NOVEL IMAGING STRATEGIES FOR THE DETECTION OF PROSTHETIC HEART VALVE OBSTRUCTION AND ENDOCARDITIS

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Novel Imaging Strategies for the Detection of Prosthetic Heart Valve Obstruction and Endocarditis

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For all the patients with a prosthetic heart valve.....

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CHAPTER 1

GENERAL INTRODUCTION

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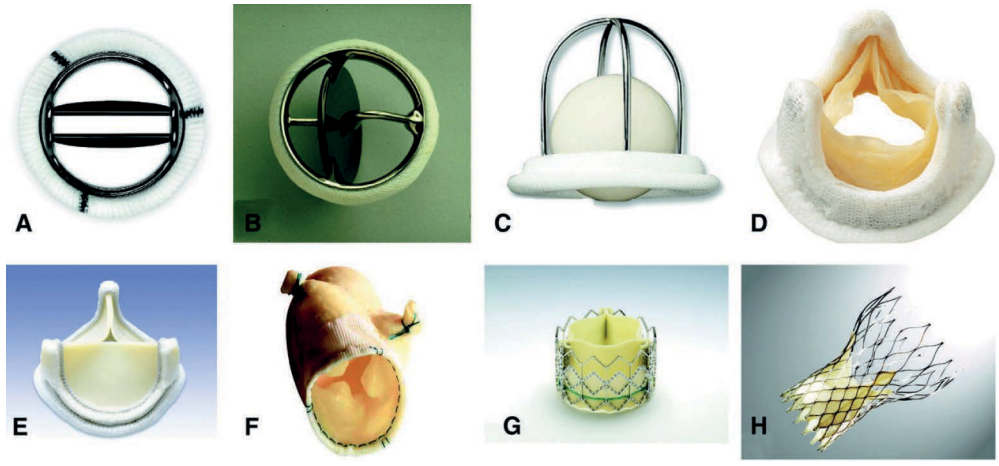
INTRODUCTION

Valvular heart disease is accompanied by a high mortality/morbidity and often requires prosthetic heart valve (PHV) replacement in order to improve quality of life and survival [1]. The number of PHV implantations is expected to rise due to ageing, growth of the population and the development of catheter-based techniques for valve replacement in patients who were inoperable before these techniques emerged. In 2003, the total number of patients that required heart valve replacement was approximately 290.000 worldwide. This annual incidence will increase and is estimated to rise to 850.000 in 2050 [2]. Depending on patient characteristics and preference either a mechanical or biological PHV (Figure 1) can be chosen. Although prosthetic heart valve implantation is often a lifesaving procedure the major drawback of both mechanical and biological PHV implantations is development of dysfunction, which is potentially life threatening. The reported incidence of PHV dysfunction varies from 0.01%-6.0 % per patient year [3]. This incidence is dependent on valve position, valve composition, patient characteristics, patient compliance and the nature of dysfunction which can be divided into three main groups; 1. (para)valvular leakage, 2. endocarditis and 3. obstruction [3]. Moreover, PHV dysfunction is accompanied by high mortality and morbidity, dependent on the cause and severity of dysfunction.

Figure 1



A. *Bileaflet mechanical prosthesis.* ***B.*** *Tilting disk mechanical prosthesis* ***C.*** *Ball in cage mechanical prosthesis.* ***D.*** *Biological prosthetic heart valve* ***E.*** *Biological prosthetic heart valve* ***F.*** *Homograft prosthesis* ***G & H.*** *Transcatheter biological prosthetic heart valves. On courtesy of Pibarot et al.*[45]

Clinically, it may be difficult to recognize PHV dysfunction as patients may be asymptomatic or present with a broad spectrum of symptoms such as fatigue, decreased exercise tolerance, (decompensated) heart failure, new or changing murmurs, signs of systematic embolization, fever or sepsis. As symptoms may be non-specific, the imaging of PHV's plays a pivotal role in the rejection or correct detection of PHV dysfunction. Combined transthoracic and transesophageal echocardiography (TTE and TEE) has a high diagnostic accuracy for the detection of pathological PHV leakages and their severity. TTE/TEE are mostly adequate to detect their location

and discriminate valvular from a paravalvular leakages [4-7]. Consequently diagnostic dilemmas are mostly solved after performing TTE and TEE, provided that the PHV leakage was not in the clinical context of (suspected) endocarditis. In contrast, PHV obstruction and endocarditis cases often raise diagnostic challenges even after performing echocardiography [3]. For this reason this thesis focusses mainly on PHV endocarditis and obstruction.

PHV obstruction

After the PHV implantation biological and mechanical PHV's are susceptible to develop (acquire) obstruction which may be caused by either degeneration, pannus or thrombosis formation. When the PHV obstruction is present directly after the operation the most likely cause is patient prosthesis mismatch (PPM). Theoretically other less frequent causes can be: 1. malpositioning of the PHV in the outflow tract, 2. obstruction by very early postoperative thrombosis, 3. leaflet obstruction by a suture. When a patient presents with a PHV obstruction in the chronic postoperative phase PPM can be differentiated from acquired obstruction by comparison of the effective orifice area of the initial postoperative TTE (around 6 weeks after implantation) and the most recent TTE [1]. This underscores the importance of this initial echocardiogram which should be performed in the setting of a visit to the outpatient-clinic. In acquired obstruction the pathological mechanism between biological and mechanical PHV's is different. After PPM is excluded the cause of acquired obstruction in biological PHV's is often calcifying degeneration, resulting in leaflet restriction. Theoretically another less frequent cause can be pannus formation around the stent struts. The therapeutical consequence of significant obstruction of a biological PHV in a symptomatic patient is re-operation (if clinically possible) [1]. Therefore additional diagnostics are not required in biological PHV obstructions as they do not change patient management. In contrast to biological PHV's, acquired mechanical PHV obstruction is usually not caused by degeneration, but mainly by pannus or thrombosis [8, 9]. Differentiation between these causes is very important as it may result in major therapeutical differences since obstructive thrombosis may require fibrinolysis and/or heparine infusion, whereas this is strictly contra-indicated in obstructive pannus [9-11]. In clinical practice, the differentiation between obstructive thrombus and pannus remains challenging though very important when fibrinolysis is considered. Clinical parameters are not reliable enough to differentiate, therefore ESC guidelines advocate confirmation of thrombus formation by TTE, TEE and fluoroscopy when fibrinolysis is considered [1]. TTE is a diagnostic screening tool with a good diagnostic accuracy for PHV obstruction compared to invasive catherization, however the origin of obstruction cannot be identified reliably by TTE [12]. Therefore combined additional imaging with fluoroscopy and TEE is advised. Fluoroscopy however may detect both leaflet restriction in pannus and thrombus and is consequently non-discriminative [13]. Therefore TEE is added to improve diagnostic accuracy, however echocardiographic assessment is hampered by acoustic shadowing caused by the PHV which contains metal and obscures adjacent anatomical structures for a correct diagnostic assessment. For this reason pannus and/or thrombus masses are often missed by TEE [12, 14]. In case of detection of a PHV mass, two small studies have been published investigating the capability of TEE to discriminate between pannus and thrombus [15, 16]. As all echocardiographic predictors for thrombus in both studies were in contradiction, reliable differentiation remains difficult by TEE. As a consequence of the aforementioned, additional imaging techniques for the differentiation of thrombus and pannus are required. This may be

provided by multidetector-row computed tomography (MDCT). However, only a few small and retrospective studies are available investigating this subject. Although clinically important, a systematic review or meta-analysis which provides an evidence based imaging strategy for differentiation between pannus and thrombus in mechanical PHV's is currently not available. In chapter 6 of this thesis however we will provide this information.

PHV endocarditis

PHV endocarditis occurs with an incidence of 0.3-1.2% per patient year and is complicated by peri-annular extensions (mycotic aneurysms and abscesses) in 50 % of cases [17-19]. This is associated with an in hospital mortality of 30 % which may even rise to 50 % when Staphylococcus Aureus is the bacterial agent [18-21]. According to the modified Duke criteria (Table 1), echocardiography plays a pivotal role in the establishment of the diagnosis of PHV endocarditis [22]. The two major Duke criteria are positive blood cultures and a positive echocardiogram for signs of PHV endocarditis (Table 1). The first criterion however is often negative (23%-37%) in patients with definite PHV endocarditis [18, 20, 21]. For that reason, reliable echocardiography is even more important to establish the definite diagnosis in patients with suspected PHV endocarditis. TTE is the first line clinical screening tool for the detection of PHV endocarditis but often fails to detect positive signs of PHV endocarditis [20, 21, 23]. TEE has incremental value when combined to TTE, but still life-threatening signs of PHV endocarditis may be missed in up to 30 % of cases [17, 24]. Therefore ruling out PHV endocarditis by echocardiography incorporates uncertainty, clinically resulting in a low threshold of long lasting antibiotic treatment. New imaging modalities are very welcome in PHV patients suspected for endocarditis in order to improve diagnostic accuracy and to choose the correct treatment strategy. For example, PHV endocarditis complicated by uncontrolled infection (peri-annular abscesses and mycotic aneurysms) should not be missed as this is an indication for urgent surgical intervention, whereas non-complicated PHV endocarditis (without peri-annular extension) may initially be treated by antibiotics alone [25].

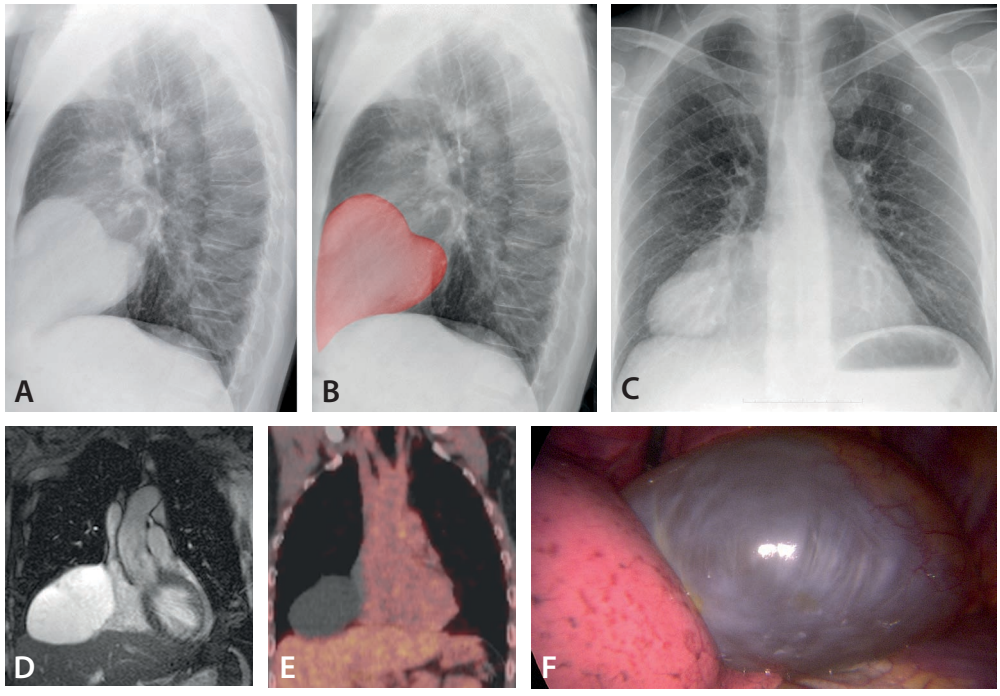
Additional imaging modalities

The Figure "a real heart sign" (Figure 2) shows a non-PHV case in which additional imaging on top of the routine imaging (two dimensional echocardiography and X-ray), is of complementary value for determining the correct diagnosis and treatment strategy. The presented patient had non-specific clinical symptoms, as PHV endocarditis and obstruction patients also often have. TTE and chest X-ray detected an abnormal structure close to the right ventricle, however the exact cause was not clear. Additional Magnetic Resonance Imaging (MRI) showed a pericardial mass, but still a malignancy could not be ruled out. Therefore Fluorodesoxyglucose Positron Emission Tomography (FDG-PET) scan including localizing computed tomography (CT) for attenuation correction was added. FDG-PET/CT detected a low metabolic status of the tumor, consistent with a pericardial cyst and not a malignancy. This additional imaging resulted in a correct diagnosis, confirmed by surgical exploration and pathological examination. The latter imaging strategy may be of additional value in PHV dysfunction patients as well.

Table 1: Modified Duke Criteria for infective endocardis[22]

Major Criteria
Bloodcultures positive: *Typical microorganism from two separate blood cultures: Streptococcus Viridans, Streptococcus Bovis, HACEK Group, Staphylococcus Aureus; community-acquired enterococci, in absence of a primary focus *or* *Microorganism from persistently positive blood cultures: At least two positive bloodcultures drawn > 12 hours apart *or* all of three *or* a majority of ≥ four separate cultures positive with the first and last drawn at least 1 hour apart *or* *Single positive blood culture for Coxiella burnetii *or* phase 1 IgG antibody titer > 1:800
Echocardiography *Echocardiography positive for infective endocarditis: Vegetation, Abscess, New partial dehiscence of PHV *New valvular regurgitation
Minor Criteria
*Predisposition: predisposing heart condition such as PHV *or* injection drug use *Fever: temperature > 38 degrees Celcius *Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhages, Janeway lesions. *Immunologic phenomena: glomeronephritis, Osler's nodes, Roth's spots, rheumatoid factor *Microbiological evidence: positive bloodculture that does not meet the major criterion
Definite diagnosis of Infective endocarditis
2 major criteria 1 major and 3 minor criteria 5 minor criteria
Possible diagnosis of Infective Endocarditis
1 major and 1 minor criteria 3 minor criteria

Figure 2: A Real Heart Sign



*A 39-year-old man presented in the emergency department (ED) with shortness of breath. Physical examination was unremarkable besides hyperventilation with an oxygen saturation of 100%. His symptoms subsided spontaneously in the ED. However, the chest x-ray (**A** to **C**) demonstrated a coincidental right paracardiac mass on the postero-anterior view and presented as a "real heart sign" on the lateral view, suggestive of a pericardial cyst. On echocardiography and cardiac magnetic resonance imaging (MRI) (**D**) the free lateral wall of the right atrium and tricuspid annulus were compressed by a fluid-filled mass, without hemodynamic consequences. On MRI, malignancy could not be excluded. Positron emission tomography/computed tomography excluded malignant disease (**E**). For prevention of hemodynamic consequences for the right atrium and ventricle, the mass was successfully drained and removed during video-assisted thoracoscopic surgery (**F**). Pathological examination confirmed the diagnosis of a pericardial cyst.*

Cardiac magnetic resonance imaging (MRI) is an established technique for imaging a broad spectrum of cardiac pathologies especially dynamic anatomical as well as functional assessment of the cardiac chambers and native cardiac valves. MRI imaging is safe beneath a value of 3 TESLA for all PHV's (both biological and mechanical) as no significant interruption of valve motion nor overheating were detected [26, 27]. Furthermore, serial MRI imaging is safe due to the lack of radiation exposure and less stringent renal function thresholds for gadolinium contrast medium compared to iodinated contrast material. For optimal images however a regular heart rhythm and frequent breath-holds are required which may be cumbersome for sick patients [28]. The largest diagnostic problem however are artefacts caused by the PHV resulting in a minimal additional imaging role of MRI for PHV obstruction or endocarditis [28]. However for the detection and quantification of

PHV leakages, cardiac MRI may have a diagnostic role as anatomical imaging closely around the PHV is not required. Phase contrast based analysis can namely be performed sub-or supravalvular resulting in the detection and quantification of PHV (para)valvular leakages [29-31].

Cardiac 18-Fluorine-Fluorodesoxyglucose Positron Emission Tomography combined with a localizing (low dose) CT that is also used for attenuation correction (FDG-PET/CT) is a novel and promising imaging modality in PHV endocarditis. PET scanning is based on the detection of annihilation photons released when the radionuclide 18 Fluorine (18-F) emits positrons. 18-F labelled to fluorodesoxyglucose (18F-FDG) is a molecule which is internalised in the mitochondria of human cells via a passive uptake-mechanism in the same way as glucose. Unlike glucose, 18F-FDG is not metabolised but trapped in the human cell. As infected cells consume more glucose compared to normal non-infected tissues, this results in accumulation of 18F-FDG in infected tissues, emitting larger amounts of positrons compared to non-infected tissues. The problem of cardiac PET scanning is that cardiac myocytes have a relative high glucose uptake compared to cells in other organs. Therefore it is important to force the heart to pre-dominantly fatty acid metabolism. This can be accomplished by a 24-hour low carbohydrate diet (last 12 hours fasting). As a result non infected myocardial cells have no or very low 18F-FDG uptake. Consequently, when a patient adheres to a low carbohydrate diet, high cardiac 18F-FDG uptake is suggestive for myocardial infection/inflammation. Taking into account the former, for the detection of the exact origin of PHV obstruction and differentiation of pannus from thrombus, FDG-PET/CT seems useless as pannus and thrombus both have a low metabolic status which cannot be differentiated from the bloodpool. In contrast, FDG-PET/CT may be very useful in PHV endocarditis. Very recently Saby et al. showed in a prospective study that the diagnostic accuracy of PHV endocarditis improved when 18F-FDG-PET/CT was added as a major criterion to the modified Duke criteria [32]. It can be concluded that FDG-PET/CT is a promising imaging tool for PHV endocarditis with peri-annular extension, however the sensitivity for vegetations is a concern as PET imaging has a lower spatial resolution compared to TEE and MDCT. Therefore, cardiac FDG-PET/CT should be combined with a technique that supplies superior anatomical imaging with a high spatial resolution such as TEE or even ECG-gated contrast enhanced MDCT [33]. Moreover, the specificity of FDG-PET/CT imaging is a concern as the basal FDG uptake around PHV's is not reported in literature. This normal FDG uptake pattern is crucial for interpretation of the specificity, especially in the early post-operative phase (< 1 year). In this timeframe postoperative inflammation may be a major issue and could result in false positive imaging. In chapter 4 answers to the above mentioned concerns about FDG-PET/CT imaging in PHV endocarditis will be provided.

Multidetector-row computed tomography (MDCT) has recently emerged as a promising novel imaging technique to evaluate PHV's that provides complementary diagnostic information to echocardiography in patients with suspected PHV endocarditis and obstruction [34-38]. The technique uses electrocardiographic (ECG) gating to overcome artefacts related to the movement of the heart during the cardiac cycle. To study opening and closing kinetics of the PHV a retrospective protocol with a minimum of 10 phases per heart cycle is required. Scans are contrast enhanced with a contrast concentration of >300mg/ml and injection rate of > 4-6 mL/sec. The heart rate

during scanning should be regular and preferably around 60 beats/minute. With the cine mode, leaflet motion during the whole heart cycle can be viewed [39]. Taking these recommendations into account, MDCT results in the ability to perform fluoroscopy to study leaflet motion and opening/closing angles. Reconstruction of the acquired images provides three dimensional assessment of the PHV in any plane in each phases of the heart cycle. The contrast enhancement supplies anatomical imaging resulting in the possibility to detect PHV thrombi, pannus, vegetations, paravalvular leakages, mycotic aneurysms and even abscesses [39].

Only small retrospective case series on MDCT in PHV obstruction are present [36-38]. These small studies suggest an additional diagnostic value of MDCT in PHV obstruction. Ueda et al. recently published on nine patients with acquired mechanical aortic PHV obstruction secondary to pannus, confirmed by surgical exploration [37]. In these patients echocardiography including TEE detected no masses, however MDCT detected subvalvular masses with an anatomical configuration matching pannus in all patients. Houndsfield units of the subvalvular masses were significantly higher compared to the Houndsfield units of the ventricular septum. Symersky et al. studied patients with acquired PHV obstruction of unknown cause [38]. Compared to echocardiography, MDCT had an additional value in the detection of thrombus, pannus and subvalvular membranes.

Only one dedicated prospective study on PHV endocarditis is reported [35]. Fagman et al. showed in a surgically confirmed subpopulation (n=16) of their study that MDCT was able to provide good detectability of both vegetations and abscesses in patients with PHV endocarditis [35]. The analysis of combined CTA and TEE improved the diagnostic accuracy even more. However in this small single centre study reviewers were blinded for TEE results which does not resemble routine clinical practice. Therefore, more and larger prospective studies are required investigating the additional value of CTA on top of routine clinical practice including TTE/TEE in PHV endocarditis and obstruction. Such a study is provided in chapter 3.

Three dimensional TEE (3D-TEE) is performed with a multiplane probe including a 3D matrix-array. 3D full-volume (4-7 beat stitch) data sets allow offline image editing using the multiple plane reconstruction (MPR) mode and freehand cropping mode. This provides wide-angled 3D datasets with the ability to manipulate and crop images not limited to conventional 2D planar views. This enables visualization of PHV valves, but theoretically also vegetations and peri-annular extensions, at angles not previously possible [40]. Sugeng et al. investigated the visibility of PHV ring and leaflets by 3D-TEE, which were less visible in aortic PHV's compared to mitral PHV's [41]. The ability to detect vegetations and/or peri-annular extensions however was not investigated. Only a few case reports concerning signs of aortic PHV endocarditis detected by 3D-TEE are reported in literature and only one small case series (n=4) reported on three mitral and one tricuspid PHV [42]. Theoretically 3D-TEE allows identification not only of vegetations, but also of discrete valvular dehiscences and their associated regurgitation jets if 3D color images are rendered [40]. In the field of PHV obstruction, one dedicated study on the additional value of 3D-TEE was recently published [43]. This study shows that in mechanical mitral PHV's 3D-TEE has additional value on mass detection compared to 2D-TEE. For the additional value of 3D-TEE in aortic PHV obstruction only a few case reports are published, but no dedicated studies are performed [44]. While TEE probes are standardly equipped with 3D matrix arrays increasingly, studies on this technique for PHV obstruction and endocarditis are still very scarce, although most welcome.

OUTLINE OF THIS THESIS

This thesis will determine and compare the diagnostic role of routine imaging techniques (fluoroscopy and two-dimensional TTE/TEE) in PHV endocarditis and obstruction. Moreover, it will focus on the additional value of novel techniques such as 3D-TEE, FDG-PET/CT and MDCT and evaluate their first implementations in clinical practice. In part 1 we will elaborate on PHV endocarditis and in part 2 on PHV obstruction.

PART 1

The clinical diagnostic role of TTE and TEE in PHV endocarditis has never been systematically reviewed nor meta-analyzed. In **Chapter 2** a meta-analysis is provided, not only to determine and compare the diagnostic accuracy of TTE and TEE, but also the diagnostic role of MDCT in patients with (suspected) PHV endocarditis. In **Chapter 3** a prospective cross sectional study is presented to determine the complementary diagnostic value of MDCT compared to the clinical routine workup including TTE/TEE in patients with suspected PHV endocarditis. Moreover, this study presents the impact of MDCT on patient treatment. **Chapter 4** explores the additional value of hybrid imaging by MDCT and FDG-PET in PHV endocarditis patients with mainly negative or inconclusive echocardiography. Moreover this study supplies baseline FDG-uptake values around normal functioning PHV's. In **Chapter 5** the additional value of 3D-TEE is compared to 2D TTE/TEE for the detection of vegetations and/or peri-annular extensions in patients with aortic PHV endocarditis. Further, it explores the possibility to detect inflammatory involvement of the proximal coronary arteries in case of peri-annular extension by 2- and 3D-TEE which is important for the pre-operative strategy.

PART 2

The diagnostic role of non-invasive imaging techniques for determination of the cause of acquired mechanical PHV obstruction has not been systematically reviewed and determined. In **Chapter 6** a systematic review is provided to determine and compare the diagnostic role of TTE, TEE, fluoroscopy and MDCT for detection of the exact cause of acquired mechanical PHV obstruction. Based on the results we will suggest an evidence-based imaging strategy for differentiation of obstructive thrombus from pannus as this has therapeutical consequences in case thrombolysis is considered. In **Chapter 7** the additional diagnostic value of MDCT for a variety of PHV dysfunction etiologies that includes thrombus and pannus formation is shown. In **Chapter 8** an extraordinary case is described in which MDCT was able to detect small thrombi on the hinge points of a bi-leaflet mechanical PHV, whereas these thrombi were not detected by TTE/TEE. In **Chapter 9** the diagnostic accuracy of coronary angiography by retrospectively ECG-gated MDCT primarily performed for the detection of PHV dysfunction is explored. This is clinically important as in thrombosed aortic PHV's requiring re-operation, invasive coronary angiography (CAG) should mostly be performed. However CAG is also relatively contra-indicated as invasive catheters may dislocate thrombi, resulting in distal embolization. **Chapter 10** encloses the general discussion and conclusions in which we will elaborate on aforementioned studies and provide future perspectives.

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PART 1

PROSTHETIC HEART VALVE ENDOCARDITIS

CHAPTER 2

ARE NOVEL NON-INVASIVE IMAGING TECHNIQUES REQUIRED IN PATIENTS WITH SUSPECTED PROSTHETIC HEART VALVE ENDOCARDITIS? A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background and Objectives: Accurate detection of the signs of prosthetic heart valve (PHV) endocarditis is crucial for patient management and outcome. However the diagnostic accuracy of transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and multidetector-row computed tomography (MDCT) for the detection of PHV endocarditis has not been systematically reviewed. Therefore the objective of this study is to determine and compare the diagnostic accuracy of TTE, TEE and MDCT in patients with (suspected) PHV endocarditis.

Methods: Studies published between 1985 and 2013 identified by a Pubmed and Embase search and cross-referencing were assessed. Studies were included if; (1) studies reported on the non-invasive index tests TTE, TEE or MDCT; (2) studies provided data on PHV endocarditis as the condition of interest; (3) imaging results were verified against one of the following reference standards (surgical inspection/autopsy or clinical follow-up) which enables the extraction of 2-by-2 tables.

Results: Twenty articles met the inclusion criteria for PHV endocarditis. TTE, TEE and MDCT + TEE had a pooled sensitivity/specificity for vegetations of 29%/100%; 82%/95% and 88%/94% respectively. The pooled sensitivity/specificity of TTE, TEE and MDCT + TEE for peri-annular complications was 36%/93%, 86%/98% and 100%/94% respectively.

Conclusions: TEE has a good sensitivity and specificity to establish the diagnosis of PHV endocarditis which is associated with a high mortality. Although MDCT data are limited, this review shows that MDCT on top of TEE may further improve the sensitivity to detect peri-annular complications.

INTRODUCTION

Left-sided native heart valve disease often requires prosthetic heart valve (PHV) implantation, especially in the aortic position. In 2003, the total number of patients who required heart valve replacement was approximately 290.000 worldwide. This annual incidence will increase mainly due to ageing and is estimated to rise to 850.000 in 2050 [1]. Although prosthetic heart valve implantation is a lifesaving surgical procedure, its major drawback is the occurrence of complications such as PHV obstruction or PHV endocarditis. PHV endocarditis is a life-threatening disease with an incidence of 0.3-1.2% per patient per year [2].

In clinical practice, PHV endocarditis presents with a heterogeneous spectrum of clinical symptoms such as fever, heart failure symptoms or systematic embolization. According to the modified Duke criteria, echocardiography plays a pivotal role in the establishment of the diagnosis of PHV endocarditis [3]. Transthoracic echocardiography (TTE) is the first line clinical screening tool for the detection of PHV endocarditis but often fails to detect positive signs of PHV endocarditis, such as vegetations and peri-annular complications (abscesses/mycotic aneurysms). Transesophageal echocardiography (TEE) can have incremental value to TTE but may still fail to detect life-threatening signs of PHV endocarditis. Multidetector-row computed tomography (MDCT) has recently emerged as a promising novel imaging technique to evaluate PHV's. It may provide complementary diagnostic information to echocardiography in patients with suspected PHV endocarditis [4].

The purpose of this systematic review is to determine and compare the diagnostic accuracy of TTE, TEE, and MDCT + TEE in patients with (suspected) PHV endocarditis.

