three and also has a limited availability. The method is time consuming and requires a special diet.

The workup of patients with suspected PVE should include both TEE and ECG-gated CT. ECG-gated CT is less operator-dependent than TEE and can be performed at the local hospital with the images being sent to a tertiary center for evaluation. ECG-gated CT can facilitate early diagnosis when TEE results are equivocal, and it provides information that can influence surgical decision-making. ^{18}F-FDG PET/CT is a valuable tool when the diagnosis remains unclear after TEE and ECG-gated CT have been performed. The method might also add information regarding extension and activity of the infection. However, the value of ^{18}F-FDG PET/CT in surgical decision-making has not yet been studied. In the early postoperative period, imaging findings must be interpreted with caution, and repeated TEE/ECG-gated CT examinations might be valuable for studying the evolvement of findings over time.

In Gothenburg, information from ECG-gated CT performed in the prospective study during 2008–2015 (paper I and IV) was used when the endocarditis team evaluated the patients, and the method is now part of the routine clinical workup of PVE patients. If CT detects signs of perivalvular extension of infection and TEE is negative or inconclusive, the patient is considered to have a local uncontrolled infection and is evaluated for surgery. From 2013 onwards, ^{18}F-FDG PET/CT has been used when results from TEE and ECG-gated CT are inconclusive regarding the diagnosis or extension of infection (paper III). The European Society of Cardiology (ESC) confirms that this diagnostic strategy is appropriate in the updated guidelines for the management of IE published in 2015 [17]. In the ESC guidelines, a modification of the diagnostic criteria is suggested where two imaging findings have been added as major criteria in the diagnosis of endocarditis:

1. Based in part on results from paper I, where ECG-gated CT was shown to have comparable diagnostic performance to TEE in the diagnosis of PVE, one new major criterion is the detection of paravalvular lesions by cardiac CT.
2. In patients with a prosthetic valve, abnormal activity around the site of implantation detected by ^{18}F-FDG PET/CT (if the prosthesis has been present for >3 months) or radiolabelled leukocyte SPECT/CT is now considered a major criterion [17].
A diagnostic algorithm is proposed in the guidelines where both cardiac CT and ^{18}F-FDG PET/CT can be used as second-line imaging when the initial evaluation with echocardiography shows no definite PVE according to the Duke criteria but high suspicion of endocarditis remains [17].

In 2015, the American Heart Association also published updated guidelines for the management of IE [133]. These guidelines have a more conservative approach and do not support the inclusion of imaging criteria from modalities other than echocardiography in the diagnostic workup [133]. Because both ECG-gated CT and ^{18}F-FDG PET/CT are relatively new imaging methods, the optimal use in the workup of PVE patients remains to be shown.

Conclusions

- ECG-gated CT has comparable diagnostic performance to TEE in patients with aortic PVE.

- Increased aortic wall thickness (> 5mm) beyond three months postoperatively significantly increases the likelihood of PVE.

- The level of ^{18}F-FDG uptake in the prosthetic valve area shows good diagnostic performance in the diagnosis of PVE. The ^{18}F-FDG uptake around non-infected aortic prosthetic valves is low.

- ECG-gated CT provides additional information over TEE regarding perivalvular extension of infection, which can influence surgical decision-making. ECG-gated CT provides a non-invasive coronary angiogram and can in most cases replace invasive coronary angiography in the preoperative evaluation.

Future Perspectives

Cardiac magnetic resonance imaging (MRI) is used for evaluating valve dysfunction and quantifying valve stenosis and regurgitation [134]. Cardiac MRI is considered safe with most available valve prostheses [135]. However, cardiac MRI is not currently used in the diagnosis of endocarditis. Case reports have described the detection of vegetations [136-138], paravalvular abscess [139], and pseudoaneurysm [140] in patients with aortic and mitral valve endocarditis. Recently a small study showed that MRI might be of use in patients with endocarditis [141], but no larger studies have been performed. A possible advantage of MRI compared to CT is that MRI is superior in tissue characterization, and it has the potential to detect edema and contrast enhancement in the aortic root as signs of infection. The temporal resolution is also higher with MRI than with CT, which might be of importance in the detection of mobile vegetations. Furthermore, MRI can quantify a valvular/paravalvular leak with velocity-encoded phase-contrast imaging. It is possible that a paravalvular leak can be characterized with 4D flow imaging, a new technique that can describe complex flow patterns and that does not require breath-holding [142]. Disadvantages of MRI are that most sequences require repeated breath holds and that it is a relatively long procedure, which can be difficult for ill patients. Another problem is artifacts from the metal in mechanical prosthetic valves, which probably makes the method less useful in these patients. Development of methods for metal artifact reduction might overcome this problem in the future.