METHODS

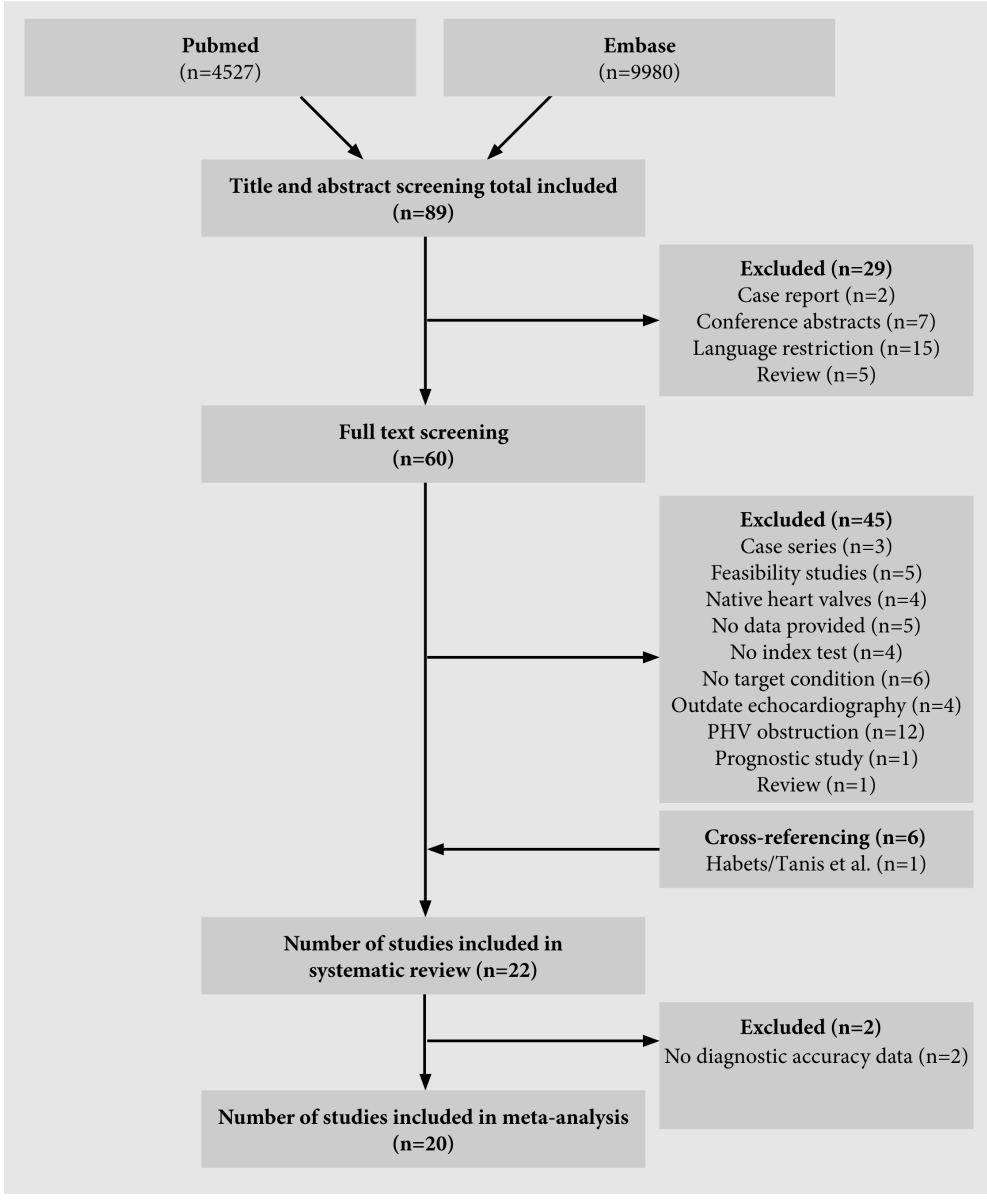
Literature search

A systematic electronic search was performed in the Pubmed and Embase databases for original publications published until July 23th 2013. Language was restricted to English articles and publications before 1985 were excluded. Key search terms included the non-invasive imaging modalities (TTE, TEE and MDCT), prosthetic heart valves and corresponding synonyms. The detailed search terms are shown in supplement 1. For all included full-text papers, cross-referencing was performed.

Selection of publications

After removal of duplicates, the titles and abstracts were independently screened by two reviewers (JH and WT). Articles were included if 1. studies reported on one of the following non-invasive index tests : TTE, TEE or MDCT 2. studies provided data on PHV endocarditis as the condition of interest. 3. imaging results were verified against the reference standard of surgical inspection/autopsy or clinical follow-up, which enables the extraction of 2-by-2 tables. Full-text publications of the included articles were obtained. These full-text publications were assessed by two reviewers (JH and WT) independently. In a consensus meeting, the two reviewers extensively discussed the full-text publications and data extraction.

Figure 1 Systematic literature search



Quality assessment

Information on patient population, study enrolment, non-invasive imaging modalities and reference standard was collected. Studies were systematically assessed for quality, based on the validated Quality Assessment of Diagnostic Accuracy Studies (QUADAS) II checklist [5]. This checklist assesses the risk of bias and clinical applicability of studies based on different domains: 1. patient selection, 2. index test, 3. reference standard and 4. flow and timing.

Data analysis

Diagnostic accuracy of the different imaging modalities was assessed for the detection of the following signs of PHV endocarditis: vegetations, peri-annular complications (abscesses, mycotic aneurysms/pseudoaneurysms), PHV dehiscence and PHV endocarditis in general. These different signs of interest were defined according to echocardiographic criteria; 1. vegetations, defined as irregularly shaped, oscillating masses, adherent to and distinct from the myocardium; 2. abscesses, defined as irregularly shaped, inhomogeneous paravalvular enclosed masses within peri-annular region, myocardium or pericardium; 3. mycotic aneurysms/pseudoaneurysms, defined as echo-free perivalvular cavities with flow communicating with the cardiovascular lumen; and 4. PHV dehiscence, defined as rocking motion of a prosthetic heart valve [2, 6]. PHV endocarditis in general included one or more of the above mentioned signs of PHV endocarditis.

Forest plots of sensitivity and specificity with their corresponding 95% confidence intervals (CI) were generated, stratified by the different target conditions, and within each forest plot data were grouped by the different index tests (TTE, TEE and MDCT + TEE). The bivariate random effects model was used to obtain and compare summary estimates of sensitivity and specificity for the different index tests. The bivariate approach simultaneously models pairs of (logit transformed) sensitivity and specificity from studies, thereby incorporating any correlation that might exist between sensitivity and specificity. The model uses a random effect approach for both sensitivity and specificity, allowing for heterogeneity beyond chance due to clinical and methodological differences between studies. In case the results displayed no more variation than expected by chance, models were simplified to fixed effect pooling of sensitivity or specificity or both. To compare index tests, we extended the bivariate model with a covariate indicating the type of index test. Such a model calculates different summary estimates for sensitivity and specificity for each index test and also provides a formal statistical test whether differences are statistically different. The non-linear mixed models procedure (PROC NLMIXED) of SAS 9.2 was used to estimate the parameters of the bivariate models. P-values below 0.05 were considered as statistically significant.

RESULTS

Search results

The systematic electronic search yielded a total of 89 publications after screening of titles and abstracts. Sixty full-text versions of studies were obtained and 45 studies were excluded because of different reasons (Figure 1). Cross-referencing of all included full-text articles resulted in six additional articles. Furthermore, our recent accepted paper was added for completeness [7]. The final selection of articles included 22 studies for the systematic review. Two studies reporting on PHV endocarditis were excluded from meta-analysis because no diagnostic accuracy data were available [8, 9]. As a result, twenty studies were meta-analyzed.

PHV endocarditis

In the systematic review twenty-two studies reporting on the detection of signs of endocarditis using echocardiography (TTE/TEE) were included (Table 1) [7-27]. Three studies reported on MDCT findings [7, 10, 28]. Data were prospectively (dedicated data collection; *n*=11; 50%) and retrospectively (routine care data; *n*=11; 50%) collected (Table 1). Inclusion period occurred completely or partially ≤1990 in 15 (68%) of the studies. The reference standard was exclusively

Table 1 | PHV endocarditis study characteristics

Authors	Journal / Year	Number of patients included (number of PHVs)	Source data	Inclusion period	Study population	Index test	TEE probe	Reference standard
Mugge et al. [22]	JACC 1989	26 (26)	Dedicated data collection	1984-1987	Surgical exploration	TTE/TEE	NR	Surgery/autopsy
Taams et al. [27]	Br Heart J 1990	12 (12)	Dedicated data collection	1984-1988	Suspected for target condition	TTE/TEE	Monoplane	Surgery/clinical follow-up
Daniel et al. [13]	NEJM 1991	34 (34)	Dedicated data collection	1984-1989	Surgical exploration	TTE/TEE	NR	Surgery/autopsy
Khanderia et al. [18]	Circulation 1991	6 (9)	Routine care data	1988-1989	Surgical exploration	TTE/TEE	Monoplane	Surgery/autopsy
Pedersen et al. [23]	Chest 1991	10 (11)	Dedicated data collection	NR	Suspected for target condition	TEE	NR	Surgery/clinical follow-up
Shively et al. [26]	JACC 1991	11 (11)	Dedicated data collection	1988-1989	Suspected for target condition	TTE/TEE	NR	Clinical diagnosis
Birmingham et al.* [9]	Am Heart J 1992	2(2)	Routine care data	1988-1990	Suspected for target condition	TEE	NR	Modified Von Reyn criteria
Herrera et al. [15]	Am J Cardiol 1992	9 (9)	Routine care data	NR	Suspected for target condition	TTE/TEE	NR	Surgery/autopsy
Karalis et al. [17]	Circulation 1992	11 (11)	Routine care data	1988-1991	TEE positive for target condition	TTE/TEE	Mono/biplane	Surgery/autopsy
Aguado et al. [12]	Chest 1993	13 (14)	Routine care data	1979-1989	Surgical exploration	TTE	NA	Surgery/autopsy
Daniel et al. [14]	Am J Cardiol 1993	33 (33)	Dedicated data collection	1984-1990	Surgical exploration	TTE/TEE	Monoplane	Surgery/autopsy
Mohr-Kahaly et al.[21]	J Am Soc Echocardiogr. 1993	30 (34)	Dedicated data collection	1987-1991	Surgical exploration	TTE/TEE	Mono/biplane	Surgery/autopsy
Sochowski et al.* [8]	JACC 1993	21 (32)	Routine care data	1988-1990	Suspected for target condition	TEE	Monoplane	Clinical follow-up
Leung et al. [19]	Br Heart J 1994	6 (6)	Routine care data	1989-1993	Surgical exploration	TTE/TEE	Mono/bi/multiplane	Surgery/autopsy
Lowry et al. [20]	Am J Cardiol 1994	32 (32)	Routine care data	1989-1992	Suspected for target condition	TEE	Mono/biplane	Surgery/clinical follow-up
Choussat et al. [11]	European Heart Journal 1999	43 (43)	Routine care data	1989-1993	Surgical exploration	TTE/TEE	Mono/bi/multiplane	Surgery/autopsy
San Roman et al. [25]	Am J Cardiol 1999	87 (87)	Routine care data	NR	Surgical exploration	TEE	Bi/multiplane	Surgery/autopsy
Roe et al. [24]	Am Heart J 2000	34 (34)	Routine care data	1988-1995	Suspected for target condition	TEE	Bi/multiplane	Surgery/clinical follow-up
Hill et al. [16]	Am J Cardiol 2007	26 (26)	Dedicated data collection	2000-2005	Surgical exploration	TEE	Multiplane	Surgery/autopsy
Feuchtner et al. [10]	JACC 2009	6 (6)	Dedicated data collection	2006-2007	Surgical exploration	TEE/MDCT	Bi/multiplane	Surgery/autopsy
Fagman et al. [28]	Eur Radiol. 2012	16 (16)	Dedicated data collection	2008-2011	Surgical exploration	TEE/MDCT	Bi/multiplane	Surgery/autopsy
Habets/Tanis et al. [7]	Int J Cardiovasc Imaging. 2013	28 (28)	Dedicated data collection	2010-2012	Suspected for target condition	TTE+TEE/MDCT	Multiplane	Surgery/clinical follow-up

* Not included in meta-analysis because of no available prosthetic heart valve endocarditis data; ** episodes
NA = Not Applicable; NR = Not Reported; MDCT = multidetector-row CT; PHV = Prosthetic Heart Valve; TTE = transthoracic echocardiography; TEE = transesophageal echocardiography

Table 1 | (Continued) PHV endocarditis study characteristics

Authors	Journal / Year	Assessment of index test without knowledge of reference standard	Interval between reference standard and index test	All patients the same reference standard	All patients included in data analysis
Mugge et al. [22]	JACC 1989	Yes	17±2 days (mean±SD)	Yes	No
Taams et al. [27]	Br Heart J 1990	Yes	1-7 days	No	Yes
Daniel et al. [13]	NEJM 1991	Yes	≤ 7 days	Yes	Yes
Khanderia et al. [18]	Circulation 1991	Yes	NR	Yes	Yes
Pedersen et al. [23]	Chest 1991	Yes	NR	No	No
Shively et al. [26]	JACC 1991	Yes	NR	Yes	No
Birmingham et al.* [19]	Am Heart J 1992	Yes	NR	Yes	Yes
Herrera et al. [15]	Am J Cardiol 1992	Yes	NR	Yes	Yes
Karalis et al. [17]	Circulation 1992	Unclear	NR	Yes	No
Aguado et al. [12]	Chest 1993	Yes	NR	Yes	Yes
Daniel et al. [14]	Am J Cardiol 1993	Yes	57±16 days (mean±SD)	Yes	Yes
Mohr-Kahaly et al. [21]	J Am Soc Echocardiogr.1993	Unclear	14±3 days (mean±SD)	Yes	Yes
Sochowski et al.* [8]	JACC 1993	Unclear	NR	Yes	No
Leung et al. [19]	Br Heart J 1994	No	NR	Yes	No
Lowry et al. [20]	Am J Cardiol 1994	Unclear	NR	No	Yes
Choussat et al. [11]	European Heart Journal 1999	Unclear	Unclear	Yes	Yes
San Roman et al. [25]	Am J Cardiol 1999	Yes	Unclear	Yes	Yes
Roe et al. [24]	Am Heart J 2000	Unclear	NR	No	Unclear
Hill et al. [16]	Am J Cardiol 2007	Yes	≤ 7 days	Yes	No
Feuchtner et al. [10]	JACC 2009	Yes	≤5 days (1 patient 6 weeks)	Yes	No
Fagman et al. [28]	Eur Radiol. 2012	Yes	NR	Yes	No
Habets/Tanis et al. [7]	Int J Cardiovasc Imaging. 2013	Yes	14 days	No	Yes

* Not included in meta-analysis because of no available prosthetic heart valve endocarditis data
NR = Not Reported; PHV = Prosthetic Heart Valve; SD = Standard Deviation

surgical inspection or autopsy in 14 (64%) studies. In eight studies (36%), clinical criteria and/or follow-up were mentioned as the reference standard. A minority of the studies (*n*=8, 36%) included multi-plane TEE assessment. Most studies (*n*=14, 64%) did not report on the interval between the index and reference test. Two studies had a long time interval (>2 weeks) between index test and reference standard [14, 22]. The other six studies (27%) had an acceptable time interval (≤2 weeks) [7, 10, 13, 16, 21, 27]. Assessment of the index test was blinded (without knowledge of the reference standard) in 15 (68%) studies. In six of the 22 studies (27%), it was unclear if this assessment was blinded and in one study no blinding was performed [19]. All patients had the same

Figure 2: Sensitivity of TTE, TEE and TEE+MDCT for PHV vegetations and peri-annular extensions.

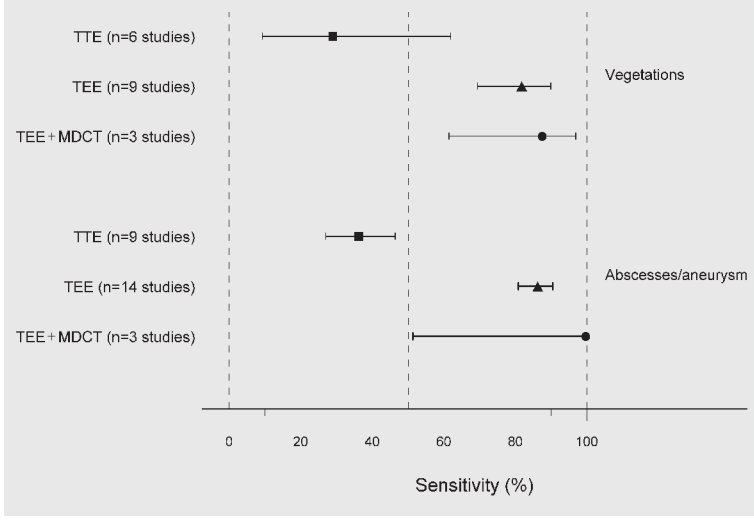
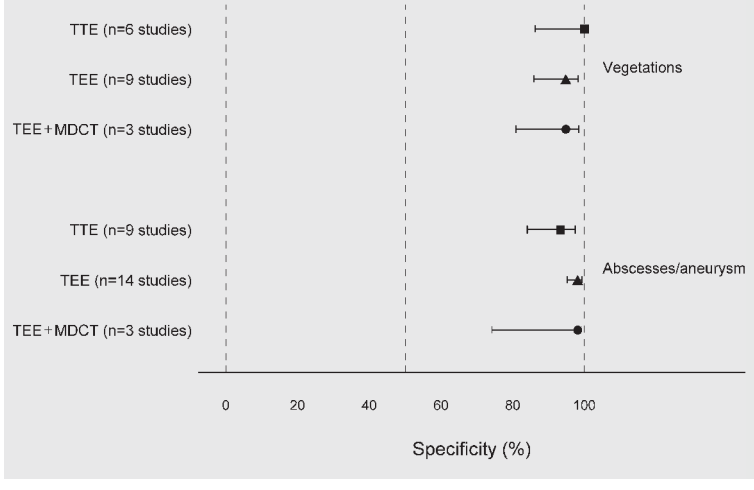


Figure 3: Specificity of TTE, TEE and TEE+MDCT for PHV vegetations and peri-annular extensions.



reference standard in 17 (77%) studies. In 12 (54%) studies all patients were included in the data-analyses. In the meta-analysis, the previously mentioned signs of PHV endocarditis were analysed. Diagnostic accuracy measures for the detection of signs of PHV endocarditis could be extracted in twenty studies (*n*=473 patients). (Table 1)

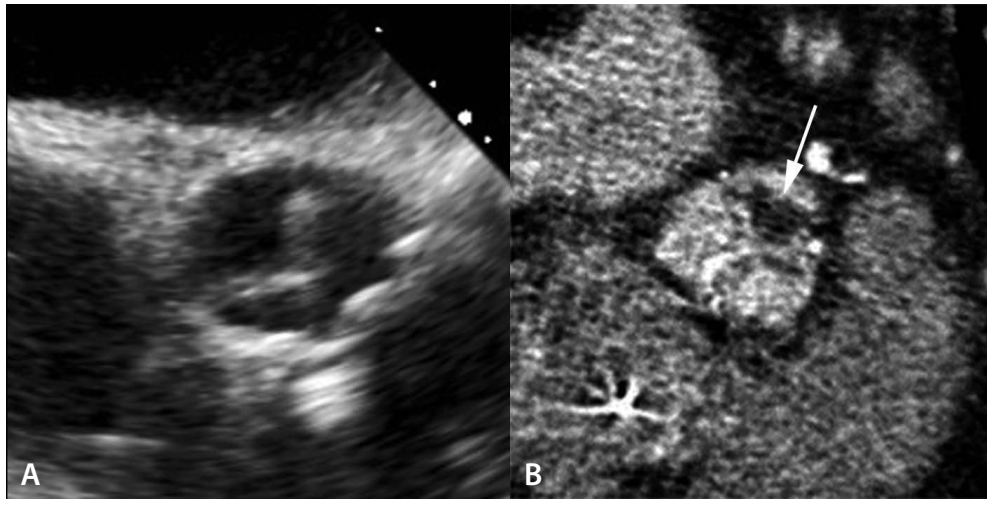
Vegetations

In Figure 2 and 3, sensitivity and specificity of TTE (n=63), TEE (n=113) and MDCT + TEE (n=50) for the detection of vegetations are presented. The pooled TTE sensitivity and specificity for the detection of vegetations are 29% [95%CI: 9-62%] and 100%[95%CI: 86-100%], respectively. TEE (82%[95% CI: 69%-90%]) and MDCT + TEE (88%[95%CI: 61-97] are more sensitive than TTE (both p<0.01). No significant difference was found between TEE and TEE + MDCT (p=0.60). No significant differences are found in specificity between TTE and TEE/ MDCT+TEE (96%[95%CI: 81-99%] / 94%[95%CI:81-98%]) (p=0.12).

Peri-annular complications

In Figure 2 and 3, sensitivity and specificity of TTE (n=172, TEE (n=412), and MDCT + TEE (n=50) for the detection of peri-annular complications are presented. The pooled TTE sensitivity and specificity for the detection of peri-annular complications are 36% [95%CI: 27-46%] and 93% [95%CI: 84-97%], respectively. One study reported 3 false positive (43%) TTE examinations [10]. TEE (86% [95%CI: 81%-90%]) and MDCT + TEE (100% [95% CI; 51-100%]) are more sensitive than TTE (p≤0.03). In one study, TEE missed five out of the 14 (36%) peri-annular complications in patients with aortic PHV endocarditis [14]. No significant difference was found between TEE and TEE + MDCT (p=0.18). No significant differences are found in specificity between TTE and TEE (98%[95%CI: 95-99%]) (p=0.07) (Figure 3).

Figure 4: Detection of a vegetation by MDCT

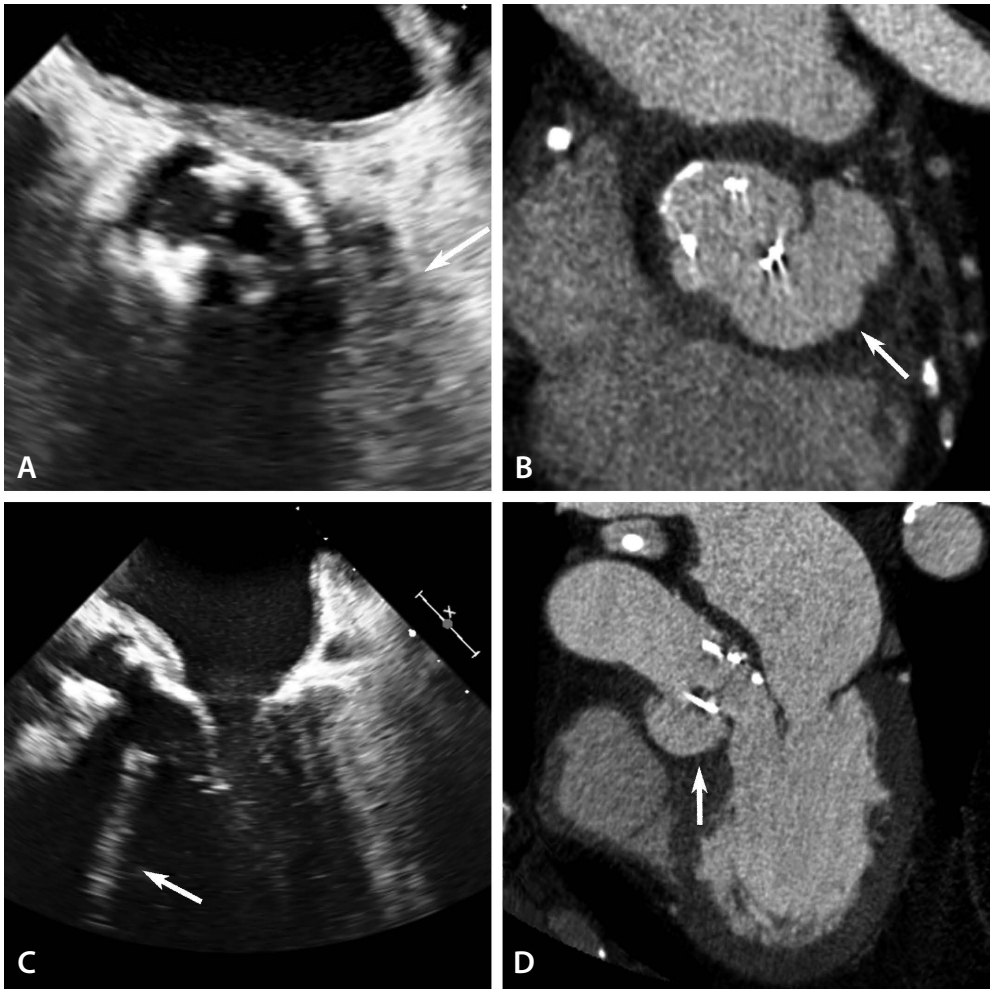


*Patient with a Mitroflow bioprosthesis in the aortic position. The short axis TEE did not show a vegetation (**A**). The MDCT short axis view demonstrated a vegetation on the former left coronary cusp (arrow) (**B**).*

PHV dehiscence

The pooled TTE (n=18) sensitivity and specificity for the detection of PHV dehiscence are 11% [95%CI: 1-73%] and 100% [95%CI: 72-100%], respectively. No significant difference in sensitivity and specificity was found between TTE and TEE (n=60) (sens 94% [95%CI: 37%-100%] and spec 97% [95%CI: 84-99%]) (p≥0.05). One study reported on the detection of PHV dehiscence by MDCT (n=16) [28] . Fagman et al. [28] reported seven cases of PHV dehiscence both detected by TEE and MDCT. However, TEE detected three additional cases of PHV dehiscence.

Figure 5: Mycotic aneurysm mainly located near the former left cusp



*Patient with a biological Carpentier Edwards Perimount PHV in the aortic position. Assessment of the former left coronary cusp region is hampered by acoustic shadowing (arrows) in the short axis TEE view (**A**) and 0 degree TEE view (**C**). Short axis (**B**) and 0 degree MDCT (**D**) images are not hampered by valve-related artifacts and visualized a large (3.4x2.1cm) mycotic aneurysm (arrows). PHV = prosthetic heart valve; TEE = transesophageal echocardiography*

Signs of PHV endocarditis in general

The pooled TTE (n=55) sensitivity and specificity for the detection of signs of PHV endocarditis in general are 33% [95%CI: 24-42%] and 100%[95%CI: 76-100%], respectively. TEE (n=114) is more sensitive (86% [95%CI: 77%-92%]) than TTE (p<0.001). No significant differences are found in specificity between TTE and TEE (95% [95%CI: 82-99%]) (p=0.29). Only one study (n=28) reported on the detection of signs of endocarditis in general by MDCT [7]. In this study, sensitivity of MDCT + TEE (100%) was higher than TEE (95%) alone.

DISCUSSION

We systematically reviewed the literature on TTE, TEE and MDCT for detection of signs of PHV endocarditis. Despite the limited number of studies reporting on the diagnostic accuracy of these imaging modalities, non-invasive imaging plays a key role in the establishment of the diagnosis PHV endocarditis and has important clinical implications for patient management and outcome. The main findings are that TEE is more sensitive than TTE for the detection of both vegetations and peri-annular complications. However, TEE still misses life-threatening peri-annular extensions and vegetations (Figure 4 and 5). The addition of MDCT to TEE can improve the detection of these peri-annular extensions and vegetations. However, limited data are available at the moment resulting in broad confidence intervals.

According to the QUADAS 2 assessment, several studies had a risk of bias and/or clinical applicability. This included patient selection (only re-operated patients), old studies (including monoplane TEE assessment), unreported blinding for the reference standard and interval between index test/reference standard (Table 1).

In clinical practice, PHV endocarditis remains a difficult diagnosis to establish and is based on the modified Duke criteria [3]. For the fulfilment of the Duke criteria, a positive echocardiogram is one of the two important major criteria, and is defined as the presence of a vegetation, abscess, PHV dehiscence or new (para)valvular regurgitation. PHV endocarditis differs from native valve endocarditis as it presents more often with peri-annular extension [29], with an incidence of (53-55% of the cases). In contrast to native valve endocarditis, blood cultures are often negative (23%-37%) and imaging by echocardiography is hampered by acoustic shadowing of the PHV [11, 13, 25]. Furthermore, PHV endocarditis with a peri-annular extension has a higher 6-month mortality than patients without peri-annular complications (30% vs 8%, respectively) [16]. With Staphylococcus Aureus as the causative micro-organism mortality may even further increase up to 54% [16]. Other relevant independent predictors of early mortality are age, renal failure and the presence of AV block [11, 13, 16, 25, 30].

Detection of life-threatening abscess formation and mycotic aneurysms with non-invasive imaging is crucial for timely surgical intervention which can improve clinical outcome [31]. In this meta-analysis, TEE proved to have a good sensitivity (86%), and was superior to TTE (36%) for the detection of abscesses or mycotic aneurysms because of superior spatial resolution and the close relationship between the TEE probe and the heart. However, TEE still missed approximately 15% of the life-threatening abscesses and mycotic aneurysms. These missed peri-annular extensions were mainly located at the anterior side of the aortic root which is obscured by acoustic shadowing [13, 16, 21, 27]. In some cases, TTE can have additional diagnostic value in the detection of anterior located abscesses because assessment of this region is not hampered by acoustic

shadowing [27]. In clinical practice, it is unacceptable to miss peri-annular complications of PHV endocarditis. Therefore, complementary non-invasive imaging is required. Also, to decrease the number of false positives (2-7%) with echocardiography, additional non-invasive imaging might be valuable to reduce the risk of unjust exposure to a re-operation.

This meta-analysis demonstrated that MDCT can provide additional relevant diagnostic information in this high-risk patient group and should be considered as a complementary imaging technique to the routine clinical workup (TTE/TEE) especially in patients with suspected aortic PHV endocarditis. Besides MDCT, other imaging tools (3D TEE and FDG-PET/CT) may improve the detection of peri-annular extension. At this moment, no prospective studies are published on the diagnostic value of 3D-TEE for detection of peri-annular complications in patients with PHV endocarditis. This technique could be especially valuable in patients with contraindications for MDCT evaluation mainly because of renal impairment. Recently, Saby et al. [32] prospectively studied the diagnostic accuracy of FDG-PET/CT to diagnose prosthetic heart valve (PHV) endocarditis and to assess the complementary value of PET/CT as a major criterion in the modified Duke criteria in 72 patients with suspected PHV endocarditis. The reference standard was defined as 3 months clinical follow-up (82% of cases) and/or pathological modified Duke criteria (18% of cases). The sensitivity and specificity of FDG-PET for PHV endocarditis was 73% and 80 % respectively. When FDG-PET was added as a new major criterion to the modified Duke criteria, the sensitivity rose from 70 to 97 %. This add-on value of FDG-PET is more or less comparable to the complementary value of MDCT to echocardiography found in this meta-analysis. Moreover, the results of the study of Saby et al. demonstrated that PET/CT missed vegetations in 9/20 (45%) PHV endocarditis cases that did not have any other signs of PHV endocarditis. The authors mentioned in the discussion that FDG-PET/CT had an inferior spatial resolution compared to TEE. This meta-analysis shows that the addition of MDCT to TEE not only may improve the sensitivity for the detection of peri-annular extensions but also for vegetations. Despite the inferior spatial resolution compared to TEE and MDCT, FDG-PET/CT provides additional metabolic information which can be of value to differentiate between active inflammation or not. However, no reference values for FDG-uptake around PHV's are present and therefore specificity is a concern [33]. Besides signs of PHV endocarditis, FDG-PET-CT can detect extra-cardiac infectious foci which can be relevant for patient management (i.e. splenic abscess). Therefore, it is even suggested to combine contrast-enhanced MDCT and FDG-PET to determine treatment strategy [34]. More prospective studies are required to determine the exact value and position in the diagnostic algorithm of the above-mentioned additional diagnostic modalities.

Limitations

This systematic review and meta-analysis has some limitations. Firstly, in the majority of the studies a selected population was examined namely a surgically explored group. Therefore, the data provided in this meta-analysis (PHV endocarditis) can not be simply extrapolated to individual patients with suspicion on PHV endocarditis. Furthermore, patients with negative imaging findings will often not undergo re-operation and therefore this specific patient category was often not included in the data analysis in many studies. This paper advocates for more prospective diagnostic cross-sectional studies which are required to determine the exact value of novel non-

invasive imaging modalities (3D-TEE, MDCT and FDG-PET/CT) in patients with suspected PHV endocarditis. Secondly, the exact location of missed peri-annular complications and the sort of TEE probe used (mono/bi/multiplane) was not provided in many studies. Therefore, meta-regression could not be performed for these covariates. Thirdly, the time interval between index test and reference standard was not reported or too long in a considerable part of the studies. Time interval is crucial for the reliability of diagnostic accuracy measures. At last, limited MDCT data were available (n=50). This resulted in large confidence intervals for the pooled estimates of MDCT + TEE. More prospective MDCT studies are required to confirm the promising findings of this meta-analysis.

CONCLUSIONS

TEE has a good sensitivity and specificity to establish the diagnosis PHV endocarditis and detect complications associated with high mortality. However, TEE still misses a substantial number of PHV endocarditis signs. MDCT in addition to echocardiography may improve diagnostic accuracy in patients with suspected PHV endocarditis, especially for life-threatening peri-annular extensions requiring urgent re-operation. Further prospective studies are required to determine the diagnostic value and position in the diagnostic algorithm of novel additional imaging modalities (3D TEE, MDCT and FDG-PET/CT).

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CHAPTER 3

CARDIAC COMPUTED TOMOGRAPHY ANGIOGRAPHY RESULTS IN DIAGNOSTIC AND THERAPEUTIC CHANGE IN PROSTHETIC HEART VALVE ENDOCARDITIS

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ABSTRACT

Purpose: Echocardiography may miss prosthetic heart valve (PHV) endocarditis which advocates for novel imaging techniques to improve diagnostic accuracy and patient outcome. The purpose of this study was to determine the complementary diagnostic value of cardiac computed tomography angiography (CTA) to the clinical routine workup including transthoracic and transesophageal echocardiography (TTE/TEE) in patients with suspected PHV endocarditis and its impact on patient treatment.

Methods: A diagnostic prospective cross-sectional study was chosen as design. Besides clinical routine workup (including TTE/TEE), CTA was performed to assess its diagnostic accuracy and complementary diagnostic/therapeutic value. For the diagnostic accuracy, the reference standard was surgical findings or clinical follow-up. To determine the complementary diagnostic/therapeutic value an expert-panel was used as reference standard.

Results: Twenty-eight patients were included. CTA resulted in a major diagnostic change in six patients (21%) mainly driven by novel detection of mycotic aneurysms by CTA. Furthermore, treatment changes occurred in seven patients (25%) compared to clinical routine workup. Diagnostic accuracy of routine clinical workup plus CTA was superior to clinical routine workup alone for the detection of PHV endocarditis in general, vegetations and peri-annular extension.

Conclusion: This study demonstrates that CTA and clinical workup including TTE and TEE are complementary in patients with PHV endocarditis. Therefore, CTA imaging has to be considered after clinical routine workup in patients with a high suspicion on PHV endocarditis.

INTRODUCTION

Prosthetic heart valve (PHV) endocarditis is a life-threatening disease with an incidence of 0.3-1.2% per patient year [1]. Patients can present with a broad spectrum of symptoms such as fever, sepsis, heart failure symptoms, new or changing murmur or signs of systematic embolization but may be absent. Therefore, PHV endocarditis is a difficult diagnosis to establish based on these clinical symptoms alone. The modified Duke criteria [2], in which echocardiography plays a key role, are used to establish a definite or possible diagnosis of PHV endocarditis. The two major Duke criteria are positive blood cultures and a positive echocardiogram for signs of PHV endocarditis [2]. The first criterion is often negative (23%-37%) in patients with definite PHV endocarditis [3-5]. For that reason, reliable echocardiography is even more important to establish the definite diagnosis in patients with suspected PHV endocarditis.

Non-invasive transthoracic echocardiography (TTE) is the first line imaging modality to detect signs of PHV endocarditis. However, TTE often fails to detect vegetations, novel or increased paravalvular regurgitation and mycotic aneurysms/abscesses as signs of PHV endocarditis [3, 4, 6]. After TTE imaging, semi-invasive transesophageal echocardiography (TEE) is routinely performed. TEE has a good sensitivity and specificity but still misses life-threatening complications such as mycotic aneurysms and abscesses in upto 30% of patients [3-5, 7-15]. This is mainly caused by acoustic shadowing of the PHV which obscures adjacent anatomical structures and hampers diagnostic assessment. These mycotic aneurysms and abscesses are not rare (53-55%) in patients with PHV endocarditis and are associated with a high mortality (30-54%) [4, 9]. The detection of these life-threatening mycotic aneurysms and abscesses with non or semi-invasive imaging is therefore crucial to initiate timely surgical intervention in order to improve clinical outcome [16].

Cardiac computed tomography angiography (CTA) is a promising novel non-invasive imaging technique to evaluate patients with (suspected) PHV endocarditis [7, 17-19]. At present, no clinical studies are available which investigate the complementary diagnostic value of CTA in patients with suspected PHV endocarditis and its implications for treatment strategy. The aim of this study was to determine the complementary diagnostic value of cardiac CTA to the clinical routine workup (including TTE and TEE) in patients with suspected PHV endocarditis and its implications on treatment strategy.

METHODS

Study design

A prospective diagnostic cross-sectional study was designed in the tertiary setting. This study has been approved by the institutional review board (IRB) [IRB number 10-008] and informed consent was obtained from all patients.

Study population

From May 2010 until July 2012, patients aged 18 years or older with suspected PHV endocarditis were enrolled. PHV endocarditis was suspected on the basis on clinical symptoms, physical examination, electrocardiogram and laboratory testing. These patients were referred for TTE and TEE to detect signs of PHV endocarditis. Patients who underwent both TTE and TEE as part of the routine clinical work-up were eligible for inclusion. Six patients with renal impairment (glo-

Table 1 Study population

Twenty-eight patients			
Age		63±13	
Gender (male)		22 (79%)	
PHV position		Aortic Mitral Aortic and mitral	24 (86%) 3 (11%) 1 (4%)
PHV type		Mechanical Biological	18 (64%) 10 (36%)
Initiated antibiotic treatment before clinical presentation		9 (32%)	
Fever		20 (71%)	
Systolic / diastolic blood pressure		129±20 mmHg / 70±11 mmHg	
Heart rate		80±19 beats per minute	
New murmur		6 (21%)	
Endocarditis stigmata		2 (7%)	
Congestive heart failure		6 (21%)	
Systematic embolization		8 (29%)	
Creatinine		97 (81-111)	
GFR (ml/min)		45-60 >60	5 (18%) 23 (82%)
Leucocyte count		9.7 (7.3-13.1)	
C-reactive protein		76 (45-135)	
Blood culture positive		16 (57%)	
Micro-organism		Streptococcus (pneumoniae/mitis/viridans/oralis/bovis) Staphylococcus aureus Staphylococcus epidermidis Proprioni Enterococcus faecalis	5 (31%) 3 (19%) 4 (25%) 2 (13%) 2 (13%)
Sepsis		12 (43%)	
Novel atrioventricular block		6 (21%)	
Suspicion of PHV endocarditis	early late	9 (32%) 19 (68%)	
Definite Duke criteria met		17 (61%)	

GFR = glomerular filtration rate; PHV = prosthetic heart valve

merular filtration rate (GFR) <45) were excluded. After obtaining informed consent, additional CTA imaging was performed in twenty-eight patients.

Study population characteristics

The following patient characteristics were prospectively collected: age, gender, the presence of fever, congestive heart failure, sepsis, systemic embolization to vital organs and initiated antibiotic treatment before clinical presentation. Further, PHV characteristics (PHV position, type of prosthesis and date of implantation) were collected. Physical examination was performed during clinical presentation and the following parameters were collected: blood pressure, heart rate, and the presence of endocarditis stigmata and new or changed murmur on auscultation. Laboratory testing included blood culture testing, C-reactive protein level, leukocyte count, creatinine and GFR. The electrocardiogram at clinical presentation was assessed for new AV-blocks.

Transthoracic and transoesophageal echocardiography

TTE and TEE was performed with state-of-the-art probes and image acquisition was performed

according the clinical guidelines [1, 7, 20]. Echocardiographic evaluation focused on the detection of signs of PHV endocarditis: vegetations, new or increased paravalvular leakage, mycotic aneurysms or abscesses and PHV dehiscence. These signs were defined according to the ESC guidelines as follows: (1) vegetations, defined as irregularly shaped, oscillating or non-oscillating masses, adherent to and distinct from the myocardium; (2) abscesses, defined as irregularly shaped, inhomogeneous paravalvular enclosed masses within the periannular region, myocardium or pericardium; (3) mycotic aneurysms or pseudoaneurysms were defined as echo-free perivalvular cavities with flow communicating with the cardiovascular lumen; and (4) paravalvular leakage, defined as blood flow outside the PHV ring with or without rocking motion.

Cardiac Computed Tomography Angiography

CT acquisition

CTA was preferably performed within three days after TEE. Patients underwent CTA imaging preferably on a 256-slice CT system or alternatively on a 64-slice system (iCT and Brilliance 64, respectively, Philips Medical Systems, Cleveland, Ohio). After a scout view, a unenhanced prospectively ECG-triggered acquisition of the PHV region only was performed with the following acquisition parameters: 120kV, 30mAs, collimation 128x0.625, gantry rotation time 270 ms and pitch 0 for the 256-slice CT system. The acquisition parameters for the 64-slice CT system were: 120kV, 55mAs, collimation 64x0.625, gantry rotation 0.40 and pitch 0. Data were reconstructed (slice thickness 0.9mm, increment 0.45) for the 75% phase of the ECG-interval with filtered back projection. Subsequently, a contrast-enhanced retrospectively ECG-gated CT acquisition was performed with the following parameters: 120kV, 600-700mAs, collimation 64 or 128x0.625, gantry rotation time 420 or 270-330 ms and pitch 0.20 or 0.16-0.18. Gantry rotation time and pitch were dependent on heart rate.

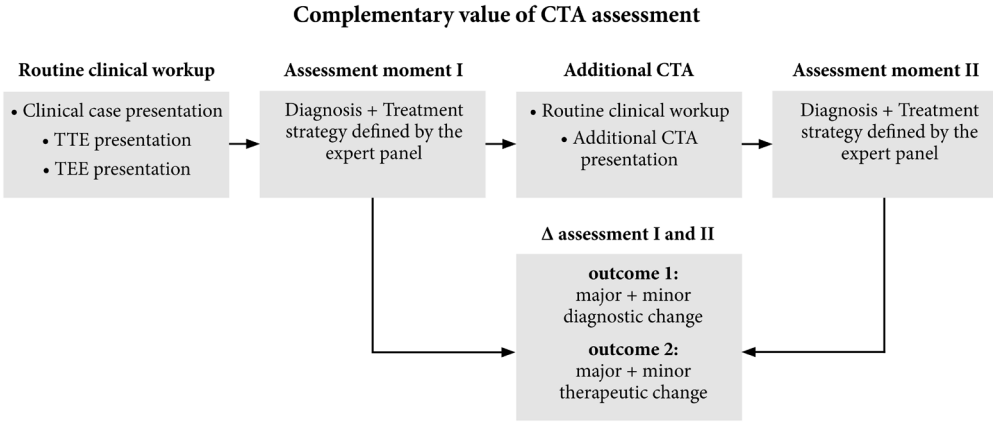
A dual (400mg jopromide/ml) or triphasic (300ml jopromide/ml) contrast administration protocol was used. A locator was placed in the descending aorta. When the threshold of 100 HU was reached, data acquisition was initiated after a post-threshold delay of 8 seconds. The mean flow rate was set to 5.0-6.7cc/second. Total contrast volume for the triphasic injection protocol was dependent on patient body weight (BW), scan duration and the added delay. Iodine flow varied between 1.6 (BW<70kg), 1.8 (BW 70-85kg) and 2.0 gram (BW>85kg) iodine/sec. In the first phase, only contrast medium was injected. Secondly, a mixture of 30% contrast medium and 70% saline is administered followed by a saline flush. For the dual phase injection protocol, 100cc contrast was followed by a saline flush. Added delay varied between 6-8 seconds. The effective radiation dose was estimated from the product of the total dose-length product indicated by the scanner (including all parts of image acquisition) and a conversion coefficient (k= 0.0145mSv/[mGyx cm]) [21].

Image reconstruction

Data were reconstructed (slice thickness 0.9mm, increment 0.45) equally spaced for each 10% interval of the ECG-interval resulting in 11 datasets (including an additional 75% ECG-phase). Images were transferred to a clinical workstation and analyzed using dedicated software (Extended Brilliance Workstation, Philips Medical Systems, Philips, Best, the Netherlands). Diastolic and systolic imaging data sets were reconstructed in orthogonal imaging planes (in plane, parallel and

perpendicular to the prosthetic valve) and used for image evaluation. Additional reconstructions similar to the standard echocardiographic views were reconstructed if needed as well from the same CT datasets. During analysis, it is important to differentiate between vegetations and beam-hardening artefacts because both are hypodense. However, artefacts and vegetations can be differentiated based on the fact that vegetations are often oval and irregular circumscribed hypodense abnormalities and beam hardening artifacts are linear within the direction of the beam.

Figure 1: Flowchart of Study Design



TTE = Trans Thoracic Echocardiography. TEE = Trans Esophageal Echocardiography. CTA = Computed Tomography Angiography. Δ = difference

Reference standard and outcome measures

Complementary value of cardiac CTA to clinical routine workup

An expert panel was used to determine the additional diagnostic value of cardiac CTA and its impact on treatment strategy (Figure 1). The expert-panel consisted of two cardiac surgeons, two cardiologists and two radiologists with an interest in PHV imaging. In the expert-panel consensus meeting, each case was presented in the following sequence: (1) clinical routine workup (clinical history, physical examination, laboratory testing, TTE and TEE) and followed by (2) the cardiac CTA examination. After each of the two assessment moments, the expert panel determined a consensus on the diagnosis and treatment strategy (Figure 1). A standardized scoring form was used. The primary outcome measures were (1) the complementary diagnostic value of CTA to clinical workup in patients with suspected PHV endocarditis and (2) its impact on treatment strategy. Major and minor diagnostic changes caused by CTA were distinguished. Major diagnostic change was defined as the novel detection of a vegetation or abscess/mycotic aneurysm by CTA. In case of abscesses and/or mycotic aneurysms absent on echocardiography, a major diagnostic change was scored if CTA detected an abscess or mycotic aneurysm. Minor diagnostic change was defined as detection of an increased number and/or size of peri-annular extensions (mycotic aneurysms/abscesses) or better depiction of the relationship of the peri-annular extension with relevant cardiac structures such as coronary arteries compared to clinical routine workup. A major treatment strategy change based on CTA was defined as conversion from conservative to surgical treatment

or visa versa. Minor treatment strategy change was defined as change of surgical strategy (i.e. aortic valve replacement vs. aortic allograft implantation).

Diagnostic accuracy

The diagnostic accuracy was determined for PHV endocarditis in general, vegetations and peri-annular complications (mycotic aneurysms/abscesses). PHV endocarditis in general was defined as any positive imaging sign of PHV endocarditis (vegetations, new or increased paravalvular leakage and peri-annular complications). Vegetations and peri-annular complications were defined in the echocardiography section. The reference standard used to determine diagnostic accuracy were surgical, microbiological and/or pathological findings or in patients treated conservatively clinical follow-up (at least one month). Successful conservative treatment was defined as uncomplicated clinical follow-up with unchanged TTE examination. Diagnostic accuracy was determined for the clinical routine workup (including both TTE and TEE) and clinical routine workup plus CTA.

Data-analysis

Data analysis was performed in SPSS software (version 15). Continuous variables are presented as means ± standard deviation (SD) or medians and interquartile range (IQR) dependent on the data distribution. Parametric data distribution was assessed with QQ-plots and Kolgomorov-Smirnov test. Categorical variables are presented in numbers (percentages). Diagnostic and therapeutic changes are expressed in numbers and percentages. Diagnostic accuracy measures (sensitivity, specificity, positive and negative predictive values) including 95% confidence intervals (CI) were calculated.

RESULTS

Patient population

Twenty-eight patients with a high suspicion of PHV endocarditis were included in this prospective diagnostic cross-sectional study. Relevant study population characteristics are given in Table 1. In this study population with a high suspicion of PHV endocarditis, blood cultures were positive in 16 (57%) patients and the modified Duke criteria were met in 17/28 (61%) patients. Cardiac CTA examinations were performed on 256-slice (n=26) and 64 –slice CT systems (n=2). Median radiation exposure was 11.8 mSv (IQR 11.2-12.8). The diagnosis of the clinical routine workup (including both TTE and TEE) and clinical routine workup plus CTA is presented per patient in Table 2. Median interval between TEE and CTA was 0 days (IQR 0-1 day, range 0-17 days). In this population, 16 of the 28 patients (57%) underwent reoperation and these patients were positive according to the modified Duke criteria in 11 (69%) of the cases. Median interval between cardiac CTA and reoperation was 14 days (IQR 6-70). The other twelve (43%) patients, who were Duke positive in 50% of the cases, were treated successfully with antibiotics. In the study population, the median clinical follow-up was 5.5 (IQR 3-9) months with 89% (n=25) endocarditis free survival. One patient (number 24, Table 2) (4%) died in hospital after surgical treatment. Two patients (number 22/28, Table 2) had recurrence of PHV endocarditis in the re-operated group: one patient was re-operated twice and one patient was treated successfully with antibiotics.

Table 2 Major and minor diagnostic change after MDCT examination

PID	Diagnosis Clinical workup (including TTE/TEE)	Diagnosis Clinical workup (including TTE/TEE/MDCT)	Major diagnostic change	Minor diagnostic change	Additional diagnostic value MDCT	Surgical confirmation / AB
1	Multiple mycotic aneurysm RCC+NCC	Multiple mycotic aneurysms RCC+NCC	-	Yes	Better depiction extensiveness mycotic aneurysm, former RCC	Yes
2	Single mycotic aneurysm RCC	Single mycotic aneurysm, RCC	-	Yes	MDCT depicted calcifications in aneurysm wall (old origin)	AB
3	Single mycotic aneurysm NCC/LCC	Single mycotic aneurysm NCC/LCC	-	Yes	Better depiction extensiveness mycotic aneurysm, former NCC	Yes
4	No abnormalities	No abnormalities	-	-	-	AB
5	Single mycotic aneurysm NCC	Single mycotic aneurysm NCC	-	-	-	No**
6	Single mycotic aneurysm RCC	Multiple mycotic aneurysms RCC	-	Yes	Better depiction extensiveness mycotic aneurysm, former RCC	Yes
7	Paravalvular leakage due to endocarditis	Paravalvular leakage due to single mycotic aneurysm RCC	Yes	-	Mycotic aneurysm, former RCC	Yes
8	Vegetation	Vegetation Single mycotic aneurysm RCC	Yes	-	Mycotic aneurysm, former RCC	Yes
9	Paravalvular leakage due to endocarditis	Paravalvular leakage due to endocarditis	-	-	-	AB
10	No abnormalities	No abnormalities	-	Yes	Discrimination between mycotic aneurysm, former NCC and deep sinus	AB
11	Single mycotic aneurysm NCC	Single mycotic aneurysm NCC	-	-	-	AB
12	Paravalvular leakage due to endocarditis	Paravalvular leakage due to single mycotic aneurysm LCC	Yes	-	Mycotic aneurysm, former LCC	Yes
13	Single mycotic aneurysm NCC	Multiple mycotic aneurysms RCC+NCC	-	Yes	Mycotic aneurysm, former RCC	Yes
14	No abnormalities	No abnormalities	-	-	-	AB
15	Paravalvular leakage	Paravalvular leakage	-	-	-	AB
16	No abnormalities	No abnormalities	-	-	-	AB
17	Vegetation	Vegetation Single mycotic aneurysm LCC	Yes	-	Mycotic aneurysm, former LCC	Yes
18	Pathological valvular leakage	Pathological valvular leakage Vegetation	Yes	-	Vegetation	Yes
19	Single mycotic aneurysm RCC	Single mycotic aneurysm RCC	-	Yes	Better depiction extensiveness mycotic aneurysm, former RCC	AB
20	No abnormalities	Vegetations	Yes	-	Vegetations	AB
21	Paravalvular leakage due to single mycotic aneurysm	Paravalvular leakage due to single mycotic aneurysm	-	Yes	Better depiction extensiveness aortic root mycotic aneurysm	Yes
22	Single mycotic aneurysm NCC	Multiple mycotic aneurysms NCC supra/subvalvular	-	Yes	Better depiction extensiveness mycotic aneurysm, former NCC	Yes
23	Vegetation	Vegetation	-	-	-	AB
24	Two abscesses* LCA	Multiple mycotic aneurysms RCC	-	Yes	Mycotic aneurysm, former RCC	Yes
25	Vegetation	Vegetation	-	-	-	AB
26	Single mycotic aneurysm NCC	Multiple mycotic aneurysms NCC+RCC	-	Yes	Better depiction extensiveness mycotic aneurysm, former RCC	Yes
27	Single abscess* NCC	Vegetation	-	Yes	Vegetation	Yes
28	Vegetation Single mycotic aneurysm NCC	Vegetation Multiple mycotic aneurysm NCC+LCC	-	Yes	Better depiction extensiveness mycotic aneurysm	Yes
			6/28 (21%)	13/28 (46%)		

* missed by MDCT; ** Surgical exploration did not confirm the presence of the mycotic aneurysm detected both by TEE and MDCT

AB = antibiotic treatment; LCA = left coronary artery; LCC = left coronary cusp; MDCT = multidetector computed tomography; NCC = non-coronary cusp; PID = patient id; RCC = right coronary cusp; TTE = transthoracic echocardiography; TEE = transesophageal echocardiography.

Complementary value of cardiac CTA to clinical routine workup

Diagnostic change

In six out of the 28 (21%) patients, CTA resulted in a major diagnostic change which was confirmed by surgical exploration in five (83%) patients. The other patient (number 20, Table 2) was treated successfully with antibiotics. These major diagnostic changes included detection of four additional mycotic aneurysms (RCC *n*=2; LCC *n*=2) and two vegetations. MDCT imaging also provided information that resulted in minor additional diagnostic changes in 13/28 (46%) patients (Table 2).

Treatment strategy change

The treatment strategy changed after CTA compared to clinical routine workup in 7 out of 28 (25%) patients. In one patient (number 17, Table 2), CTA detected a large mycotic aneurysm (former LCC, which was missed by clinical routine workup. This changed the treatment strategy from intravenous antibiotic treatment to urgent surgical exploration with implantation of an allograft and therefore was classified as major treatment change. In the other six patients, only the surgical strategy changed (minor treatment change): additional aortic root surgery instead of only PHV replacement (allograft in 3, Bentall procedure in 2 and addition of a pericardial patch in 1).

Diagnostic accuracy

In Supplement 1 and 2, diagnostic accuracy data for PHV endocarditis in general, vegetations and peri-annular complications (mycotic aneurysm/abscesses) are presented.