Leukocyte SPECT/CT is a nuclear medicine imaging method that has been used in PVE patients [143]. With this method, the patient's own white blood cells are labeled with ^{99m}Tc and the SPECT scanner detects the distribution of white blood cells in the body. A site of infection means accumulation of white blood cells, and the method has shown high specificity in the diagnosis of PVE [143]. However, the method is time-consuming and expensive because the patient's white blood cells need to be collected beforehand. The method might have a value in the early postoperative period where ^{18}F-FDG PET/CT can be false positive due to postoperative inflammation [121].

Three-dimensional TEE provides 3D-images of the aortic valve, and a small publication has suggested that the method might have additional value compared to 2D TEE in the diagnosis of PVE [144]. Larger comparative studies are needed

to determine whether this method can improve the diagnostic performance of TEE.

The technique of ECG-gated CT might be further refined by the use of dual energy. Dual energy means that two CT datasets are acquired with the use of different tube potentials [145]. The technique generates a virtual non-contrast dataset that can replace the unenhanced acquisition and thus might lower the radiation dose [146]. Low-energy images improve the detection of iodine and could make it easier to detect contrast enhancement in the aortic wall and surrounding soft tissue as a sign of infection.

The temporal resolution of the ^{18}F-FDG PET/CT examination can be improved with ECG-gating of the PET acquisition, and this is a method that is already in use and might facilitate the detection of activity around the prosthetic valve [116]. This scan can be combined with ECG-gated CT in the same imaging session to provide both high-resolution morphological images and information about activity [116].

Sammanfattning på svenska

Protesendokardit (PVE) är en infektion på och/eller runt en inopererad klaffprotes, vilket är ett tillstånd med hög dödlighet. Antibiotika används som behandling men i många fall behövs också kirurgi. Diagnosen är svår att ställa och den undersökningsmetod som rutinmässigt används är transesofagealt ultraljud (TEE; ultraljud via matstrupen). Fynden kan vara svårtolkade vid PVE och en del fall undgår korrekt diagnos. Det finns därför behov av kompletterande undersökningsmetoder för att förbättra diagnostiken.

I avhandlingen har två nya undersökningsmetoder som har potential att användas vid diagnostik av PVE i aortaklaffen studerats. Elektrokardiografistyrd datortomografi (EKG-styrd CT) ger högupplösta skiktröntgenbilder av hjärtat. ^{18}F-fluorodeoxyglukos positron emission tomografi/datortomografi (^{18}F-FDG PET/CT) avbildar sockerkonsumtionen i kroppens vävnader med hjälp av en radioaktiv isotop i kombination med skiktröntgen. Metoden används huvudsakligen i cancerdiagnostik men lokalt ökad sockerkonsumtion kan också ses vid infektion.

I delarbete I och IV undersöktes patienter med PVE i aortaklaffen med TEE och EKG-styrd CT (2008-2015). De två undersökningsmetoderna hade olika styrkor. TEE påvisade i fler fall bakteriepålagringar (vegetationer) på klaffbladen samt tecken på att klaffprotesen lossnat. EKG-styrd CT gav säkrare information om tjockleksökning i aortarotens vägg och tömda varhärdar kring klaffprotesen, vilka utgör tecken på att infektionen spridit sig från klaffen in i kärlväggen. Om man använde sig av båda metoderna i utredningen av patienter med PVE kunde fler fall med behov av kirurgi identifieras än om endast den ena metoden användes. EKG-styrd CT avbildar även kranskärlen och kunde i de flesta fall ersätta traditionell kranskärlsröntgen i utredningen inför operation.

I delarbete II studerades väggtjockleken i aortaroten hos personer som opererats med klaffprotes i aorta. Väggtjockleken var ökad direkt efter operationen som en följd av det kirurgiska ingreppet. Efter tre månader hade väggtjockleken normaliserats. Patienter med PVE hade i de flesta fall ökad väggtjocklek i aortaroten som tecken på att infektionen engagerat kärlväggen. En väggtjocklek >5 mm (senare än tre månader efter operation) var ett känsligt och användbart tecken på PVE.

I delarbete III jämfördes ^{18}F-FDG PET/CT hos personer med klaffprotes med och utan PVE. ^{18}F-FDG-upptaget var lågt kring klaffprotesen hos personer utan

PVE. Patienter med PVE hade ett förhöjt ^{18}F-FDG-upptag och upptagsnivån var användbar i diagnostiken av PVE.

Sammanfattningsvis kan både EKG-styrd CT och ^{18}F-FDG PET/CT vara komplement till TEE och öka säkerheten i diagnostiken av PVE.

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