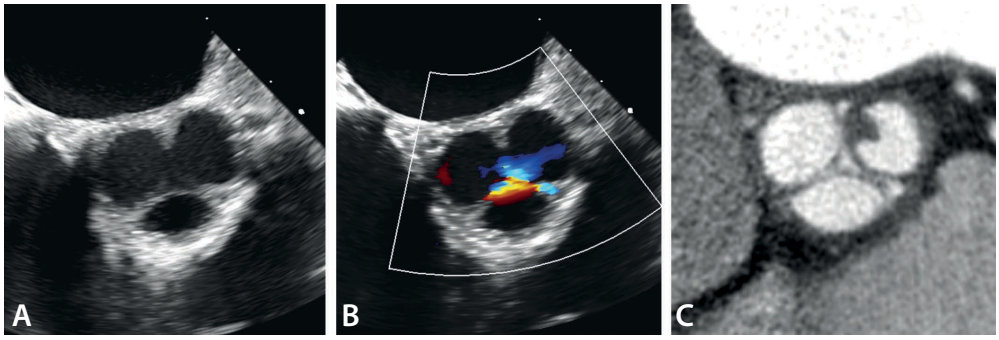
PHV endocarditis in general

Sensitivity and specificity for PHV endocarditis in general were 95% and 83% for the routine clinical workup (including TTE/TEE). For clinical routine workup plus CTA, sensitivity and specificity for PHV endocarditis in general increased to 100% and 83%, respectively. In the false positive patient (number 5, Table 2), routine workup and the routine workup plus CTA detected one mycotic aneurysm located at the former NCC that was not confirmed during surgical exploration. In the other 15 re-operated patients (94%), imaging findings were confirmed by surgical exploration. In one patient (number 18, Table 2), the routine workup missed a vegetation which was detected by MDCT and confirmed at surgery (Table 2). However, time interval between TEE and MDCT was 17 days in this patient.

Vegetations

Sensitivity and specificity for the detection of vegetations were 63%/100% for clinical routine workup and 100%/100% for clinical routine workup plus CTA, respectively. Echocardiography missed three vegetations in patients with biological (*n*=2, Figure 2) and mechanical PHV's (*n*=1). In one patient (number 20,) surgical exploration was not performed (Table 2).

Figure 2: Detection of a vegetation by MDCT



*Patient 20 with an allograft in the aortic position. The short axis TEE view demonstrated a tricuspid aortic valve with central mal-coaptation and no evidence of a vegetation (**A**). Color doppler imaging (**B**) revealed a moderate central aortic regurgitation. The short axis MDCT image demonstrated a vegetation on left coronary cusp(**C**)*

Peri-annular complications

Eighteen patients had 26 peri-annular complications (mycotic aneurysms *n*=23; abscesses *n*=3) (Table 2). Sensitivity and specificity were 68%/91% for the clinical workup and 100%/91% for the clinical workup plus CTA, respectively. Routine clinical workup missed eight mycotic aneurysms mainly located around former RCC (*n*=5) which were correctly detected by CTA (Figure 3). However, CTA also missed three abscesses which were detected by TEE and confirmed by surgery located around the left coronary artery (Figure 4) and non-coronary cusp in two patients (number 24/27, Table 2). The clinical workup (including TTE and TEE) detected all abscesses and CTA detected all mycotic aneurysms resulting in a total sensitivity of 100% combining all imaging modalities.

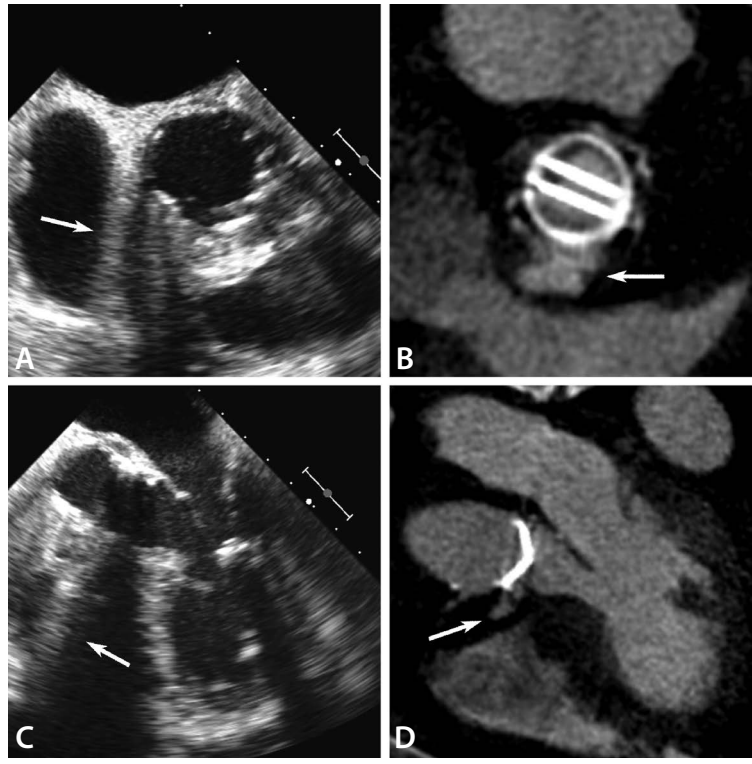
DISCUSSION

Our study demonstrates the additional diagnostic value of cardiac CTA to clinical routine workup (including TTE and TEE) and its impact on treatment strategy. Furthermore CTA detected all mycotic aneurysms (*n*=8) that were missed by echocardiography, whereas echocardiography detected all abscesses (*n*=3), which were missed by CTA. CTA also provided additional diagnostic information on the extensiveness of the mycotic aneurysms that was valuable for the surgical planning.

Complementary value of cardiac CTA to clinical routine workup

Cardiac CTA imaging resulted in a major diagnostic change compared to the routine clinical work-up in 21% of patients and resulted in a change of treatment strategy in 25% of patients: in one patient it converted medical treatment to urgent surgery and in six others it changed the surgical strategy. Besides treatment strategy change, cardiac CTA can provide in patients considered for reoperation additional information on the presence of coronary artery disease, the presence and location of coronary bypassgrafts, calcifications in the ascending aorta (cross-clamping) and the relationship between coronary arteries and peri-annular extension. Most PHV types do not

Figure 3: Mycotic aneurysm located near the former right coronary cusp



*Patient 8 with a mechanical bileaflet St Jude PHV in the aortic position. Assessment of the former right coronary cusp is hampered by acoustic shadowing (arrows) in the short axis TEE view (**A**) and 0 degree TEE view (**C**). Short axis (**B**) and 0 degree MDCT (**D**) images are not hampered by valve-related artifacts and visualized a mycotic aneurysm (arrows).*

hamper coronary assessment [22]. In patients with sufficient image quality of coronary arteries invasive conventional coronary angiography may be omitted.

Diagnostic accuracy

In this study, this clinical workup had a good sensitivity/specificity (95%/83%) to establish the diagnosis of PHV endocarditis mainly in patients with aortic PHV's (*n*=25). This is in line with previous publications [4-6, 23, 24]. Sensitivity raised to 100% after addition of a complementary CTA examination. In three patients, clinical routine workup missed the vegetation which was detected by CTA. However, in two of these three patients the predefined time interval (≤3 days) from clinical workup to CTA was exceeded. In the subgroup analyses without these two patients, the sensitivity of the clinical routine workup increased substantially from 63% to 83% for the detection of vegetations. However, the sensitivity of the clinical routine workup plus CTA remained 100% in this group.

In PHV endocarditis is the detection of peri-annular complications of paramount importance as it is with a high mortality compared to uncomplicated PHV endocarditis and requires surgical

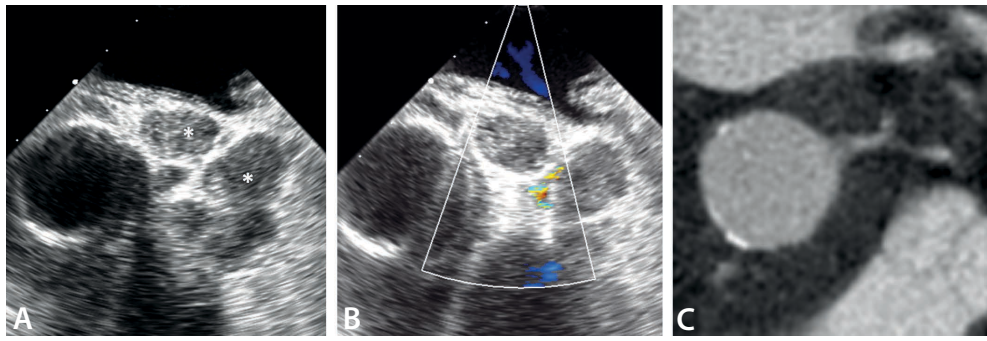
treatment. Our study shows that for the detection of peri-annular complications clinical workup and cardiac CTA are complementary. Echocardiography detected all abscesses (*n*=3) which were missed by CTA. The reason for the false negative CTA findings is probably the absence of contrast in enclosed masses (e.g. abscesses). In retrospect, aspecific aortic wall thickening was present on the abscess locations detected with echocardiography. In contrary, CTA detected all mycotic aneurysms (*n*=8) that were missed by echocardiography. Importantly this was the first and only sign of peri-annular extension in four patients resulting in a major diagnostic change (Table 2). The mycotic aneurysms missed by echocardiography in patients with aortic PHV's were mainly located in the former RCC region (anterior side of aortic root). Diagnostic assessment of this region is often hampered by acoustic shadowing during TEE examination. The complementary approach (combining echocardiography and CTA) did not fail to identify peri-annular complications and had therefore a sensitivity of 100% in the detection of complicated PHV endocarditis.

Previous studies on the value of cardiac CTA in the evaluation of PHV endocarditis are scarce [7, 19]. Fagman et al. compared CTA to TEE in twenty-seven patients with aortic PHV endocarditis [19]. Sixteen patients underwent surgical exploration. In contrast to our study, the conservatively treated group (*n*=11) was not included in the analysis resulting in a selection bias. This study also found that cardiac CTA and TEE are complementary in the detection in peri-annular extension. However, Fagman et al.[19] did not examine the complementary value of cardiac CTA to the normal clinical routine workup but compared CTA to TEE (replacement design). Furthermore, this study provided no insights on treatment strategy change in patients with PHV endocarditis. Feuchtner et al.[7] evaluated the value of CTA in a small patient population (*n*=6) with suspected PHV endocarditis. This study also compared CTA to TEE instead of using an add-on design. Furthermore, in this study also only re-operated patients were included resulting in a selection bias. This study found that CTA better depicted the extensiveness of mycotic aneurysms which is in line with our results.

Limitations

First, twelve patients did not undergo surgical exploration. However, in the non-operated patients clinical follow-up data was collected. This is the methodology to analyze the clinically relevant suspected population. Second, median interval (14 days) between imaging and surgical reoperation was relatively long. However, no novel pathological findings were found during surgical exploration. Third, CTA evaluation has some disadvantages namely radiation exposure and administration of iodinated contrast agents. In this patient population with concomitant high mortality and morbidity, these risks are defendable. Fourth, five potential study participants were not enrolled because of renal impairment (GFR<45) and is important for the clinical implementation of CTA in patients with suspected PHV endocarditis. At last, a relatively small number of patients (*n*=28) were included resulting in large confidence intervals for diagnostic accuracy measures.

Figure 4: Abscess formation in PHV endocarditis



*Patient 24 with a bileaflet mechanical St Jude PHV in the aortic position. A short axis TEE supravalvular view demonstrated two echolucent cavities (*) around the left coronary artery without color flow (**B**) suggestive for abscess formation. The color flow is present in the left coronary artery. Short axis supravalvular MDCT image demonstrates aortic wall thickening as a aspecific sign of aortitis but did not visualize the abscesses. The two abscesses were confirmed during surgical exploration.*

CONCLUSION

This study demonstrates that cardiac CTA and clinical workup including TTE and TEE are complementary to establish the diagnosis of PHV endocarditis and to detect peri-annular complications. Cardiac CTA imaging resulted in a major diagnostic change compared to the routine clinical work-up in 21% of patients and results in a change of treatment strategy in 25% of patients, Therefore, we advise to include cardiac CTA imaging in the diagnostic work-up of every patient with suspected PHV endocarditis.

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CHAPTER 4

FUSION OF CARDIAC COMPUTED TOMOGRAPHY ANGIOGRAPHY AND 18F-FLUORODESOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY FOR THE DETECTION OF PROSTHETIC HEART VALVE ENDOCARDITIS

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ABSTRACT

Background: Signs of prosthetic heart valve (PHV) endocarditis can be missed with transthoracic and transesophageal echocardiography (TTE and TEE). Diagnostic accuracy may be improved by adding computed tomography angiography (CTA) or 18F-fluorodesoxyglucose positron emission tomography including low dose CT (FDG-PET/CT). The aim of this study is to investigate the role of fused/combined imaging with CTA and FDG-PET/CT in PHV endocarditis cases, and to determine the normal FDG uptake values around non-infectious PHV's as these are not known.

Methods: A retrospective analysis was performed on 33 PHV patients that underwent echocardiography, CTA and FDG-PET/CT for PHV analysis. Patients were divided into three groups: PHV endocarditis cases (group A; n=15); control patients with normal PHV's that underwent imaging between 1-4 months (group B; n=9) or ≥ 4 months (group C; n=9) after PHV implantation. Diagnostic results of CTA and/or FDG-PET/CT imaging were compared to TTE/TEE results, surgical findings and clinical follow-up. Standardized uptake value (SUV) ratios, defined as the maximal FDG uptake around the PHV ring divided by the mean uptake in the descending aorta, were acquired for FDG-PET/CT scans in cases and controls.

Results: Group A: 14/15 PHV endocarditis cases had peri-annular extension and 7/15 had a vegetation, all confirmed by surgical inspection. FDG-PET/CT detected all peri-annular extensions correctly but missed all vegetations. After fusion with CTA all vegetations were also detected correctly. Compared to TTE/TEE fused imaging was of additional value in 8/15 PHV cases with surgery as reference standard. Group B/C: All controls (except one) were free of significant FDG uptake. The one false positive FDG-PET/CT was observed in a patient with a pericardial patch. SUV ratios around the PHV ring were significantly ($p<0.001$) higher in PHV peri-annular extension cases (group A); 4.2 (IQR 3.8-5.3) compared to controls (group B+C); 2.0 (IQR 1.8-2.3). Additionally, extra-cardiac infections were found by FDG-PET/CT in 10/33 patients.

Conclusion: Fused FDG-PET/CT and CTA imaging is a promising tool for the correct detection of signs of PHV endocarditis, even early after implantation. A SUV ratio of > 2.5 appears to be a reasonable cut-off value to detect peri-annular extension in PHV endocarditis.

INTRODUCTION

Prosthetic heart valve (PHV) endocarditis is a feared potentially life-threatening complication that occurs with an incidence of 0.3-1.2% per patient year [1]. In PHV endocarditis the incidence of peri-annular extension (abscesses/mycotic aneurysms) is approximately 50%, which has a hospital mortality of 30%, rising to 50% when Staphylococcus Aureus is involved [2-6]. Early detection is crucial since these complications have major therapeutic consequences. Uncomplicated PHV endocarditis may sometimes be treated with antibiotics alone, whereas the development of an abscess or mycotic aneurysm is an indication for urgent surgery [7]. Unfortunately, in PHV endocarditis with peri-annular extension the modified Duke criteria are less reliable, because blood cultures often remain negative (23%-37%) [2, 3, 6, 8]. In addition, echocardiography is hampered by acoustic shadowing and reverberations of the PHV and therefore also less reliable. Nevertheless, echocardiography is still considered as the corner stone for diagnosis of endocarditis. Although transesophageal echocardiography (TEE) is superior to transthoracic echocardiography (TTE), it may still fail to detect a peri-annular abscess or mycotic aneurysm in up to 30% of cases [2, 5, 6, 9-13]. Cardiac computed tomography angiography (CTA) is not hampered by acoustic shadowing, but CTA alone can still miss peri-annular complications [14]. Moreover, detection of abnormal peri-annular anatomy (i.e. pseudoaneurysms in the aortic root) after PHV implantation is not uncommon and differentiation between active or absent inflammation by anatomical imaging alone is extremely difficult because of the lack of metabolic information. Addition of 18F-fluorodesoxyglucose positron emission tomography (FDG-PET) may provide this additional metabolic information [15, 16]. A low-dose non-ECG-gated, non-contrast enhanced CT scan is performed in conjunction with the FDG-PET scan for attenuation correction [17]. It provides some anatomical information but for the highly mobile structures of the aortic root and PHV leaflets the temporal resolution is inadequate. As a consequence FDG-PET/CT alone has shown to be sensitive for peri-annular extensions, but vegetations are frequently missed [18]. Fusion of FDG-PET with ECG-gated cardiac CTA results in combined state-of-the-art anatomical and metabolic imaging. This may provide valuable additional information for correct detection of peri-annular extensions *and* vegetations in PHV endocarditis. However, no normal FDG uptake values around PHV rings that are free of endocarditis are known, although theoretically sterile inflammation as part of normal post-operative healing or foreign body immune responses after PHV implantation may result in false positive PET imaging. The aim of this study is to investigate the FDG uptake values around PHV's in PHV endocarditis and to compare these results to the early and chronic post- operative phase for controls free of endocarditis. Moreover, the additional value of this hybrid imaging technique for the detection of signs of PHV endocarditis will be compared to the echocardiography and surgical results (if available), or clinical follow-up.

METHODS

Patient selection:

We performed a retrospective analysis of PHV patients that underwent echocardiography, cardiac CTA and FDG-PET/CT for PHV analysis. Patients were identified by a search performed from January 2011 until September 2013 in the database of the Nuclear Medicine department of the University Medical Center Utrecht. Patients that underwent FDG-PET/CT for PHV analysis were selected. Additional patient information, CTA and TTE/TEE results were also retrieved from the hospital database. Informed consent was not necessary and waived by the Medical Ethical Committee since diagnostics were all performed on clinical grounds in this retrospective analysis. In addition, we included 7 patients that participated in a prospective study to investigate the normal FDG uptake after PHV implantation in patients with no suspicion for endocarditis. The study protocol for this prospective study was approved by the local Medical Ethical Committee. These 7 patients all provided written informed consent for performing CTA and FDG-PET/CT. Patients were divided into three groups: Group A consisted of PHV endocarditis cases. Group B consisted of PHV patients free of endocarditis that underwent FDG-PET/CT early after PHV implantion (between 1- 4 months). Group C consisted of PHV patients free of endocarditis that underwent FDG-PET/CT late after PHV implantion (≥ 4 months). PHV endocarditis (Group A) was defined as; 1.patients fulfilling the modified Duke criteria for endocarditis. 2. patients with signs of PHV endocarditis during surgical inspection. PHV's free of endocarditis (Group B+C) were defined as PHV's in which endocarditis was excluded/not present; 1. an alternative focus of infection was detected or clinical follow-up including laboratory parameters, TTE/TEE and CTA rejected PHV endocarditis. 2. patients not suspected for PHV dysfunction that underwent CTA and FDG-PET/CT for study purposes.

Transthoracic and Transesophageal echocardiography:

All patients underwent two dimensional TTE and TEE (Philips ie33) with modern 1.7-3.2 MHz probes and > 5.0 MHz probes respectively. Evaluations were focused on the detection of signs of PHV endocarditis. Findings as reported by the clinical cardiologists were used for the analysis.

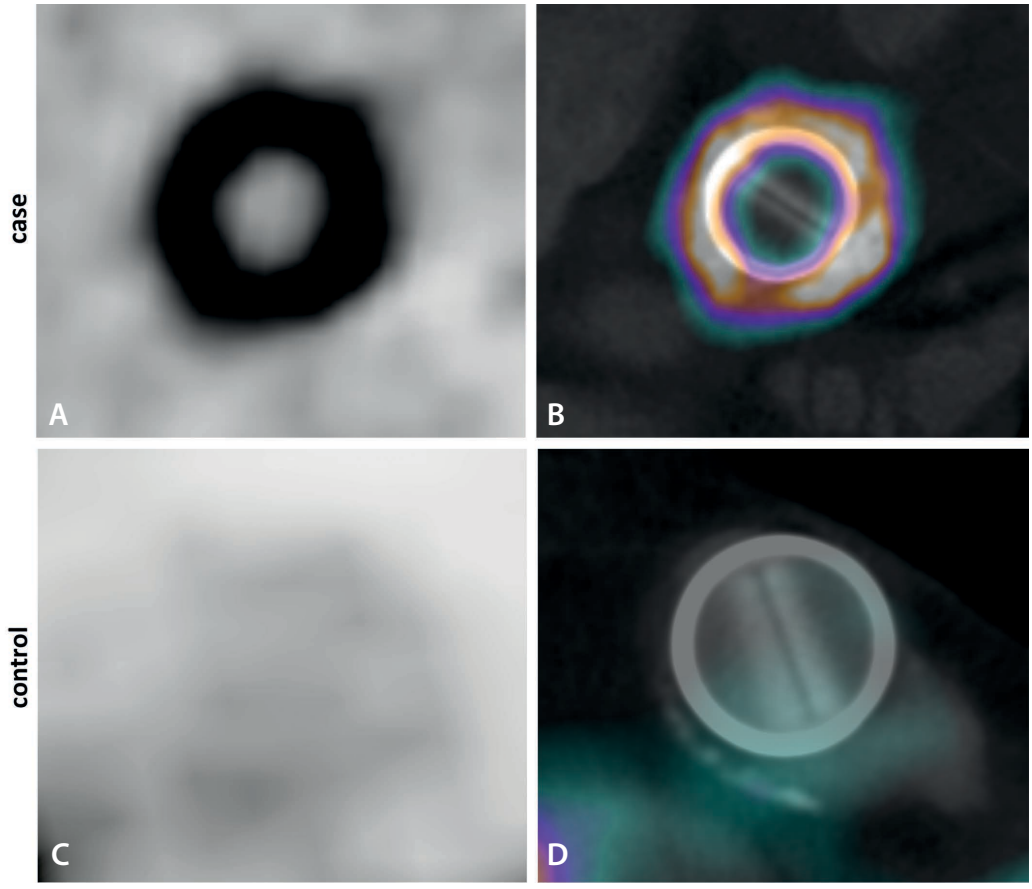
CTA acquisition:

Contrast-enhanced retrospectively ECG-gated or prospectively ECG-triggered acquisition was performed on a 256-slice or dual-source CT system (iCT, Philips Medical Systems or Somatom Flash Siemens) using standard acquisition protocols as used for coronary imaging. Findings as reported by the clinical radiologist were used for the analysis.

18F-Fluorodesoxyglucose Positron Emission Tomography with low dose CT:

FDG-PET/CT was performed after at least 24 hours of low carbohydrate diet (of which the last 12 hours are spent fasting) [17, 19]. Patients received an intravenous injection of FDG at 2.0 MBq/kg of body weight. Patients were hydrated with 1000 milliliters of water 1 hour prior to image acquisition. FDG-PET scans were acquired using a FDG-PET scanner (Siemens Biograph mCT 40-slice, Germany). Approximately 1 hour after FDG injection, the FDG-PET scan was performed. A total-body emission PET scan was obtained with 3-minute acquisitions per bed position using a 3-dimensional acquisition mode. After PET scanning, a low dose CT was performed

Figure 1: Case versus Control



Panel A and B: *Patient 5 with an aortic bileaflet mechanical PHV including Bentall tube implanted 16 months previously and multiple blood cultures positive for Proprionii Bacterium. TTE and TEE did not show abnormalities and modified Duke criteria were not fulfilled. Because of high suspicion of PHV endocarditis, an additional CTA (panel* ***C****) was performed which detected no vegetations, but some aortic wall thickening (8 millimetres, arrows) around the PHV ring. For confirmation purposes an additional FDG-PET was performed (panel* ***B****) showing severe FDG-uptake at the level of the aortic PHV. Widespread peri-annular extension of endocarditis around the whole PHV was detected, which was an indication for urgent surgery. Both CTA and FDG-PET/CT individually made the correct diagnosis as subsequent surgical inspection and pathological examination of the aortic PHV confirmed widespread peri-annular PHV endocarditis and absence of vegetations* ***Panel C and D:*** *No baseline uptake values for PHV's are reported in the literature. Panel* ***C*** *and* ***D*** *however show the FDG-PET alone (****C****) and the fused with CTA (****D****) of a pulmonic PHV without endocarditis (Late control, PHV 16 table 2). Quantitative measurement of the standardized uptake value (SUV) ratios (defined as the maximum SUV value adjacent to the PHV ring divided by the mean SUV value of the blood pool in the descending aorta) may be of additional help for the detection of peri-annular extensions. In the presented control and case SUV ratios were 1.4 (2.2/1.6) and 6.5 (9.7/1.5) respectively*

for attenuation correction. After performing the FDG-PET scan, automatic fusion with the low dose CT was performed with manual repositioning as needed in order to assess FDG-PET uptake around the PHV. Findings as reported by the nuclear physician were used for the analysis.

Combined/Fused CTA and FDG-PET/CT analysis:
In the combined/fused analysis the individual CTA diagnosis for the detection of vegetations was leading as it is known that FDG-PET/CT alone may miss vegetations in a large amount of cases[18]. For the detection of peri-annular extensions the individual FDG-PET/CT diagnosis was leading in the combined/fused analysis.

Scoring FDG-PET uptake after fusion of FDG-PET and CTA:
After fusion of FDG-PET images and CTA (Figure 1), FDG uptake around the PHV was scored by a nuclear physician. Uptake of FDG was scored both qualitatively (none, mild, moderate, severe uptake) and quantitatively using the standardized uptake value (SUV) ratio defined as the maximum SUV value adjacent to the PHV ring divided by the mean SUV value of the blood pool in the descending aorta.

Endpoints and statistics:
The correct detection of peri-annular extension and vegetations by FDG-PET/CT and CTA scans was determined, both individually and after fusion. by comparing them to the reference standard; 1.visual inspection for signs of endocarditis at surgery, 2.clinical follow-up including imaging results (echocardiography and CTA). The additional diagnostic value of fused FDG-PET/CT and CTA compared to TTE/TEE results was determined. Furthermore, median SUV ratios including inter quartile range (IQR) were determined and compared between group A and group B+C. Statistical analysis to determine differences between median SUV ratios for cases and controls was performed by Mann-Whitney U testing. Finally, the percentage of extra-cardiac infectious foci (metastatic and/or primary infections) detected by whole body FDG-PET/CT was determined for cases and controls.

RESULTS

Group A (n=15): consisted of PHV endocarditis cases all confirmed by surgery (Table 1). All cases underwent TTE, TEE, cardiac CTA and FDG-PET/CT before surgery with a time interval from TEE to FDG-PET/CTA of ≤ 3 days in all patients, except for patient 5. This patients admission was complicated by a intracerebral haemorrhage, which was a contra-indication for follow-up TEE's. This resulted in a time interval of 19 days between TEE and FDG-PET/CTA. 14/15 PHV's had a peri-annular extension and 7/15 a vegetation at surgical inspection. All PHV's of cases were in the aortic position including six Bentall prostheses.

Blood cultures were positive in 13/15 (87%) cases and before surgery the modified Duke criteria for definite endocarditis were met in 10/15 (67%) cases. Compared to the reference standard the presence/absence of a vegetation and peri-annular extension was correctly detected after echocardiography (TTE and TEE) in 13/15 (87%) and 7/15 (47%) cases respectively (Table 1). On top of echocardiography all cases underwent CTA. This increased the sensitivity of vegetations from

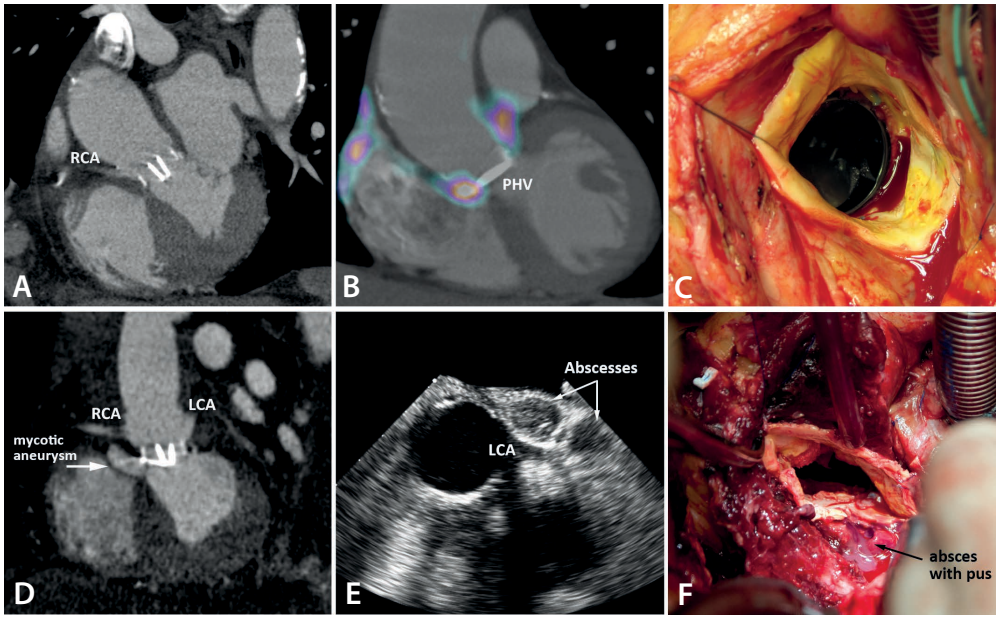
Table 1: PHV endocarditis cases: PHV characteristics, diagnosis on surgical exploration and imaging results for PHV vegetations and extension (peri-annular abscesses and mycotic aneurysms)

Case	PHV type / Months after implan-tation	Blood cultures	Surgical Inspection	TTE+TEE Vegetation Extension	CTA Vegetation Extension	FDG- PET/CT Vegetation Extension	Fused CTA + FDG-PET Vegetation Extension	Additional value of CTA + FDG-PET/CT (Compared to TTE/ TEE)	SUV ratio around PHV ring (SUV max/SUV descending AO)	Extra cardiac infection focus detection by FDG-PET/CT
1	AVR-M Bentall 26	Actino-bacillus	Vegetation + Extension +	Missed Missed	Correct Correct	Missed Correct	Correct Correct	Vegetation and extension detected	7.9 (15.0/1.9)	None
2	AVR-M 238	S.Aureus	Vegetation – Extension +	Correct Missed	Correct Missed	Correct Correct	Correct Correct	Extension detected	4.3 (6.9/1.6)	None
3	AVR-Bio 10	S.Aureus	Vegetation + Extension +	Correct Missed	Correct Correct	Missed Correct	Correct Correct	Extension detected	3.6 (7.5/2.1)	None
4	AVR-M 67	Strepto coccus Pneum.	Vegetation + Extension +	Correct Correct	Correct Correct	Missed Correct	Correct Correct	None	5.1 (9.7/1.9)	Spleen abscess
5	AVR-M Bentall 16	Propionii Bacterium	Vegetation – Extension +	Correct Missed	Correct Correct	Correct Correct	Correct Correct	Extension detected	6.5 (9.7/1.5)	none
6	AVR-M 156	S.Aureus	Vegetation- Extension +	Correct Correct	Correct Correct	Correct Correct	Correct Correct	None	4.0 (8.4/2.1)	Osteomyelitis toe
7	AVR-M 2	None	Vegetation – Extension +	Correct Possible	Correct Possible	Correct Correct	Correct Correct	Confirmation of extension	3.8 (7.2/1.9)	None
8	AVR-Bio Bentall 8	Entercoc. Faecalis	Vegetation – Extension +	Correct Correct	Correct Correct	Correct Correct	Correct Correct	None	2.7 (5.3/2.0)	Pneumonia
9	AVR-Bio Bentall 20	None	Vegetation - Extension +	Correct Possible	Correct Correct	Correct Correct	Correct Correct	Confirmation of extension	4.8 (7.6/1.6)	None
10	AVR-M Bentall 26	S. Aureus	Vegetation + Extension +	Correct Missed	Correct Correct	Missed Correct	Correct Correct	Extension detected	4.5 (12.2/2.7)	Spleen abscess
11	AVR-M Bentall 15	S. Aureus	Vegetation - Extension +	False positive Missed	Correct Correct	Correct Correct	Correct Correct	Vegetation excluded Extension detected	5.9 (9.4/1.6)	None
12	AVR-M	Neisseria Elongata	Vegetation + Extension +	Correct Correct	Correct Correct	Missed Correct	Correct Correct	None	3,8 (5.3/1.4)	Colon carcinoma
13	AVR-M	S. Aureus	Vegetation – Extension +	Correct Correct	Correct Correct	Correct Correct	Correct Correct	None	3.2 (5.5/1.7)	Spondylodisciitis
14	AVR-Bio	Enterococ-Faecalis	Vegetation + Extension -	Correct Correct	Correct Correct	Missed Correct	Correct Correct	None	2.1 (3.6/1.7)	None
15	AVR-Bio	S. aureus	Vegetation + Extension +	Correct Correct	Correct Correct	Missed Correct	Correct Correct	None	3.9 (6.2/1.6)	None

AVR-M: Mechanical Aortic Valve Replacement, AVR-Bio: Biological Aortic Valve Replacement, CTA: Computed Tomography Angiography, FDG-PET/CT: 18F-Fluorodesoxyglucose Positron Emission Tomography including low dose CT, SUV: Standardized Uptake Value, TEE: Transesophageal echocardiography, TTE: Transthoracic Echocardiography, PHV: Prosthetic Heart Valve, PHV-E: Prosthetic Heart Valve Endocarditis. PVR-M: Mechanical Pulmonic Valve Replacement, ,

13/15 (87 %) to 15/15 (100%), without adding false positives. The sensitivity of peri-annular extensions rose from 7/15 (47%) to 13/15 (87%). CTA missed one abscess (patient 2, Figure 2) and was inconclusive in another (patient 7, Figure 3). The individual FDG-PET/CT however detected all peri-annular extensions correctly (Figure 4) but missed all vegetations (Figures 5 and 7). Combining/fusion of FDG-PET/CT and CTA detected the presence/absence of all vegetations and peri-annular extensions correctly with surgical exploration as the reference standard in all patients. In case 14 a vegetation was present but no periannular extension. In this case FDG-PET/

Figure 2: Early complicated PHV endocarditis detection



*Patient 2: Patient with a bileaflet mechanical PHV in aortic position since 20 years, presenting with fever and subsequently four consecutive blood cultures positive for Staphylococcus Aureus. Despite a high clinical suspicion for endocarditis, TTE/TEE as well as CTA (**A**) were unremarkable. Modified Duke criteria were not fulfilled. However, FDG-PET/low dose CT revealed high uptake around the aortic PHV with a SUV ratio of 4.3 (6.9/1.6). After fusion with the cardiac CTA the high uptake was demonstrated around the PHV near the proximal right and left coronary artery (RCA and LCA) (Panel **B**). Because of persistent fever under adequate antibiotic treatment it was decided to perform surgical inspection 6 days after presentation. In contrast to the FDG-PET/CT findings, surgical inspection did not reveal macroscopic PHV abnormalities (Panel **C**), although no inspection under the ring was performed, nor biopsies taken from this area. Eight days after this surgery, additional CTA and TEE were performed because of stroke and persistent fever. Now CTA revealed a mycotic aneurysm beneath the RCA origin (Panel **D**) and TEE (panel **E**) now showed two abscesses around the LCA, all confirmed by urgent re-operation. Panel **F** shows the aortic root after explantation of the PHV, with pus in the LCA region (arrow). Retrospectively, only FDG-PET/CT detected these findings at a very early stage. After fusion with CTA the involvement of the coronary arteries in the infected area was imaged, which is also important for the pre-operative surgical strategy. Moreover, because CTA was performed no invasive coronary angiography was needed anymore.*

CT remained negative, however the concomitant CTA (but also TEE) detected the vegetation correctly. In cases with proven peri-annular extension (n=14, case 14 excluded), the median SUV ratio of the FDG-PET uptake around the PHV ring was: 4.2 (IQR 3.8-5.3), with SUV ratios all above 2.6 (table 1 and 3). The qualitative uptake score was moderate to severe in all these cases (except case 14). None of the cases had clear uptake on the leaflets suggestive for vegetations.

Table 2: FDG-PET/CTA results for PHV controls early (Group B) and late (Group C) after implantation

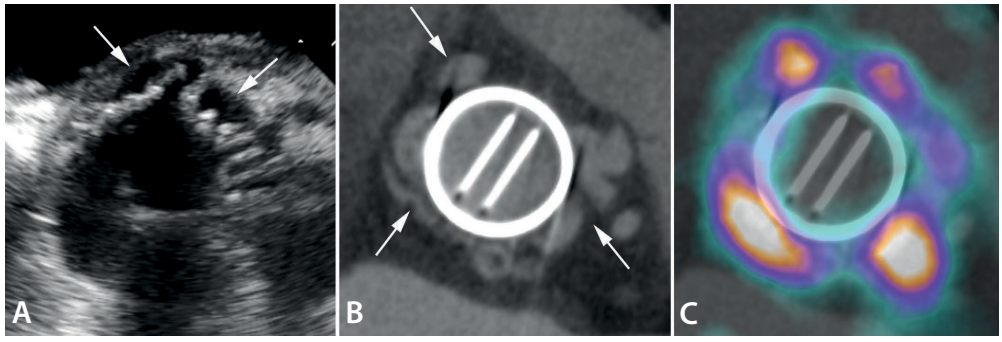
Late Controls (Group C)	Type of PHV	TTE/TEE diagnosis for PHV-E	PET-CTA months after implantation	PET-CTA diagnosis for PHV-E	SUV ratio SUV max PHV/ SUV mean descending Ao	Extra cardiac finding
16	PVR-M	Negative	15	Negative	1.4 (2.2/1.6)	none
17	MVR-M	Negative	312	Negative	2.2 (3.8/1.7)	none
18	AVR-M	Negative	120	Negative	2.4 (3.1/1.3)	none
19	AVR-Bio	Negative	60	Negative	2.0 (3.0/1.5)	none
20	AVR-M Bentall	Negative	56	Negative	2.5 (3.2/1.3)	Pneumonia
21	MVR-M	Negative	120	Negative	2.0 (4.0/2.0)	none
22	MVR-M	Negative	456	Negative	2.0 (3.6/1.8)	none
23	AVR-M	Negative	22	Positive	2.9 (4.0/1.4)	none
24	AVR-M	Negative	320	Negative	1.9 (1.9/1.0)	Spondylodisciitis
Early Controls (group B)	**Type of PHV**	**TTE/TEE diagnosis for PHV-E**	**PET-CTA months after implantation**	**PET-CTA diagnosis for PHV-E**	**SUV ratio SUV max PHV/ SUV mean descending Ao**	**Extra cardiac finding**
25	AVR-Bio	Negative	3	Negative	2.1 (2.9/1.4)	Mediastinitis
26	AVR-Bio	Negative	2	Negative	2.1 (3.3/1.6)	none
27	AVR-M	Negative	1	Negative	1.8 (2.4/1.3)	none
28	AVR-M	Negative	3	Negative	1.8 (2.8/1.6)	none
29	AVR-Bio	Negative	3	Negative	1.7 (2.8/1.6)	none
30	AVR-Bio	Negative	1	Negative	2.1 (3.3/1.6)	none
31	AVR-bio	Negative	3	Negative	1.8 (2.9/1.6)	none
32	AVR-M	Negative	3	Negative	2.4 (3.9/1.6)	none
33	AVR-M	Negative	1	Negative	2.0 (4.3/2.2)	Spleen abscess

AVR-M: Mechanical Aortic Valve Replacement, AVR-Bio: Biological Aortic Valve Replacement SUV: Standardized Uptake Value. PVR-M: Mechanical Pulmonic Valve Replacement, CTA: Computed Tomography Angiography, FDG-PET/CT: 18F-Fluorodesoxyglucose Positron Emission Tomography including low dose CT, PHV: Prosthetic Heart Valve, PHV-E: Prosthetic Heart Valve Endocarditis.

Group B (n=9). Consisted of PHV's without endocarditis and early (>1 and < 4 months) after implantation (Table 2). In this group no positive FDG-PET/CTA scans were encountered according to the qualitative uptake score (all none/mild uptake) and all SUV ratios < 2.5. The median SUV ratio was 2.0 (IQR 1.8-2.1).

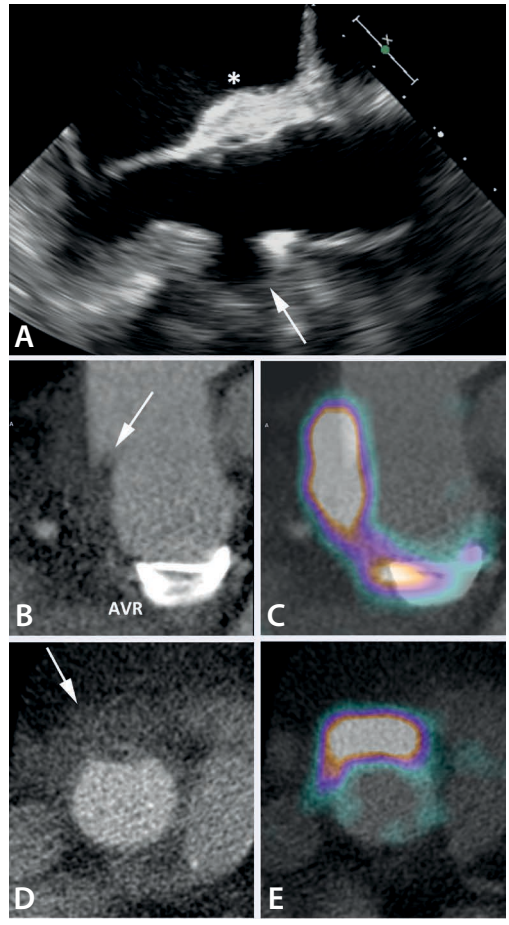
Group C (n=9). Consisted of PHV's without endocarditis late after implantation (≥ 4 months) (Table 2). CTA detected an asymmetric thickened aortic root secondary to a pericardial patch in patient 23. This resulted in moderate pathological FDG uptake with a SUV ratio of 2.9. In the other patients in this group no positive FDG-PET/CTA scans were encountered according to the qualitative uptake score (all none/mild uptake) with SUV ratios all ≤ 2.5. Median SUV ratio for group C was 2.2 (IQR 2.0-2.5).

Figure 3: Additional value for differentiation of post-operative anatomical abnormalities and endocarditis with peri-annular extension



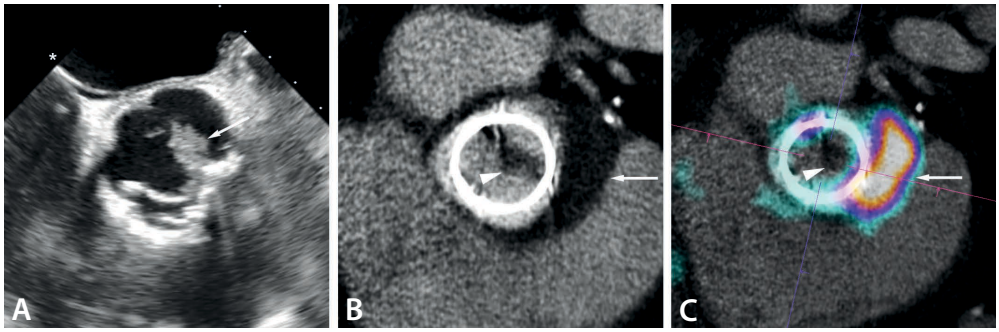
*Patient 7 was asymptomatic patient underwent a routine TTE six weeks after an uncomplicated mechanical bileaflet aortic PHV implantation. TTE revealed the suggestion of aortic root abnormalities. Blood cultures remained negative and CRP was only 68 mg/l. TEE (Panel **A**, short axis view) and CTA (Panel **B**, rotated in same view as the TEE view) revealed no vegetations, but irregular blood/contrast-filled cavities at the level of the aortic root (arrows). This was most likely compatible with multiple mycotic aneurysms, but could theoretically also be non-infected post-operative root abnormalities. Furthermore, the modified Duke criteria were not fulfilled and CRP levels decreased spontaneously. A follow-up FDG-PET/CT showed high uptake around the PHV with a SUV ratio of 3.8 (7.17/1.91), which convinced the surgeon of the need for a high risk re-operation. Fusion of the FDG-PET with the CTA demonstrated uptake in most of the aortic root abnormalities (Panel **C**). It was decided to re-operate the patient which revealed multiple mycotic aneurysms, confirmed by pathological examination. This case shows that confirmation of infection of the aortic root is possible by addition of FDG-PET and CTA to echocardiography.*

Figure 4: Diagnostic dilemma with inconclusive TTE/TEE in the context of high suspicion of PHV endocarditis



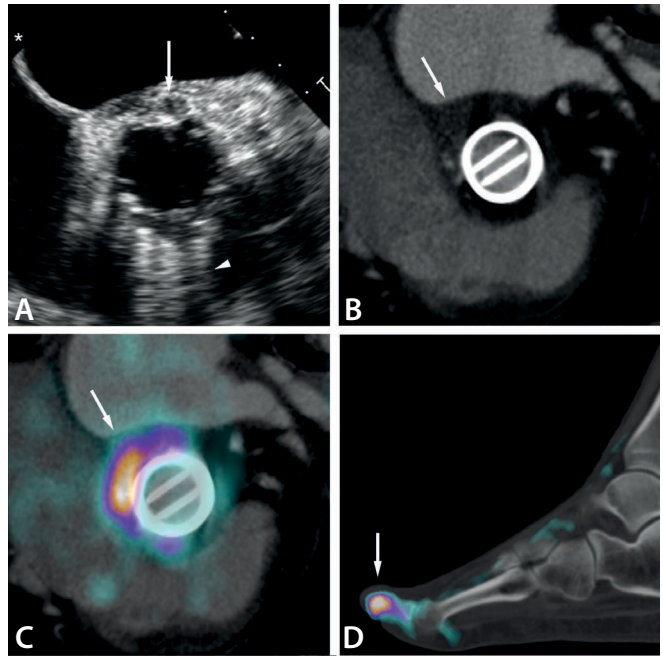
*Patient 1 Patient with a Bentall tube and St. Jude mechanical aortic PHV implanted 26 months previously, presenting with high fever and three consecutive blood cultures positive for Actinobaccilus. TEE (Panel **A**, 120 degree TEE view) was interpreted as aspecific thickening (asterix) of the **posterior** aortic wall as the outpatient clinic TTE's before the fever already showed this thickening. Modified Duke criteria were not fulfilled. The arrow points to the anterior side, where TEE imaging was hampered by acoustic shadowing. In contrast, CTA revealed not only a vegetation in the **anterior** side of the Bentall tube (arrow panel **B**), but also thickening/fatty infiltration of the **anterior** side of the Bentall prosthesis and PHV ring (arrow Panel **D**). FDG-PET/CT corroborated this observation by detecting high uptake only around the **anterior** side of the Bentall tube and PHV ring with a SUV ratio of 7.9 (15/1.9). Complicated infection of the Bentall prosthesis was diagnosed by CTA and FDG-PET/CT independently and correspondingly after fusion, confirmed by surgical inspection and pathological examination. This case shows that in contrast to echocardiography, CTA detected the vegetation and peri-annular extension. FDG-PET was of additional clinical value in confirming the peri-annular extension on the anterior side of the Bentall tube.*

Figure 5: Combined CTA and FDG/PET imaging detects both vegetations and peri-annular extensions.



*Patient 3 with a biological PHV in aortic position since 10 months, presenting with fever and four consecutive blood cultures positive for Staphylococcus Aureus. Panel **A**: Short axis TEE view shows a large vegetation (1.7 cm in length, arrow). No peri-annular extensions were observed. The modified Duke criteria were fulfilled. Panel **B**: Two days later, CTA (rotated in the same view as the short axis TEE view) detected not only the vegetation (arrowhead), but also a thickened aortic wall in the former right to left coronary cusp (arrow) indicating a peri-annular extension of PHV endocarditis, which is an indication for urgent reoperation. Retrospectively, imaging of this area by TEE (Panel A) was hampered by acoustic shadowing of the PHV. Panel **C**: FDG-PET/CT (low dose) alone missed the large vegetation (the arrowhead points to absent FDG uptake in the large vegetation), but detected high uptake around the PHV, SUV ratio 3.6 (7.5/2.1). At urgent re-operation a large vegetation and peri-annular extension around the former left coronary cusp was observed and confirmed by pathological examination. This case shows that peri-annular extensions can be missed by echocardiography, however correctly diagnosed by FDG-PET/low dose CT and CTA independently and after fusion. However, vegetations can be missed by FDG-PET/low dose CT alone.*

Figure 6: Extra-cardiac focus in proven PHV endocarditis detected by whole body FDG-PET/low dose CT

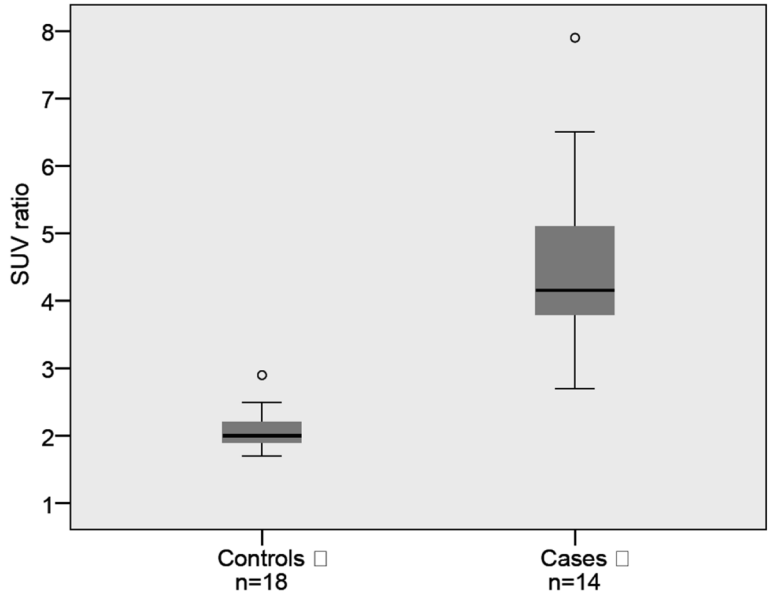


*Patient 6 with a bileaflet mechanical PHV in aortic position implanted 13 years earlier, presenting with fever and four consecutive blood cultures positive for Staphylococcus Aureus. Short axis TEE (asterix = interatrial septum, arrowhead = acoustic shadowing) revealed no vegetations but a thickened wall without color Doppler flow in the former non-coronary cusp region. This was suggestive for an abscess (Panel **A**, arrow). Panel **B**: CTA confirmed the TEE findings, showing a thickened aortic root (arrow) without significant contrast extravasations and no vegetations. FDG-PET/CT alone detected high uptake around the PHV, SUV ratio 4.0 (8.4/2.1). After fusion of the CTA with FDG-PET (Panel **C**), the thickened aortic root showed high metabolic activity (arrow), confirming abscess formation. The primary focus was most likely an infection of the fourth toe. This patient was already treated by the surgeon for this infection considered to be only a superficial infection caused by delayed healing secondary to known peripheral artery disease. However, whole body FDG-PET/CT showed the fourth toe to have osteomyelitis (Panel **D**, arrow), requiring a guillotine resection before a cardiac reoperation was performed. Subsequent PHV reoperation revealed peri-annular extension of PHV endocarditis (no vegetations), confirmed by pathological examination. This case shows that even if echocardiography correctly diagnoses PHV endocarditis with peri-annular extension, additional whole body FDG-PET/CT has additional value with therapeutic consequence.*

Cases (A) versus Controls (B+C): SUV ratios around the PHV ring were significantly ($p<0.001$) higher in the PHV peri-annular extension cases of group A; 4.2 (IQR 3.8-5.3) compared to controls (group B+C); 2.0 (IQR 1.8-2.3) (Table 3).

Extra-cardiac findings: Whole body FDG-PET/CT detected extra-cardiac infectious foci in 10/33 patients (cases + controls) (Figures 6 and 7).

Table 3: Standardized Uptake Value ratios for the discrimination of PHV endocarditis cases with peri-annular extension (n=14, Group A minus case 14 which had only a vegetation) *versus* PHV controls (n=18, Group B+C) without PHV endocarditis.



Mann-Whitney U; 4.2 (IQR 3.8-5.3) versus 2.0 (IQR 1.8-2.3), p<0.001. In the controls there is one outlier (circle), which is patient number 23 with a false positive FDG uptake due to a pericardial patch. The outlier (circle) in the case group is patient 1 which had a very high FDG-uptake (true positive). IQR: Inter Quartile Range, PHV's: Prosthetic Heart Valve, SUV: Standardized Uptake Value.

DISCUSSION

To the best of our knowledge this is the first case and control series, which demonstrates the additional value of hybrid imaging with fused ECG-gated / triggered cardiac CTA and FDG-PET/CT in PHV endocarditis. This imaging strategy correctly detected all peri-annular extensions and vegetations in PHV endocarditis cases and had additional clinical value when echocardiography results were negative or inconclusive. Except for one patient with a pericardial patch in situ, FDG-PET did not show significant FDG uptake around the mechanical PHV ring in control patients, in both the late (> 12 months) and early post-operative phase (>1 and ≤ 4 months). Median SUV ratios in complicated PHV cases were significantly higher in cases compared to controls, 4.2 versus 2.0 respectively. A SUV ratio > 2.5 appears to be a reasonable cut-off value to detect peri-annular extension in PHV cases (if no pericardial patches are implanted).

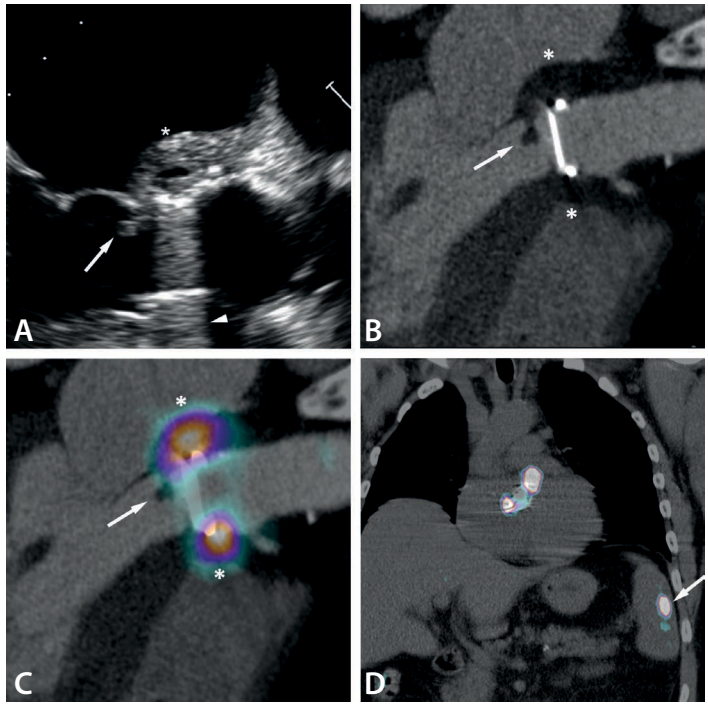
The detection of peri-annular complications in PHV endocarditis is of paramount importance as it is accompanied by a high mortality and requires urgent surgical treatment. Lit-

erature reports incidences of peri-annular complications (abscess or mycotic aneurysm) in 50 % of PHV endocarditis cases, whereas in almost all our PHV endocarditis cases peri-annular extension was observed at surgery. This very high incidence can be explained by selection bias. Namely, some included patients were already diagnosed with complicated PHV endocarditis by echocardiography and/or CTA alone and underwent an additional FDG-PET/CT scan for confirmation purposes or extra cardiac focus screening [16]. Although echocardiography missed some peri-annular extensions, it cannot be concluded that echocardiographic performance is very poor for PHV endocarditis detection, as inconclusive/negative echocardiography results were the main indication for performing additional imaging with FDG-PET/CTA. Recently two studies on cardiac CTA in the evaluation of PHV endocarditis were published [14, 20]. Feuchtner et al. [20] presented the first study that evaluated the value of CTA in six patients with suspected PHV endocarditis. All peri-annular extensions were detected by CTA. Fagman et al. [14] compared CTA to TEE in twenty-seven patients with aortic PHV endocarditis. Sixteen patients underwent surgical exploration. This study reported that cardiac CTA had complementary value compared to TEE, however peri-annular extensions were still missed by CTA. Also in the present study CTA improved diagnostic accuracy of peri-annular extensions on top of echocardiography, but still one complicated PHV endocarditis case was missed (Figure 2) and another case inconclusive (Figure 3). Additional FDG-PET/CT can be of extra value especially in such cases and possibly provides also very early detection of peri-annular extension as shown in patient 2 (Figure 2). In this case anatomical imaging (echocardiography and CTA) did not reveal evidence of complicated PHV endocarditis (abscess), however only metabolic imaging by FDG-PET/CT was able to detect complicated PHV endocarditis in a very early phase of disease. The therapeutic consequence of this observation is yet unknown, however it certainly assists the heart team, and has the potential to guide early surgical intervention with the prospect of timely prevention of further tissue damage due to the infectious process.

Saby et al. performed the first prospective study with FDG-PET/CT to improve diagnostic accuracy of PHV endocarditis and to investigate the complementary value of FDG-PET/CT as a major criterion in the modified Duke criteria. The sensitivity and specificity of FDG-PET/CT for PHV endocarditis was 73% and 80 % respectively. The study showed that FDG-PET/CT was adequate in detecting peri-annular extensions, but FDG-PET/CT missed a substantial number of vegetations (9/20, 45%) in cases with no other echocardiographic signs of PHV endocarditis. In concert with our observation FDG-PET/CT may be a promising imaging tool in the detection of PHV endocarditis with peri-annular extension, but sensitivity for vegetations is a concern as the spatial resolution of FDG-PET/low dose CT is inferior compared to TEE and an ECG-gated contrast enhanced CTA. Therefore these diagnostics (TEE and CTA) remain of additional value to detect vegetations and other anatomical abnormalities consistent with endocarditis [14, 21]. Vegetations do not show FDG uptake, probably due to the large amount of motion of the valve leaflets and vegetations resulting in blurring of the PET signal beyond the point of detectability (Figure 5 and 7). Other contributing causes of missing vegetations may be the low spatial resolution of PET imaging, the background activity of the bloodpool masking uptake in the vegetation and/or direct exposure of vegetations to antibiotics in the bloodstream which make them more prone to be sterilized.

For correct interpretation of pathological FDG uptake around PHV's with peri-annular

Figure 7: Metastatic infection in PHV endocarditis detected by whole body FDG-PET/ low dose CT



*Patient 4 with a bileaflet mechanical PHV in aortic position since 6 years, presenting with fever and seven consecutive blood cultures positive for Streptococcus Pneumoniae. Panel **A**: 120 degree TEE view showed a vegetation (arrow) and thickened wall (asterix) without color Doppler flow in the former non-coronary cusp region, suggestive of an abscess. Former right coronary cusp imaging is hampered by acoustic shadowing (arrowhead). Modified Duke criteria were fulfilled. Panel **B**: CTA confirmed the vegetation (arrow) but also showed thickened aortic walls, not only near the former non-coronary cusp, but also near the former right coronary cusp (asterixes). Panel **C**: CTA fused with FDG-PET confirmed abscess formation near the former right and non-coronary cusp (asterixes). The SUV ratio was 5.1 (9.7/1.9) at a CRP value of 77 mg/l. The vegetation (arrow) did not show FDG uptake, probably due to the large amount of motion of the valve leaflets and vegetations resulting in blurring of the PET signal beyond the point of detectability. Other contributing causes of missing vegetations may be the low spatial resolution of PET imaging, the background activity of the bloodpool and/or direct exposure of vegetations to antibiotics in the bloodstream which make them more prone to be sterilized. Additionally, whole body FDG-PET/CT showed a metastatic infection in the spleen (Panel **D**, arrow), in this case an abscess requiring percutaneous drainage. Subsequent cardiac surgery and pathological examination confirmed the vegetation and widespread peri-annular extension, requiring homograft implantation. Although Duke criteria were already fulfilled in this patient before addition of CTA and FDG-PET/CT, the additional imaging was useful as peri-annular extension was more extensive than TEE suggested. This guided the pre-operative strategy in that a homograft needed to be ordered and a metastatic infection was diagnosed which necessitated additional therapy before re-operation of the PHV.*

extension, baseline FDG-PET uptake around PHV's without endocarditis should be known. However "normal" FDG-PET uptake around PHV's has not been determined up to now. Theoretically chronic inflammation around the PHV due to post-operative healing shortly after implantation or foreign body immune responses in the chronic phase and concomitant FDG uptake could be expected, which would lead to false positive findings. In the present study we identified 18 PHV patients in whom endocarditis was excluded/not present and CTA and FDG-PET/CT was performed. According to a qualitative visual score almost all our controls had none or only mild uptake even in a cases that were 1-4 months after AVR implantation. This shows that PHV's without complicated endocarditis probably have only mild uptake in the chronic post-operative phase. Only pericardial patches may show high FDG-uptake for which reason hybrid imaging in these patients is not recommended. All other controls had SUV ratios ≤ 2.5. In contrast, all PHV endocarditis cases with peri-annular extension showed significant FDG uptake with SUV ratios all above 2.6. As a result SUV ratios may help to differentiate between the absence or presence of a peri-annular extension.

Extra cardiac infectious findings were detected by FDG-PET/CT in 10/33 patients (six cases and four controls). In our study population, 6/15 (40 %) of cases had significant extra cardiac infectious FDG uptake which may be primary or metastatic infections (Figures 6 and 7). This is in line with the study of Van Riet et al.[16] which described extra-cardiac infections detected by FDG-PET/CT in 44 % of endocarditis cases (PHV and non-PHV cases). In addition to the detection of peri-annular extension in PHV endocarditis, extra-cardiac screening is another clinically important indication for FDG-PET/CT as it may have therapeutic consequences.

Limitations

1. This study is limited to the infectious complications of the outflow PHV's of the heart. In our practice infectious complications of inflow PHV's are relatively uncommon.
2. CTA and FDG-PET/CT evaluation is accompanied by a non-trivial amount of radiation exposure. However, in patients with PHV endocarditis, who have a high risk of mortality, we feel this is justified because of the potential diagnostic and therapeutic yield. From the surgical perspective, detailed knowledge of the pathology is relevant for the decision to use allograft root replacement in case of extensive tissue destruction, an infected ascending as after a Bentall procedure. Allografts need to be ordered timely. Debridement of all infected material on the basis of visual inspection is the mainstay of surgical treatment and should be guided by optimal pre-operative imaging.
3. The number of patients included in our case and control groups are relatively low.
4. There is likely a selection bias and referral bias as we are an expert referral centre for PHV endocarditis.
5. Combined imaging by FDG-PET/CTA is accompanied by extra costs. However, early and correct detection of complicated PHV endocarditis by FDG-PET/CTA may prevent longer hospital stay, follow-up TEE's and progression of uncontrolled infection with concomitant very high mortality and morbidity. As a consequence this new imaging tool might be even cost effective.

CONCLUSION

Fused cardiac FDG-PET/CT and CTA imaging is a promising tool to correctly diagnose PHV endocarditis in patients with an inconclusive routine work-up with TTE and TEE. PHV's free of peri-annular endocarditis extension seem to be also free of significant FDG uptake, even early after implantation. SUV ratios may be of additional help for correct detection of peri-annular extension in PHV endocarditis. A SUV ratio > 2.5 appears to be a reasonable cut-off value to detect peri-annular extension in PHV cases. FDG-PET/CT may detect extra-cardiac infections, which is clinically relevant. More prospective studies are needed for correct interpretation of FDG-PET/CTA scans in PHV patients with and without endocarditis in order to confirm the results of this study.

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CHAPTER 5

THE ADDITIONAL VALUE OF THREE DIMENSIONAL TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN COMPLEX AORTIC PROSTHETIC HEART VALVE ENDOCARDITIS

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ABSTRACT

Background: Two dimensional transthoracic and transesophageal echocardiography (2D-TTE and 2D-TEE) may fail to detect signs of prosthetic heart valve (PHV) endocarditis due to acoustic shadowing. Three dimensional (3D) TEE may have additional value; however data are scarce. This study was performed to investigate the additional value of 3D-TEE for the detection of aortic PHV endocarditis and the extent of the disease process.

Methods: Retrospective analysis of complex aortic PHV endocarditis cases that underwent 2D-TTE, 2D-TEE and 3D-TEE before surgery. Echocardiograms were individually assessed by two cardiologists blinded for the outcome. Surgical and pathological inspection served as the reference standard for vegetations and peri-annular extensions (abscesses/mycotic aneurysms). To determine if the proximal coronary arteries were involved in the inflammatory process as well, computed tomography angiography findings were added to reference standard.

Results: 15 aortic PHV endocarditis cases were identified. According to the reference standard all 15 cases had peri-annular extensions, 13 of which had a close relationship with the proximal right and/or left coronary artery. In 6 out of 15 patients a vegetation was present. Combined 2D-TTE/TEE missed 1/6 vegetations and 1/15 peri-annular extensions. After addition of 3D-TEE all vegetations (6/6) and peri-annular extensions (15/15) were detected, without adding false positives. Compared to 2D-TEE, in 3/15 cases 3D-TEE resulted in better delineation of the anatomical relationship of the proximal coronary arteries to the peri-annular extensions. As a result, 3D-TEE had an additional value in 5/15 cases.

Conclusion: In complex aortic PHV endocarditis 3D-TEE may have additional value compared to 2D echocardiography.

INTRODUCTION

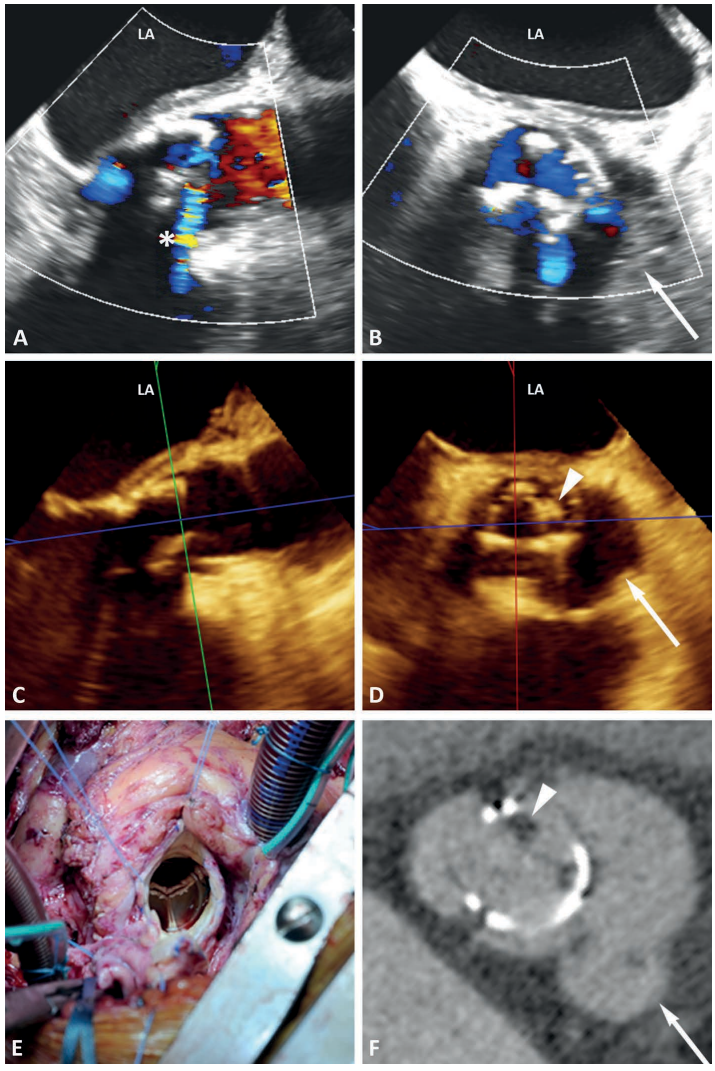
Prosthetic heart valve (PHV) endocarditis is a feared and potentially life-threatening complication that occurs with an incidence of 0.3-1.2% per patient year [1]. The diagnosis is sometimes difficult to establish as two dimensional transthoracic and transesophageal echocardiography (TTE/TEE) are hampered by acoustic shadowing. Moreover, the blood cultures may remain negative in cases of PHV endocarditis with peri-annular extension (abscess/mycotic aneurysm) [2-5]. As a consequence the modified Duke criteria are less reliable in PHV endocarditis. However, early and correct detection of PHV endocarditis is crucial since it has major therapeutic consequences. Uncomplicated PHV endocarditis may be treated with antibiotics alone, whereas the development of an abscess or mycotic aneurysm is an indication for urgent surgery [6]. Development of such peri-annular extensions is not rare and occurs in approximately 50% of PHV endocarditis cases [2, 3, 5, 7, 8]. Although transesophageal echocardiography (TEE) is superior to transthoracic echocardiography (TTE), it may still fail to detect signs of endocarditis in up to 30% of cases [2-8]. Cardiac computed tomography angiography (CTA) and (18)F-fluorodesoxyglucose/positron emission tomography (FDG-PET) have recently been introduced for PHV assessment. Diagnostic accuracy for PHV endocarditis improves when these diagnostic tools are combined with 2D-TEE [9-13] . However, CTA and PET are more expensive than echocardiography and expose patients to radiation as well as iodinated contrast in case of CTA. Data about the additional value of 3D-TEE for the correct detection of vegetations and/or peri-annular extensions in aortic PHV's are scarce. This study aims to investigate whether 3D-TEE accurately detects signs of aortic PHV endocarditis and whether it results in better delineation of peri-annular extensions with regard to important adjacent structures such as coronary arteries. The additional value of 3D-TEE will be compared to conventional 2D-TTE and 2D-TEE using surgical and/or pathological inspection as well as CTA as the reference standard.

METHODS

Patient selection: We searched the database of the cardiothoracic surgery department of the university medical center Utrecht for PHV endocarditis patients that were surgically explored from January 2010 until June 2013 and underwent 2D-TTE, 2D-TEE and 3D-TEE on the same day. Imaging studies were performed on clinical indication and therefore informed consent was not required according to our internal medical ethical board for this retrospective study.

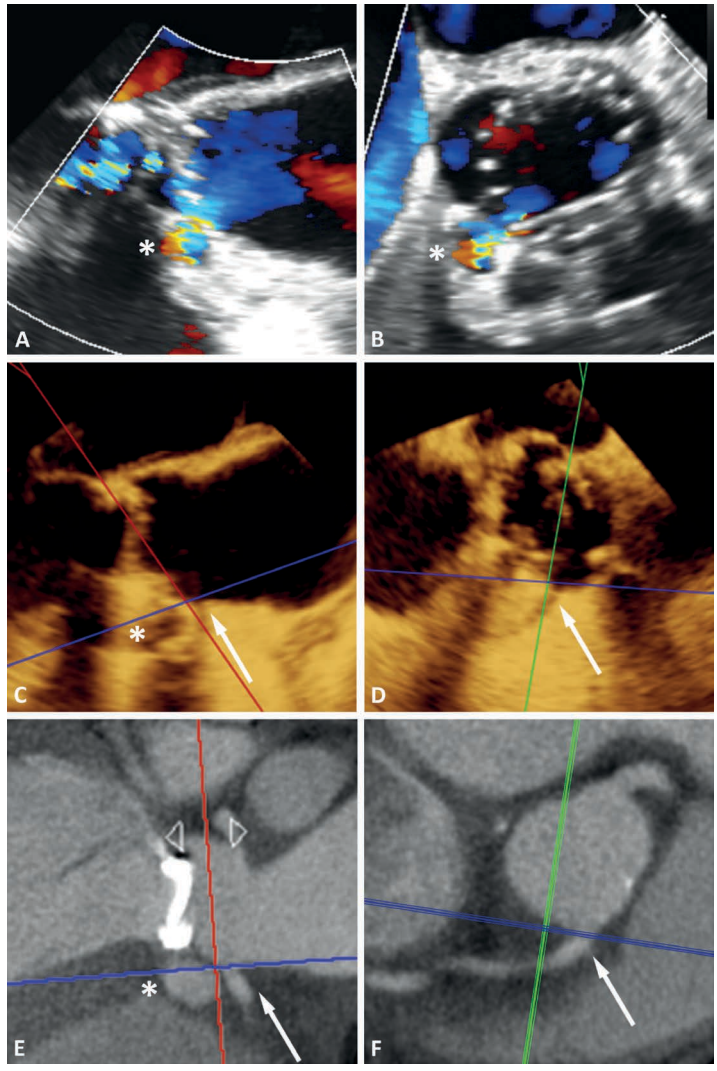
Echocardiography: All patients underwent both 2D-TTE and 2D-TEE with a commercially available ultrasound system (iE33, Philips Medical Systems, Best, The Netherlands). TTE and TEE evaluations were focused on the detection of signs of PHV endocarditis: 1. vegetations and 2. peri-annular extensions (such as mycotic aneurysms, fistulae, abscesses) defined according to the ESC guidelines [1].

Figure 1: Large mycotic aneurysm missed by 2D-TEE, but correctly detected by 3D-TEE.



*Patient 5 with a long (**A**) and short (**B**) axis 2D-TEE view detecting a paravalvular leakage with color doppler flow (*) and a vegetation. The large mycotic aneurysm (arrow) was missed by 2D-TEE due to acoustic shadowing of the PHV. 3D-TEE however (**C**/**D**, MPR mode) detected the mycotic anaeurysm as well as the vegetation correctly. Panel **E** shows the peri-operative view with thickened leaflets and multiple small vegetations. Panel **F** shows the CTA reconstructed in the same imaging plane as the 3-D TEE, confirming the vegetation and the large mycotic aneurysm.* (*) *= paravalvular leakage, arrow* (→) *= large mycotic aneurysm, arrowhead* (►) *= vegetation, LA=left atrium.*

Figure 2: Correct detection of inflammatory involvement of the proximal RCA by 3D-TEE.



*Patient 7 with a long (**A**) and short (**B**) axis 2D-TEE view detecting a cavity with color doppler flow near the former right coronary cusp of the AVR-M, suggestive of a mycotic aneurysm. 3D-TEE (**C**/**D**) detected not only the peri-annular extension, but also the right coronary artery and its close relation to the mycotic aneurysm. The crosshairs of the MPR mode in **C** resemble the same location of the cross hairs in **D**. These observations were confirmed by surgical inspection and CTA reconstructed in the same imaging plane (**E**/**F**) as the 3D-TEE (**C**/**D**).* (*) = *mycotic aneurysm, arrow* (→) = *RCA.*

In case of peri-annular extension, its anatomical relationship with the proximal RCA and/or LCA was also investigated. 2D-TTE's routinely consisted of two and four chamber apical views, subcostal views, left parasternal long and short axis views all with and without color Doppler. 2D- and 3D-TEE's were performed with a multiplane probe that included a 3D matrix-array (X7-2T). 2D-TEE of the aortic PHV was performed following routine protocols including imaging of the PHV from 0-140 degrees with and without color Doppler. The standard short axis view was obtained at three levels (subvalvular, valvular and supravalvular). 2D-TEE was followed by 3D-TEE according to acquisition recommendations defined by Lang et al. [14]. For this study 3D full-volume (4-7 beat stitch) data were acquired from the 2D-TEE short axis (around 30 degrees) and long axis 2D TEE view (around 120 degrees) during breath hold. In case of suspicion of (para)valvular leakage full-volume color Doppler data sets were acquired in most instances. Gain settings were optimized to minimize dropout of visible prosthetic leaflets and annular surfaces. Images were reviewed offline (QLAB version 8.0, Philips Medical Systems) after optimal gain and color coding. Using the multi plane reconstruction (MPR) and freehand cropping mode the 3D image data were subsequently analyzed by two independent experienced reviewers blinded for the surgical outcome.

CTA acquisition: Cardiac CTA data was often also available as these scans were performed on clinical grounds in most patients and because some patients were also participating in a prospective trial investigating the additional value of CTA in PHV endocarditis. CTA evaluation was performed by an experienced reader and focused on the detection of signs of PHV endocarditis defined according to the ESC guidelines [1] (see echocardiography section). In case of peri-annular extension, the anatomical relationship with the proximal RCA and/or LCA was assessed and described. Contrast-enhanced retrospectively ECG-gated acquisition was performed on a 256-slice or dual-source CT system (iCT, Philips Medical Systems or Somatom Flash Siemens). The following acquisition parameters were used:120kV, 600-700mAs, collimation 128x0.625mm or 2x64x0.6mm and heart rate dependent gantry rotation time (270-420ms) and pitch. A dual (400mg jopromide/ml) or triphasic (300ml jopromide/ml) contrast administration protocol was used with a flow rate of 5.0-6.7cc/second.

Data assessment: Two independent experienced reviewers blinded for the surgical and CTA outcome analyzed all echo data. Each case was presented in the following sequence with assessment moments 1 and 2: (1) clinical routine workup (clinical history, physical examination, laboratory testing, 2D-TTE and 2D-TEE) and followed by (2) 3D-TEE using the MPR and freehand cropping modes. 3D-TEE assessment was not blinded for 2D-TTE/TEE findings, reflecting clinical practice. After each of the two assessment moments the following items were scored: 1. vegetations as present or absent; 2. peri-annular extensions as present or absent; 3. if present the location of the peri-annular extensions was scored as near the former right, left or non-coronary cusp (RCC/LCC/NCC, respectively). In cases of disagreement a consensus was reached via a third physician. The reference standard for vegetations and peri-annular extensions was visual inspection during surgery and/or pathological examination.

Furthermore, an anatomical relationship of the proximal coronary arteries to peri-annnular extensions was scored as *present* when the coronary artery was in direct contact with, or close to,

Table 1: Patient characteristics

Patient	Age/Gender	PHV type	Bacterial agent in blood cultures	Duke criteria met	GFR (ml/min)	Type of surgery performed
1	74/M	AVR-M	Staphylococcus Aureus	Yes	47	Homograft
2	56/M	AVR-M	negative	No	>60	Homograft
3	51/F	AVR-M	negative	No	>60	Homograft
4	67/M	AVR-bio	negative	No	>60	Homograft
5	63/M	AVR-bio	Streptococcus oralis	Yes	35	Homograft
6	65/M	AVR bio	Staphylococcus Aureus	Yes	34	AVR-Bio
7	44/M	AVR-M	Streptococus group G	Yes	>60	Homograft
8	62/M	AVR-M	Streptococcus pneumoniae	Yes	46	Homograft
9	62/M	AVR-M	Streptococcus pneumoniae	Yes	>60	Re-AVR
10	57/M	AVR-M	Staphylococcus Aureus	Yes	<20	Re-AVR
11	65/M	AVR-M	Staphylococcus Aureus	Yes	>60	Homograft
12	59/M	AVR-M	Enterococcus faecalis	Yes	>60	AVR-M with Bentall
13	77/F	AVR-bio	Streptococcus Gemelli	Yes	40	Homograft
14	57/F	AVR-bio	Staphylococcus Aureus	Yes	50	Homograft
15	60/M	AVR-M	Neisseria	Yes	29	Homograft

Legend Table 1: Age in years, AVR=aortic valve replacement, AVR-bio=biological aortic valve replacement, AVR-M=mechanical aortic valve replacement, F=female, GFR=Glomerular filtration rate, ml/min= millilitres/minute, M=male, PHV=Prosthetic Heart Valve.

the inflammatory tissue and was *absent* when the distance between the coronary artery and the inflammatory tissue was more than approximately 7 millimeters. CTA served as the primary reference standard for assessment of the relationship between the peri-annular extensions and proximal coronary arteries. If CTA was not performed, surgical inspection/pathological examina-

tion was used as reference standard. Finally reviewers also scored the additional value of 3D-TEE on soft endpoints: 1. confirmation of 2D-echocardiographic findings 2. better depiction of the extensiveness of the peri-annular extension than on 2D- echocardiography and 3. better depiction of the relationship between peri-annular extension and other cardiac structures such as right ventricle, mitral valve, left atrium compared to 2D-echocardiography. Since this is a descriptive study, no statistics were performed on these data.

RESULTS

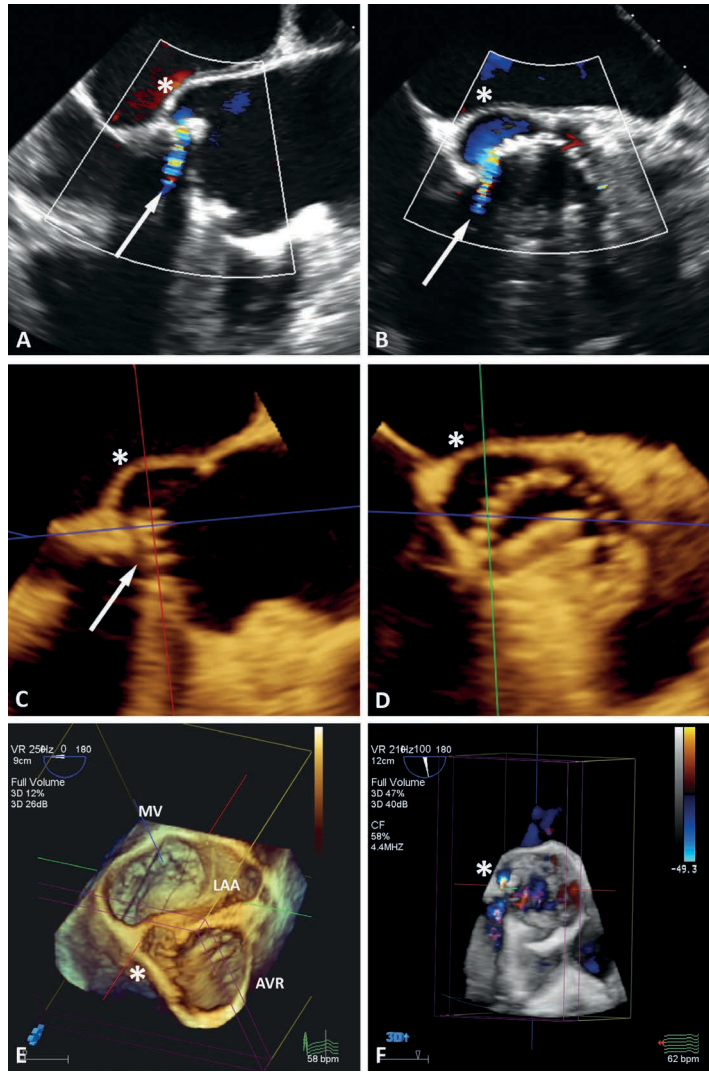
Population: In total we identified 24 PHV endocarditis cases that were operated on. For 15 out of 24 cases 2D TTE/TEE and 3D-TEE were available. Six of the 15 patients presented with early PHV endocarditis (< 1 year after implantation). All infected PHV's were in the aortic position. There were 10 mechanical and 5 biological PHV's. Blood cultures were positive in 12/15 (80%) cases and modified Duke criteria were met in 12/15 (80%) cases. CTA was performed in 13/15 patients. Other relevant patient and PHV characteristics are given in Table 1.

Endocarditis detection: All 2D- and 3D-TEE's were of sufficient image quality to identify the PHV ring and leaflets. Compared to the reference standard, the diagnosis of PHV endocarditis was correctly made after 2D-TTE and 2D-TEE in 13/15 cases (table 2). During surgical inspection 6/15 PHV cases had a vegetation. Combined 2D-TTE /TEE missed 1/6 vegetations (patient 1, table 2). No false positive vegetations were detected. After addition of 3D-TEE all vegetations (6/6) were detected correctly, and no false positives were encountered. 2D-TTE/TEE missed a peri-annular extension in 1/15 patients (Figure 1, patient 5) all other peri-annular extensions were correctly identified. Addition of 3D-TEE resulted in the correct detection of this mycotic aneurysm.

*Relationship between proximal RCA/LCA and peri-annular extensions: 2*D-TTE and 2D-TEE detected a peri-annular extension in 14/15 PHV cases. 2D-echocardiography excluded or detected inflammatory involvement of the right proximal coronary artery correctly in 7/14 cases. Addition of 3D-TEE resulted in correctly diagnosing one additional case of inflammatory involvement of the proximal RCA (Figure 2, patient 7). 2D-echocardiography excluded or detected inflammatory involvement of the proximal LCA in 10/14 cases. Addition of 3D-TEE resulted in two extra (correctly) detected cases of inflammatory involvement of the proximal LCA (12/14). In patient 5 in whom 2D-echocardiography missed the peri-annular extension, 3D-TEE could not visualize the RCA, but detected LCA involvement correctly. As a consequence in 3/14 cases, 3D-TEE resulted in better delineation of the coronary arteries in relation to the peri-annular extension compared to 2D echocardiography.

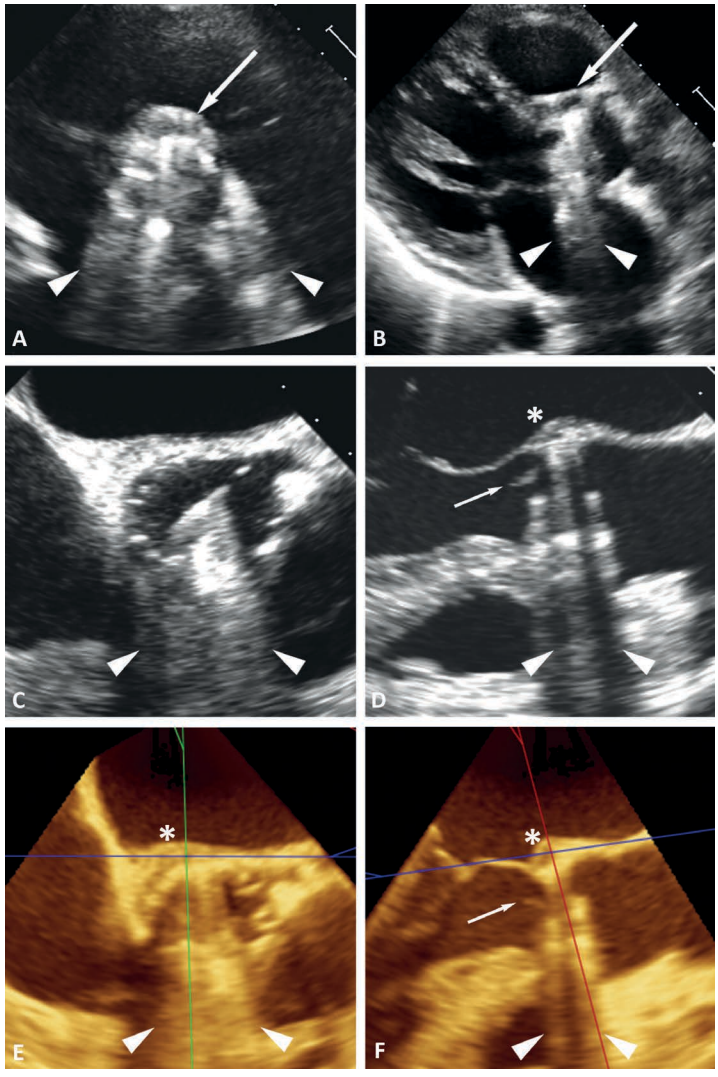
Additional value on soft end-points.
In 10/15 patients 3D-TEE did not have an additional value in terms of detection of additional vegetations, peri-annular extensions or better depiction of coronary arteries. However, in 8/10 of these cases reviewers stated that 3D-TEE was of complementary value as it confirmed the 2D diagnosis or gave a better delineation and/or extension of the peri-annular inflammation (Figure 3, patient 2). Furthermore in some cases involvement of the coronary arteries in the inflammatory process was more reliably excluded (Figure 5)

Figure 3: Confirmation of 2D-TEE findings by 3-D TEE.



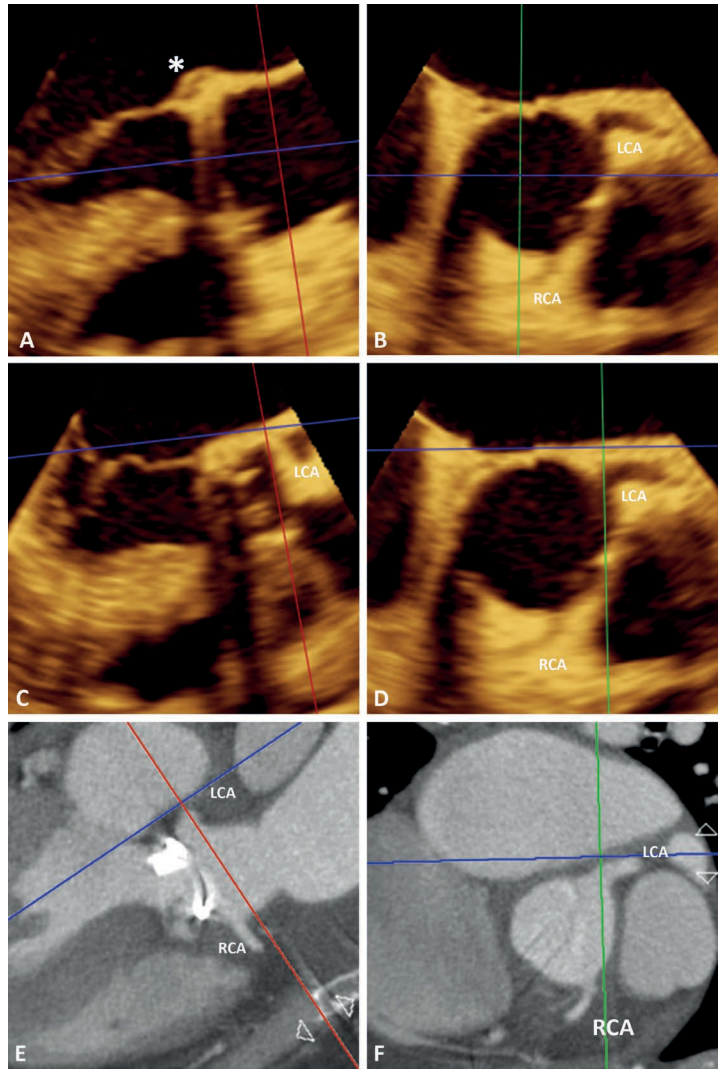
*Patient 2 with a long (**A**) and short (**B**) axis 2D-TEE view detecting a cavity with a new color Doppler flow near the former non coronary cusp of the AVR, suggestive of a mycotic aneurysm (* placed next to the mycotic aneurysm). 3D-TEE (**C**/**D**, MPR mode) confirmed this observation. The crosshairs of the MPR mode in panel **C** resemble the same location of the crosshairs in **D**. Panel E shows the 3D-cropping mode with the mycotic aneurysm and all the important surrounding structures. Panel **F** shows the 3D-color cropping mode of the AVR with the mycotic aneurysm and paravalvular leakage. (*) = next to mycotic aneurysm, arrow (→) = paravalvular leakage, LAA is left atrial appendage, MV = mitral valve.*

Figure 4: Acoustic shadowing in 2D-TTE/TEE and 3D TEE.



*Patient 15 with a short (**A**) and long (**B**) parasternal axis TTE view. 2D-TTE correctly detected the abscess near the anterior side of the AVR (arrows). Images of the posterior side of the AVR are hampered by acoustic shadowing. Short axis 2D-TEE (**C**) and long axis 2D-TEE (**D**) show not only an abscess near the former non/left coronary cusp (*), but also a vegetation (arrow). Optimal delineation of structures on the anterior side of the AVR is hampered by acoustic shadowing. Although 3D-TEE (E/F) is also hampered by acoustic shadowing, it also detects the vegetation (arrow). The crosshairs of the MPR mode resemble the same location in **E** and **F**, detecting the mycotic aneurysm to be near the former non (and not the left) coronary cusp (*), excluding a close relation with the LCA. Arrowheads (►) = acoustic shadowing, arrow (→) = vegetation, (*) = mycotic aneurysm.*

Figure 5: Exclusion of inflammatory involvement of the LCA by 3D-TEE.



Patient 15: 3D-TEE MPR mode showing the abscess near the former non coronary cusp and visualisation of the proximal RCA and LCA. Relation with the abscess and LCA could be excluded in D by moving the crosshairs to the LCA. As the crosshair in C resembles the same area, an abscess around the LCA could be excluded. This was confirmed by CTA (E/F) showing the same crosshairs. Asterix (*) = abscess, LCA=left coronary artery, RCA=right coronary artery.

DISCUSSION

This study was performed to investigate the additional value of 3D-TEE in complex PHV endocarditis. In this surgically confirmed population 2D-echocardiography performed well, however one vegetation and one abscess were missed in two different patients. Addition of 3D-TEE on top

of 2D-TTE/TEE resulted in the correct detection of all peri-annular extensions and vegetations without any false positive findings. Furthermore, 3D-TEE was of additional help in the detection of proximal coronary arteries and their relation to the infected peri-annular area. In almost all cases the reviewers stated that the offline cropping of the 3D-datasets was of additional value in terms of better depiction of the amount of inflammation and /or confirmation of the 2D-findings. This is also very important as therapeutic consequences are major.
Although 3D-TEE is also hampered by acoustic shadowing (Figure 4) wide-angled, full-volume datasets 3D-echo incorporates the ability to manipulate and crop images not limited to conventional 2D-planar views. This enables valvular visualization at angles not previously possible and to scroll through the 3D-dataset to search for subtle abnormalities and relationships between different structures. It allows identification not only of vegetations, but also of discrete valvular dehiscence and their associated regurgitation jets if 3D-color images are rendered. Furthermore, in our experience data acquisition and the offline reviewing of the 3D data is easy and in experienced hands it takes usually between five to ten minutes. However, in more complex cases it may require more time.

Especially the detection of peri-annular complications in PHV endocarditis is of paramount importance as it is accompanied by a high mortality and requires urgent surgical treatment [2, 3, 5, 7, 8]. It has been shown that 2-D echocardiography may miss PHV endocarditis signs. A few studies have recently been published investigating additional imaging techniques in PHV endocarditis patients [9-13]. Three small studies investigated the potential role of CTA[9, 12, 13]. Fagman et al. showed in a surgically confirmed subpopulation (n=16) that CTA combined with TEE improved the diagnosticaccurracy for both vegetations and abscesses in patients with PHV endocarditis [13]. Habets et al. confirmed these results and also showed that the addition of CTA to 2D-TTE/TEE resulted in a change of the therapeutic regimen in PHV patients [9]. Saby et al. prospectively studied 72 patients (29 surgically confirmed) with suspected PHV endocarditis to determine the accuracy of PET/CT (non-contrast enhanced) to diagnose PHV endocarditis and the complementary value of PET/CT as a major criterion in the modified Duke criteria [15]. The sensitivity and specificity of FDG-PET for PHV endocarditis was 73% and 80% respectively. When PET/CT was added as a new major criterion to the modified Duke criteria, the sensitivity rose from 70 to 97%. Both CTA and PET/CT studies showed that the diagnostic accuracy improved when it was combined with (2D) echocardiography. As a consequence, echocardiography will maintain its pivotal diagnostic role in PHV endocarditis. Moreover, CTA and FDG/PET have drawbacks such as extra costs, exposure to radiation and exposure to iodine contrast in case of CTA. The addition of 3D-TEE does not have these drawbacks and therefore may be even more beneficial.
Sugeng et al. investigated the visibility of PHV ring and leaflets by 3D-TEE in 40 patients, which were less visible in aortic PHV's compared to mitral PHV's. The ability to detect vegetations and/or peri-annular extensions however was not investigated [16]. Only a few case reports and small case series concerning signs of complex aortic PHV endocarditis detected by 3 dimensional echocardiography are reported in the literature [17-19]. Singh et al. reported on the additional value in detection of vegetations and peri-annular extensions by 3D-TTE in three complex AVR endocarditis cases with surgical confirmation [18]. Furthermore, Anwar et al. recently reported on the additional value of 3D-TEE in the detection of not only vegetations but also para-aortic abscesses in seven

Table 2: Echocardiography results

	Diagnosis according to the reference standard	2D-TTE + TEE	3D-TEE	Additional value of 3D-TEE
1	Abscess (NCC/LCC) Close relation abscess with RCA/LCA: -/+ Vegetation +	Correct Missed/Correct Missed	Correct Missed/Correct Correct	New vegetation detected
2	Mycotic Aneurysm (NCC) Close relation mycotic aneurysm with RCA/LCA: -/- Vegetation -	Correct Correct/Correct Correct	Correct Correct/Correct Correct	None
3	Mycotic Aneurysm (RCC/NCC/LCC) Close relation mycotic aneurysm with RCA/LCA: +/+ Vegetation -	Correct Missed/Correct Correct	Correct Missed/Correct Correct	None
4	Mycotic Aneurysm (LCC) Close relation mycotic aneurysm with RCA/LCA: -/+ Vegetation -	Correct Correct/Missed Correct	Correct Correct/Correct Correct	Relation abscess with LCA detected
5	Mycotic Aneurysm (LCC/RCC) Close relation mycotic aneurysm with RCA/LCA: -/+ Vegetation +	Missed Missed/Missed Correct	Correct Missed/Correct Correct	New mycotic aneurysm detected
6	Abscess (LCC) Close relation abscess with RCA/LCA: -/+ Vegetation +	Correct Missed/Missed Correct	Correct Missed/Missed Correct	None
7	Mycotic Aneurysm (NCC/RCC) Close relation mycotic aneurysm with RCA/LCA: +/- Vegetation –	Correct Missed/Correct Correct	Correct Correct/Correct Correct	Relation mycotic aneurysm with RCA
8	Mycotisch aneurysm (NCC/LCC) Close relation mycotic aneurysm with RCA/LCA: -/+ Vegetation +	Correct Correct/Missed Correct	Correct Correct/Correct Correct	Relation abscess with LCA detected
9	Mycotic Aneurysm (LCC/NCC) Close relation mycotic aneurysm with RCA/LCA: -/+ Vegetations-	Correct Correct/Correct Correct	Correct Correct/Correct Correct	None
10	Abscess (NCC) Close relation abscess with RCA/LCA: -/- Vegetation -	Correct Correct/Correct Correct	Correct Correct/Correct Correct	None
11	Abscess (LCC), Mycotic Aneurysm (RCC) Close relation peri annular ext. RCA/LCA: +/+ Vegetation -	Correct Missed/Correct Correct	Correct Missed/Correct Correct	None
12	Mycotic aneurysm (LCC) Close relation mycotic aneurysm with RCA/LCA: +/- Vegetation -	Correct Correct/Correct Correct	Correct Correct/Correct Correct	None
13	Mycotic Aneurysm + fistula (LCC/RCC) Close relation mycotic aneurysm with RCA/LCA +/+ Vegetations -	Correct Correct/Correct Correct	Correct Correct/Correct Correct	None
14	Mycotic aneurysm (LCC/RCC) Close relation mycotic aneurysm with RCA/LCA +/+ Vegetation +	Correct Missed/Missed Correct	Correct Missed/Missed Correct	None
15	Abscess (RCC/NCC) Close relation abscess with RCA/LCA: +/- Vegetation +	Correct Missed/Correct Correct	Correct Missed/Correct Correct	None

Legend Table 2: Correct=correctly diagnosed compared to the reference standard. LCA=left coronary artery, LCC=former left coronary cusp, Missed=not correctly diagnosed compared to the reference standard, N/A=not applicable, NCC=former non coronary cusp, RCA=right coronary artery, RCC=former right coronary cusp, + = present. - = absent.

complex aortic PHV (bio- and mechanical prosthesis) endocarditis cases [17]. Our study confirmed these preliminary findings and additionally showed that 3D-TEE is able to detect the relationship between peri-annular extensions in complex aortic PHV endocarditis and surrounding anatomical structures.

From the surgical perspective, detailed pre-operative knowledge of the extent of pathology such as the detection of inflammatory involvement of the proximal coronary arteries is relevant for the decision to use an allograft root replacement or not since these allografts need to be ordered timely. In this respect, Sasaki et al. recently showed the additional value of 3D-TEE in the evaluation of proximal coronary involvement in Type A aortic dissections [20]. Data in the present study also show additional value of 3D-TEE compared to 2D-echocardiography in the detection of involvement of the coronary arteries in the inflammation process of PHV endocarditis. However, the coronary arteries and their relationship to the peri-annular extension could not be identified in all subjects by 3D-TEE in our study (Table 2). For this indication CTA seems to remain the imaging modality of choice. However if coronary artery involvement is diagnosed this is of incremental value for the pre- operative strategy and may omit an additional CT angiography.

Limitations

1. This study is limited to the infectious complications of aortic PHV's. However in our practice infectious complications of inflow PHV's are less common. Moreover, diagnostic problems are most often encountered in aortic PHV`s, in which echocardiographic imaging is more frequently hampered by acoustic shadowing compared to mitral PHV's. Nevertheless, the additional value of 3D-TEE in PHV endocarditis other than the aortic valve remains to be investigated. 2. The number of patients included in this study is relatively low and all included individuals are from one tertiary referral centre. However, *surgically confirmed* PHV endocarditis cases are relatively rare, resulting in other high impact studies reporting on surgically confirmed PHV endocarditis with low numbers of included patients as well [3, 8, 21]. Since only surgical inspected cases are included in our study, no individuals with a suspected PHV endocarditis or "normal" PHV patients were included. Our reviewers were therefore aware of the presence of endocarditis and more focussed on detecting peri-annular extensions. This inclusion criterion was chosen to compare our 3D-TEE findings with a reference standard (surgical inspection). This may partially explain the relatively good diagnostic performance of 2D echocardiography in this study, since positive (2D) echocardiographic findings consequently had resulted in an indication for re-operation. Despite this 3D-TEE further improved the sensitivity in this study population. The specificity however remains to be investigated.

CONCLUSION

3D-TEE detects peri-annular extensions and vegetations in patients with confirmed complex aortic PHV endocarditis that can be missed by 2D-echocardiography. 3D-TEE also allows better delineation of the relation between the coronary arteries and the infected tissue. These promising results should be confirmed in larger studies that also include patients with absent and/or a suspicion of PHV endocarditis in order to establish the specific role of 3D-TEE in PHV endocarditis

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PART 2

PROSTHETIC HEART VALVE OBSTRUCTION

CHAPTER 6

DIFFERENTIATION OF THROMBUS FROM PANNUS AS THE CAUSE OF ACQUIRED MECHANICAL PROSTHETIC HEART VALVE OBSTRUCTION BY NON-INVASIVE IMAGING: A SYSTEMATIC REVIEW

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ABSTRACT

Aim: For acquired mechanical prosthetic heart valve (PHV) obstruction and suspicion on thrombosis recently updated ESC guidelines advocate confirmation of thrombus by transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and fluoroscopy. However, no evidence based diagnostic algorithm is available for correct thrombus detection, although this is clinically important as fibrinolysis is contraindicated in non-thrombotic obstruction (isolated pannus). Here, we performed a review of the literature in order to propose a diagnostic algorithm.

Methods and results: We performed a systematic search in Pubmed and Embase. Included publications were assessed on methodological quality based on the validated Quality Assessment of Diagnostic Accuracy Studies (QUADAS) II checklist. Studies were scarce (n=15) and the majority were of moderate methodological quality. In total 238 mechanical PHV's with acquired obstruction and a reliable reference standard were included for evaluation of the role of fluoroscopy, echocardiography or multidetector-row computed tomography (MDCT). In acquired PHV obstruction caused by thrombosis, mass detection by TEE and leaflet restriction detected by fluoroscopy were observed in the majority of cases (96% and 100 % respectively). In contrast, in acquired PHV obstruction free of thrombosis (pannus), leaflet restriction detected by fluoroscopy was absent in some cases (17%) and mass detection by TEE was absent in the majority of cases (66%). In case of mass detection by TEE, predictors for obstructive thrombus masses (compared to pannus masses) were leaflet restriction, soft echo density and increased mass length. In situations of inconclusive echocardiography, MDCT may correctly detect pannus/thrombus based on the morphological aspects and localization.

Conclusion: In acquired mechanical PHV obstruction without leaflet restriction and absent mass on TEE, obstructive PHV thrombosis cannot be confirmed and consequently fibrinolysis is not advised. Based on the literature search and our opinion a diagnostic algorithm is provided to correctly identify non-thrombotic PHV obstruction, which is highly relevant in daily clinical practice.

INTRODUCTION

Recently updated ESC guidelines advocate confirmation of thrombus formation by transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and fluoroscopy in acquired mechanical prosthetic heart valve (PHV) obstruction in order to justify treatment strategies such as fibrinolysis and heparine infusion [1]. After exclusion of patient prosthesis mismatch (PPM) by comparison of the TTE result with the initial postoperative TTE , the most probable cause of acquired mechanical PHV obstruction is thrombosis or pannus formation with an incidence of 0.4-6.0% per year, depending on valve type and position [2-4]. One of the treatment options of obstructive thrombosis is fibrinolysis, whereas in obstructive pannus this is contraindicated. In clinical practice, the differentiation of obstructive thrombus from isolated pannus remains challenging though very important when fibrinolysis is considered. Obstructive PHV thrombosis has an association with inadequate anticoagulation, short duration between PHV implantation and symptoms, and urgent requirement for treatment [4-6]. However, these clinical parameters are not reliable enough for differentiation in the individual patient. Furthermore, pre-test probabilities (before imaging) for obstructive pannus, thrombus or both, reported in a total of 412 cases, are respectively 6-63%, 24-81 % and 0-44% and therefore non discriminative [2,4,7,8]. For this reason, patients with acquired obstruction of their PHV require non-invasive imaging for differentiation of thrombus from pannus, which is crucial to choose the correct treatment strategy and correctly implement the guidelines in daily practise [1]. However, the diagnostic role of non-invasive imaging techniques for determination of the cause of acquired mechanical PHV obstruction has not been systematically reviewed and determined until now. The purpose of this systematic review was to determine and compare the diagnostic role of TTE, TEE, fluoroscopy and MDCT for detection of the exact cause of acquired mechanical PHV obstruction, based on currently available literature. Biological and non-obstructive PHV's were excluded because the diagnostic dilemmas mostly concern obstructed mechanical PHV's. Based on the results we will suggest an evidence-based imaging strategy for differentiation of obstructive thrombus from pannus.

METHODS

Literature search

A systematic electronic search was performed in the Pubmed and Embase databases for original publications published until 5th of November 2012. Language was restricted to English articles and publications from before 1985 were excluded because of inferior echocardiographic imaging quality and non-representative old mechanical valve types. Key search terms included the non-invasive imaging modalities (TTE, TEE, fluoroscopy and MDCT) and synonyms for prosthetic heart valves. The detailed search string is shown in Appendix I. For all included full-text papers, cross-referencing was performed.

Selection of publications

After removal of duplicates, the titles and abstracts were independently screened by two reviewers (WT and JH). Articles were included if: (1) Studies reported on one of the following non-invasive index tests (TTE, TEE, fluoroscopy or MDCT); (2) Studies provided data on features of mechanical PHV obstruction defined as: (a) leaflet restriction detected by fluoroscopy (opening

angles usually ± two Standard Deviations (±2SD) of the mean of normal opening angles [3,9]; (b) Doppler measured peak gradients greater than / Effective Orifice Area (EOA) smaller than usually ± 2SD of the mean values obtained from the patients own first postoperative TTE *or* from the reference group with normally functioning valves of the same type, size and position [10]; (3) Imaging results were verified against one of the following reference standards (surgical inspection/ autopsy or clinical follow-up/successful fibrinolysis) and (4) Retrospective thrombolysis studies that used inclusion criteria for already identified obstructive PHV thrombosis patients, were excluded because the inherent selection bias. Case reports were excluded for the same reason. Full-text publications of the included articles were obtained and assessed by two reviewers (WT and JH) independently. In a consensus meeting, both reviewers extensively discussed the full-text publications and data extraction.

PHV selection

From the included articles biological PHV's, PHV's without predefined reference standard, non-obstructive PHV's and PPM were excluded.

Quality assessment

Information on patient population, study enrolment, non-invasive imaging modalities and reference standard was collected. Studies were systematically assessed for quality based on the validated Quality Assessment of Diagnostic Accuracy Studies (QUADAS) II checklist (11). This checklist assesses the risk of bias and clinical applicability of studies based on different domains: 1. patient selection 2. index test 3. flow and timing 4. reference standard [11]. If studies had concerns in all domains they were of poor methodologically quality and if there were no concerns, of good quality. Studies with and without domains of concern, were of moderate methodologically quality.

Data analysis

The primary purpose of this review was to determine and compare the diagnostic role of non-invasive imaging modalities for diagnosing the exact cause of PHV obstruction. Based on these results an imaging strategy will be suggested for differentiation of thrombotic PHV obstruction versus non-thrombotic obstruction.

RESULTS

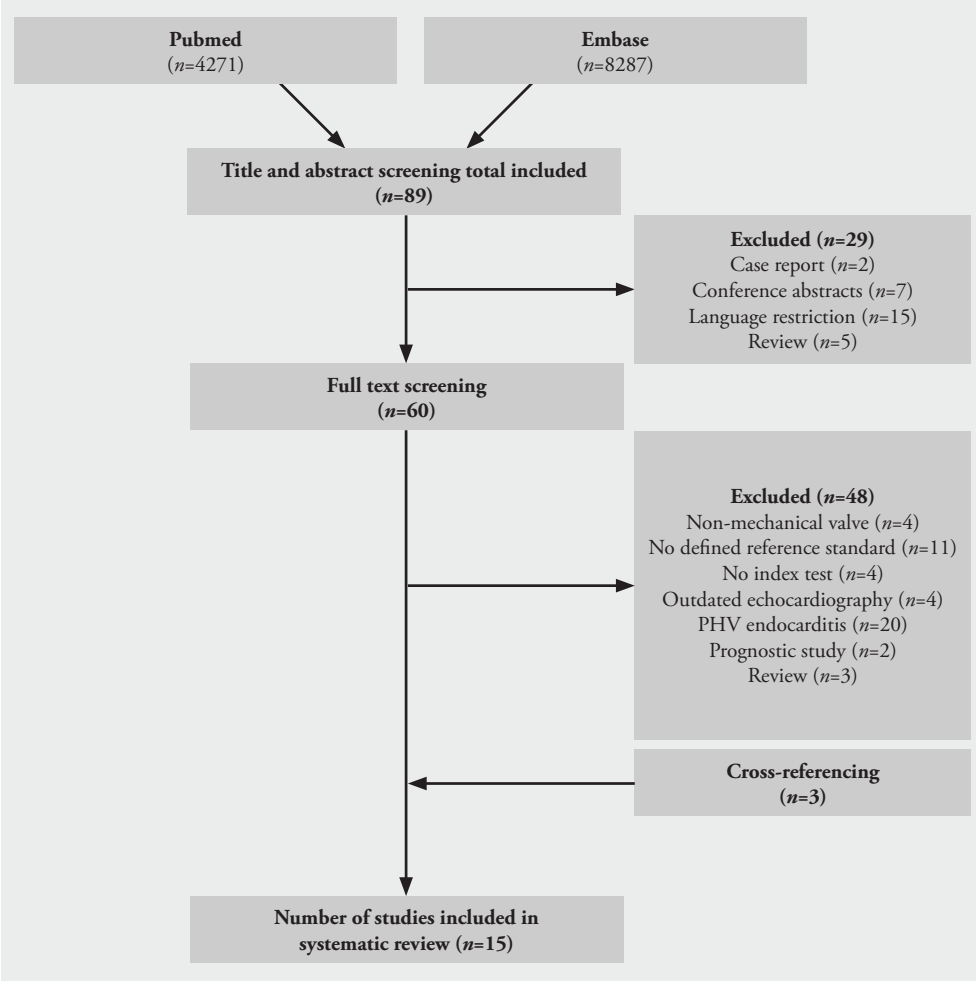
Search results

The systematic electronic search yielded a total of 4271 Pubmed and 8287 Embase publications. After screening of all titles and abstracts, 89 full-text versions of studies that matched the inclusion criteria were obtained. 77 studies were excluded because of different reasons (Figure 1). Cross-referencing of all included full-text articles resulted in three additional articles. Many studies reported on PHV dysfunction, but only a few fulfilled the inclusion criteria. In total, only 15 studies were included in this review.

Result of systematic electronic search

Table 1 demonstrates all included studies (*n*=15) that reported on the diagnostic cause of acquired mechanical PHV obstruction. The inclusion period occurred completely or partially before 1990

Figure 1: Literature search



in 20% of studies. Data were prospectively collected in 47% of studies and the assessment of the index test was blinded in 40% of studies. The interval between index test and reference standard was reported in 27% of studies and in 47% of all included studies all patients received a reliable reference standard (surgery/successful fibrinolysis). According to the QUADAS II and aforementioned data on patient selection, flow/timing, assessment of the index test and the reference standard, there are concerns regarding risk of bias and applicability in a vast majority of studies. None of studies were of good methodological quality, two had a poor methodological quality, the rest of studies moderate.

These 15 studies included a total of 671 PHV's with at least one non-invasive examination (TTE/TEE/fluoroscopy or MDCT) for the evaluation of PHV obstruction (Table 2). 433/671(65%) PHV's were excluded from the analysis for the following reasons; 1. PHV bioprosthesis (n=64) 2. Non-obstructive mechanical PHV's (n=78) 3. PPM (n= 19) 4. The absence of the predefined reference standard (n=272). In total 238 obstructed mechanical PHV's were included. The dis-

Table 1: showing the different domains of the QUADAS II checklist for all included studies (*n*=15)

Variable / First author	Journal (Year)	Inclusion period	Assessment without knowledge of reference standard	Data collection	Interval between reference standard and index test	Referene standard None (N) Surgery (S) Pathology (P) Thrombolysis (T)	All patients with reliable reference standard
Vogel [19]	Am J Card 1993	NR	Unclear	Prospective	NR	N/S	No
Aoyagi [14]	Jpn J Surg 1996	1980-1995	Unclear	Retrospective	NR	S/T	Yes
Habib [22]	Eur Heart J 1993	1989-1991	Unclear	Retrospective	NR	S/T	Yes
Barbetseas [5]	JACC 1998	NR	Yes	Retrospective	Mean 3.6 days	S+P	Yes
Aoyagi [17]	J Thor Cardio-vasc Surg 2000	1999	Unclear	Prospective	NR	N/S	No
Montorsi [12]	Am J Cardiol 2000	1994-1998	Yes	Prospective	Same day	N/S/T	No
Lin [6]	Am J Cardiol 2000	1992-1997	Yes	Retrospective	Mean 4 days or intraoperative TEE	S	Yes
Girard [12]	JACC 2001	1989-1998	Yes	Retrospective	Median 10 days	S+P	Yes
Montorsi [15]	Circulation 2003	NR	Unclear	Prospective	NR	S/T	Yes
Teshima [24]	Ann Thor Surg 2004	NR	Unclear	Prospective	NR	N/S	No
Muratori [13]	Am J Cardiol 2006	2001-2004	Unclear	Prospective	NR	N/S/T	No
Singh [23]	Echocard 2009	NR	Unclear	Retrospective	NR	N/S/T	No
Symersky [18]	Am J Cardiol 2009	2005-2008	Yes	Retrospective	NR	N/S	No
Tsai [21]	Eur Rad 2009	2005-2008	Unclear	Retrospective	NR	N/S/P	No
Ueda [20]	Circ J 2013	2003-2006	Yes	Prospective	NR	S	Yes

tribution of pannus, thrombus, combination of thrombus/pannus, or other were; 75/212(35%), 129/212(61%), 5/212(2%) and 3/212(1%) respectively. In this distribution, 26 PHV's described by Lin et al. were not included, because the two different causes of obstruction namely; thrombus and the combination of pannus/thrombus, were reported together as one group (6).

Fluoroscopy

From eleven studies reporting on obstructed PHV's and the diagnostic role of fluoroscopy, 146 PHV's could be included (Table 2).

Restricted leaflet opening: was defined as persistent diminished motion of at least one of the leaflets usually with a calculated opening angle (±2SD) different from values obtained in a reference group of patients with normally functioning valves of the same type and size and position [3]. Fluoroscopy was performed in 146 PHV's, aortic (AVR, n=69), mitral (MVR, n=73) and tricuspid (TVR, n=4). Restriction was observed by fluoroscopy in 139/146 (95%) mechanical valves, caused by either pannus alone (n=38), thrombus alone (n= 101) thrombus+pannus (n= 4) or other (n=3). All PHV's obstructed by thrombus (105/105, 100%) showed leaflet restriction by fluoroscopy (Table 3). Montorsi et al. evaluated 54 obstructive PHV's with and without leaflet restriction (13). In this study patients received surgery or fibrinolysis only when TEE detected masses. In 28 PHV's (22 mitral and 6 aortic) a mass was detected and confirmed to be thrombus after surgery or fibrinolysis. However, in this study a serious selection bias in favour of the detection of thrombus has been introduced as the 26 other patients with mainly aortic (23/26) PHV's were treated conservatively because no mass was found by TEE. Muratori et al. reported on 111 patients with and without leaflet restriction detected by fluoroscopy [13]. Fluoroscopy was superior in imaging of leaflet motion compared to echocardiography, especially in aortic PHV's. 41 of 111 patients had leaflet restriction detected by fluoroscopy. In this study also a serious selection bias was introduced because only patients with leaflet restriction (n=41) underwent surgery/fibrinolysis. This revealed thrombus as the underlying cause in all patients except one which was caused by pannus [13]. Moreover, Aoyagi et al described 20 patients with acquired mechanical PHV obstruction and a significant leaflet restriction at fluoroscopy [14]. 16/20 patients had thrombus as the cause for PHV obstruction, however the others had surgically confirmed pannus (4/20). Of note, two of four pannus cases received unjust and non-successful thrombolytic therapy before surgery [14]. In addition, another study of Montorsi et al. described seventeen patients with leaflet restriction on fluoroscopy, suspected for obstructive thrombus. They all received fibrinolysis, however in five of seventeen (29%) this was unsuccessful as pannus was the underlying cause [15]. Although the aforementioned studies [12-15], have a serious selection bias they show that leaflet restriction detected by fluoroscopy was primarily caused by thrombus, and to a lesser extent by pannus. Six other studies support this observation [16-21].

Absent leaflet restriction: seven out of 146 (5%) PHV's showed normal leaflet opening on fluoroscopy, despite significantly acquired elevated Doppler gradients. Thrombus was found in none of these PHV's, pannus (4/7) or LVOT obstruction (3/7) was the underlying cause.

Two-Dimensional Echocardiography

Six studies reported on the diagnostic role of echocardiography in acquired mechanical PHV obstruction (Table 2). TTE was used in 79 PHV's and TEE in 113. Masses were detected by TTE

Table 2: Included studies

PHV / First author	Total number of PHV's reported	Reason for exclusion PHV's (amount of excluded PHV's)	Total included PHV's (AVR/MVR/TVR)	Pannus/thrombus/both other	Fluoroscopy # Leaflet restriction +/-	Mass detected by TTE mass/total	Mass detected by TEE mass/total	MDCT results
Vogel [19]	95	No ref. standard (92)	3 (3/0/0)	1/1/1	3+/0-	NP	NP	NP
Aoyagi [14]	20	–	20 (11/5/4)	4/16/0	20+/0-	NR	NP	NP
Habib [22]	23	Non-obstructive (14)	9 (1/8/0)	0/8/1	NP	0/9	4/4	NP
Barbetseas [5]	24	–	24 (10/14/0)	10/14/0	NP	1/24	20/24	NP
Aoyagi [17]	54	No ref standard (49)	5 (5/0/0)	4/1/0	5+/0-	NR	NP	NP
Montorsi [12]	82	No ref standard (26) Non-obstructive (28)	28 (6/22/0)	0/28/0	28+/0-	NR	28/28	NP
Lin [6]	53	Non-obstructive (20)	33 (NR)	7/26 (T and T+P)	NP	NP	NR	NP
Girard [12]	92	Bio-prosthesis (43) PPM (19)	30 (30/0/0)	26/4/0	8+/3-	3/30	6/24	NP
Montorsi [15]	17	–	(0/17/0)	5/12/0	17+/0-	NR	NP	NP
Teshima [24]	16	No ref. standard (14)	2 (2/0/0)	2/0/0	2+/0-	NR	NP	Leaflet restriction and Pannus (n=2)
Muratori [13]	111	No ref. standard (70)	41 (13/28/0)	1/40/0	41+/0-	NR	NR	NP
Singh [23]	35	No ref. standard (7) Bio-prosthesis (21)	7 (1/5/1)	2/5/0	NP	2D: 3/7 (3D: 5/7)	NP	NP
Symersky [18]	15	No ref. standard (7)	8 (7/1/0)	2/0/3 3	4+/ 4-	NR	NR	Leaflet restriction 4+/4- Subvalvular tissue (n=5) Non valvular obstruction (n=3)
Tsai [21]	25	Non-obstructive (16) No ref. standard (7)	2 (2/0/0)	2/0/0	2+/0-	NR	NP	Leaflet restriction and Pannus (n=2)
Ueda [20]	9	–	9 (9/0/0)	9/0/0	9+/0-	0/9	NR	Leaflet restriction and Pannus (n=9)
Total	N=671	N=433	N=238 (100/100/5)*	75/129/5 * 3	139+/7-	7/79	58/80	N=20

*NR = not reported (although the diagnostic tool has been performed, e.g. for degree of obstruction but not for mass detection), NP: not performed at all, + = present, - = absent. # (top of table): fluoroscopy performed by cineradiography and otherwise by MDCT. *(bottom of table): distribution of obstruction cause (without Lin et al., see text results)*

Table 3: Detection of leaflet restriction by fluoroscopy in acquired PHV obstruction caused by thrombosis or no thrombosis.

	Thrombus	No thrombus	Total
Leaflet restriction	105	34	139
No leaflet restriction	0	7	7
	105	41	146

Fluoroscopy was performed in 146 PHV's, aortic (n=69), mitral (n=73) and tricuspid (n=4). Specification of the diagnosis obstructive thrombosis/pannus specified for PHV position was not possible as some studies did not report these data. Data extracted from: Vogel et al.[19] , Aoyagi et al.[14] , Aoyagi et al.[17] , Montorsi et al.[12] , Girard et al.[16] , Montorsi et al.[15] , Teshima et al.[24] , Muratori et al.[13] , Symersky et al.[18], Tsai et al.[21] , Ueda et al.[20].

in 7/79 of the obstructed PHV's. In the TEE analysis one study (n=33 patients) was excluded, because this study did not differentiate between obstructive and non-obstructive masses [6]. In total 80 obstructed PHV's were examined by TEE [5,12,16,22]. Overall mass detection (thrombus or pannus) in mitral PHV's (43/46, 93 %) was better compared to the detection of masses in aortic PHV's (19/34, 56%). In PHV thrombosis cases (8 AVR/42MVR) imaged by TEE (n=50) a mass was detected in almost all cases (48/50, 96%). Only in two AVR thrombosis cases the mass was missed. In non-thrombotic (pannus) cases (26 AVR/4 MVR) overall mass detection was poor, only in 10/30 PHV's (33%) a mass was detected (9 AVR/1 MVR, Table 4).

Only two studies have investigated the possibility of differentiation between obstructive pannus and thrombus by echocardiographic (TEE) parameters [5,6]. First, Barbetseas et al.[5] reported on 23 patients with 24 obstructed PHV's (10 aortic,14 mitral) caused by either pannus or thrombus formation. Corresponding to the fluoroscopy data, in all thrombus cases abnormal prosthetic valve motion was observed, whereas obstructive pannus cases showed leaflet valve restriction in 60% of cases. Masses were detected in 20/24 PHV's. Furthermore, thrombus masses had significantly more length (mean: 2.8± 2.5 cm versus 1.2±0.4 cm) and a significant lower video intensity ratio compared to pannus (0.46±0.14 versus 0.71±0.17). All masses with a length of > 2.0 cm or a video intensity of < 0.7 were obstructive thrombi. Lin et al. described 53 patients with operative confirmed pannus (n=19), thrombus (n=22) or both (n=12). Masses were detected by TEE in 42/53 PHV's, only 33/53 patients had PHV obstruction. Echocardiographic predictors for thrombus or pannus were investigated. In contrast to Barbetseas et al. this study failed to confirm an association with increased length and lower video intensity in thrombus masses [6]. This study identified two other echocardiographic predictors for PHV thrombosis; 1. mobile mass and 2. attachment to the occluder. However, Lin et al. also included 20/53 PHV's with non-obstructive thrombus or non-obstructive pannus. The latter is clinically less relevant. Moreover, no subgroup analysis was performed for the other 33/53 obstructed PHV's. For our research question this study has an unsuitable methodology and does not provide reliable echocardiographic predictors for obstructive thrombus or pannus discrimination.

Table 4: Detection of masses by TEE in acquired PHV obstruction caused by thrombosis or no thrombosis (pannus)

	Thrombus	No thrombus	Total
TEE mass present	48 (6 AVR/42 MVR)	10 (9 AVR/1 MVR)	58 (15 AVR/43 MVR)
Absent TEE mass	2 (2 AVR/ 0 MVR)	20 (17 AVR/3 MVR)	22 (19 AVR/3 MVR)
Total	50	30	80

AVR= mechanical prosthetic heart valve in aortic position, MVR= mechanical prosthetic heart valve in mitral position. Data extracted from: Habib et al.[22], Barbetseas et al.[5], Girard et al.[16], Montorsi et al. [12].

Three-dimensional echocardiography

No data are available on the diagnostic value of 3D TEE in acquired PHV obstruction, only a few case reports are published which are beyond the scope of this article. Only one retrospective case series study is published on the additional value of three dimensional TTE (3D TTE) compared to 2D TTE in five PHV's obstructed by thrombus and two by pannus [23]. In this study performed by Singh et al. surgery or successful fibrinolysis was the reference standard. In four out of seven (57%) patients 2D TTE missed masses, whereas 3D TTE missed only two out of seven (29%) masses. The missed masses with 3D-TTE were the two pannus cases. This small study suggests possible benefit of 3D echocardiography in detecting thrombi, however the small sample size prohibits definite conclusions [23].

Multidetector Computed Tomography

Four studies reported on the diagnostic value of MDCT. Teshima et al. reported 13 aortic PHV patients, in which MDCT detected subprosthetic tissue located on the ventricular side of the aortic PHV ring with attenuation values equal to those of the interventricular septum [24]. However, only 2 patients were operated and had surgically confirmed pannus. Symersky et al. [18] included patients with acquired PHV obstruction of unknown cause, in order to investigate the additional value of MDCT for the detection of the underlying cause of obstruction. Eight mechanical PHV's were re-operated, five patients had surgically proven thrombus and/or pannus. MDCT had detected all these masses. The three other patients had obstruction due to a suture knot (n=1) or subvalvular membrane (n=2), also correctly identified by MDCT [18]. Ueda et al. recently published on a group of nine patients with acquired mechanical aortic PHV obstruction confirmed by systolic restriction at fluoroscopy. In the patients that underwent echocardiography no masses were detected. All patients underwent MDCT, which detected subvalvular masses with an anatomical configuration matching pannus, confirmed by surgery in all patients [20]. In contrast to Teshima et al., this study reported Houndsfield units of the subvalvular masses to be significantly higher than the ventricular septum [24].

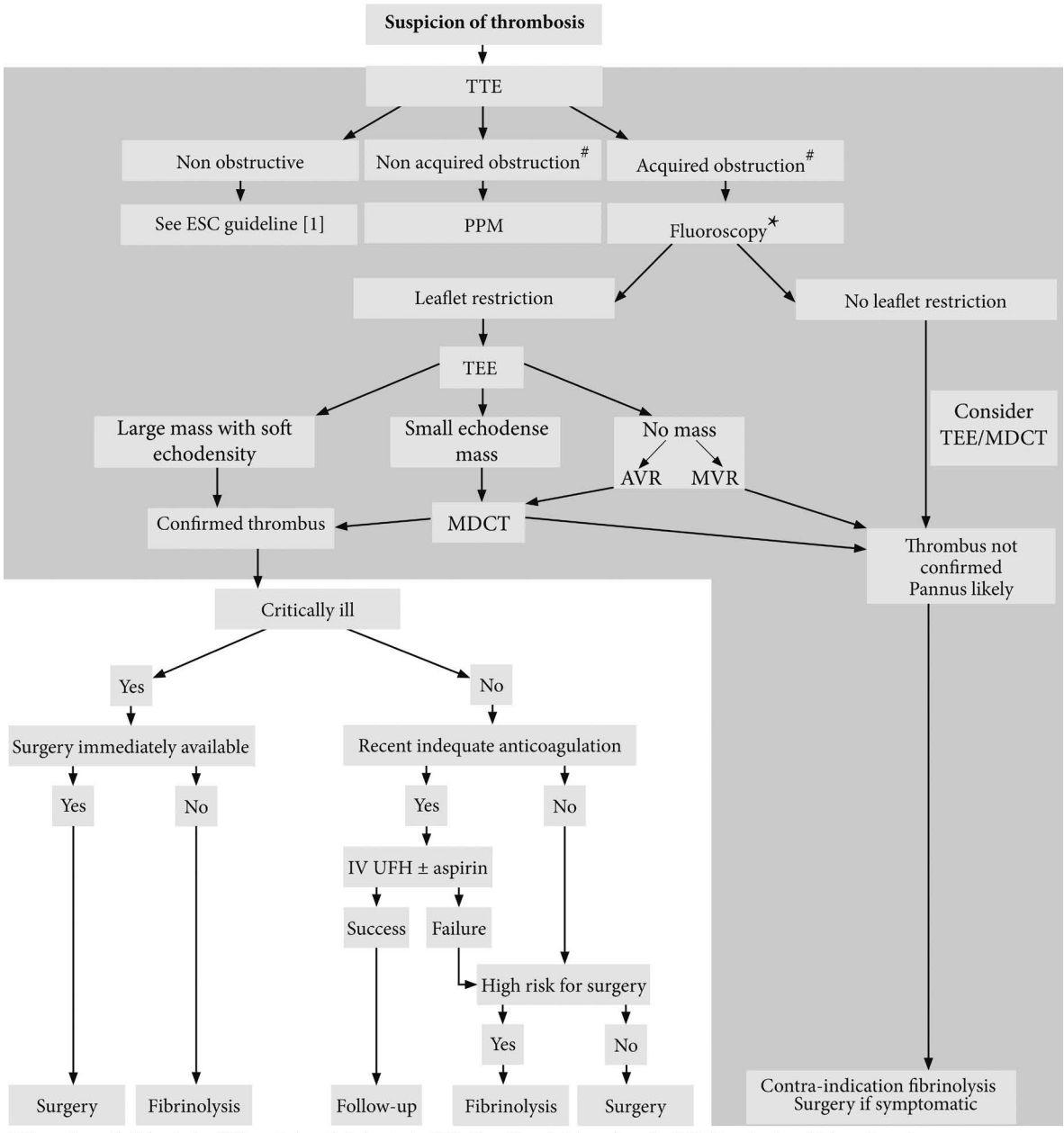
DISCUSSION

This review of the literature shows that differentiation between pannus and thrombus as the cause of acquired mechanical PHV obstruction remains challenging. However, it is clinically very important to exclude isolated pannus when fibrinolysis is considered, in order to prevent exposure to serious complications with a reported incidence varying between 17-25 % of the cases [25,26]. Despite a limited number and moderate methodological quality of studies, non-invasive imaging plays a key role in treatment decisions (surgery or fibrinolysis) in patients with obstructive PHV's. According to the recently published ESC guidelines on Valvular Heart Disease, confirmation of thrombus in patients with obstructive PHV's is required, because only PHV thrombosis can be treated by fibrinolysis (1). However, the guidelines provide no diagnostic strategy for thrombus confirmation and concomitant differentiation from pannus. Based on available literature and our opinion, we suggest an imaging strategy for this clinical problem (Figure 2).

After exclusion of non-obstructive PHV's and PPM by comparing with first post-operative TTE, we propose to perform fluoroscopy by cineradiography [12-19] or MDCT as the next diagnostic step [3,18,27,28]. Fluoroscopy in patients with acquired mechanical PHV obstruction is valuable, although an important limitation of fluoroscopy is the orientation of the PHV. For certain orientations such as an anatomically placed bileaflet mitral PHV and aortic PHV parallel to the ventricular septum, it may not be possible to obtain a good perpendicular view of the leaflets [9]. In these cases MDCT may be an alternative. If there is no leaflet restriction in patients with obstructed PHV's (high gradients/diminished EOA), thrombus is highly *unlikely* as the cause of obstruction and pannus is the most likely underlying mechanism (Table 3). Pannus is able to cause obstruction without restriction of leaflet opening, because overgrowth of fibrous tissue is located upstream of the PHV ring (Figure 3, case 1) [29]. For further confirma ion of pannus or exclusion of very rare other causes of obstruction such as PHV dislocation or re-growth of subvalvular membranes, additional MDCT and/or TEE may be considered (Figure 2).

When leaflet restriction is detected by fluoroscopy, both thrombus and pannus can be the cause of PHV obstruction (Table 3,5 and Figure 3 case 2/3). Furthermore, pannus can be superposed by thrombosis and therefore co-exist. In this situation we advise to perform a TEE for mass detection. If a mass is not present or not visible, thrombosis cannot be confirmed and surgery is the only defendable treatment strategy in symptomatic patients. Fibrinolysis studies already showed that TEE detected masses in all thrombosis cases, however mass detection by TEE was the main inclusion criterion in these retrospective studies [26,30,31]. These studies were not included in the present systematic review because there was no diagnostic dilemma regarding PHV obstruction, namely PHV thrombosis was already diagnosed. However, the present study also showed that obstruction by thrombosis is almost always accompanied by mass detection by TEE (Table 4). Although, this conclusion may be confounded as the thrombotic group with mass detection by TEE concerns mostly mitral PHV's (Table 4), in which imaging is less hampered by acoustic shadowing compared to other PHV's. Nonetheless, in case of detection of a mass more than 2.0 cm (especially if attached to the leaflet and of low echo density) the treatment flowchart of the ESC guidelines for confirmed thrombosis can be followed and fibrinolysis is one of the treatment options [1,5] (Figure 2). Considering the lower sensitivity of thrombus detection by TEE in obstructed aortic PHV's, in case of absent (or small) mass detection an additional MDCT can be performed for thrombus detection in order to avoid surgery in patients eligible for fibrinolysis.

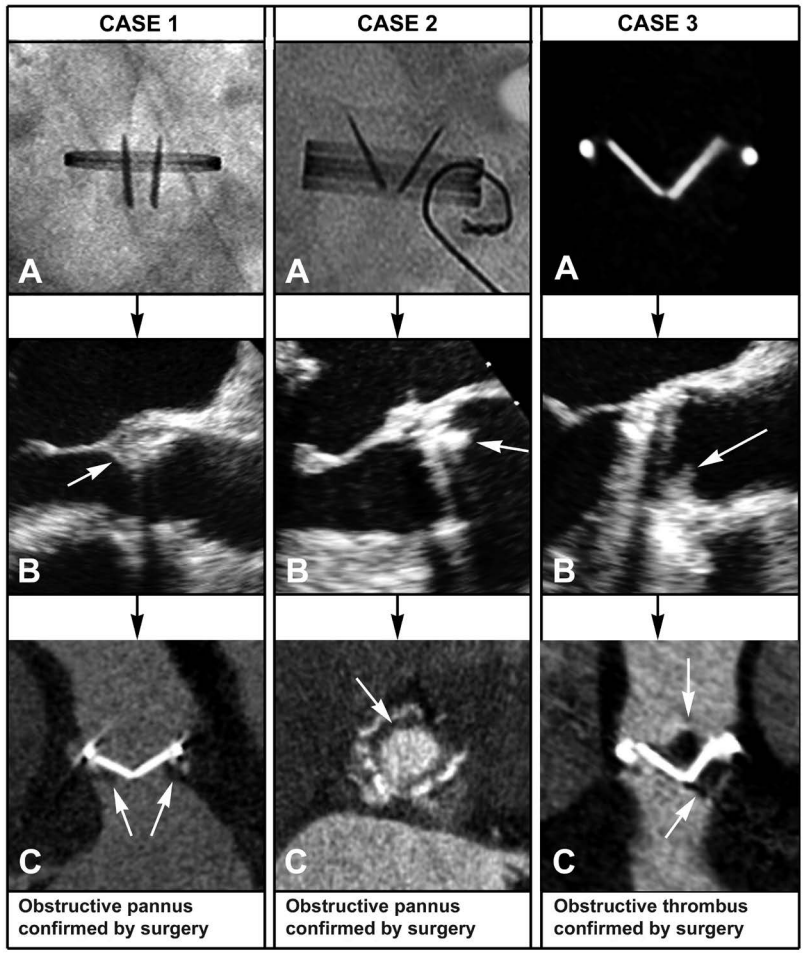
Figure 2: Advised diagnostic and therapeutic algorithm for suspected left sided mechanical PHV thrombosis.



AVR = aortic prosthetic heart valve. MVR = mitral prosthetic heart valve. TTE = Trans Thoracic Echocardiography. TEE = Trans Esophageal Echocardiography.
MDCT = Multidetector-row computed tomography. PPM = patient prosthesis mismatch.
*By cineradiography or MDCT. #Compared to postoperative baseline TTE.

The therapeutic strategy (white background) was adapted from the ESC guideline [1]. Grey background is the proposed imaging strategy based on this systematic review, but also partly guided by our own opinion and clinical experience.

Figure 3: Patients with acquired mechanical PHV obstruction and suspicion on thrombosis.



*Case 1: (**A**) Normal systolic opening angles of a aortic St. Jude mechanical PHV detected by fluoroscopy. (**B**). 120 degree TEE, arrow pointing at subprosthetic tissue at the ventricular side. (**C**) MDCT in the diastolic phase with arrows pointing at the hypodense subvalvular tissue only located on the ventricular side curved along the PHV ring which was pannus confirmed by surgery.*

*Case 2: (**A**) Both leaflets show systolic restriction at fluoroscopy (**B**) Aortic Tophat PHV imaged by TEE (120 degrees) with arrow pointing at the PHV ring and its concomitant acoustic shadowing. (**C**) MDCT shows hypodense subprosthetic tissue only on the ventricular side curved along the PHV ring which was pannus confirmed by surgery.*

*Case 3: (**A**) Both leaflets show systolic restriction detected by MDCT. (**B**) 120 degree TEE view with arrow pointing at an oscillating mass at the aortc side of the St. Jude PHV. (**C**) MDCT shows an irregular shaped and hypodense mass directly attached to the occluder on the ventricular and aortic side which was thrombus confirmed by surgery.*

Table 5: Criteria for identification of obstructing PHV thrombosis versus pannus

	Obstructive Thrombus	Obstructive Pannus	Patient prosthesis mismatch
Non imaging criteria	*Mitral/right sided PHV's *Low INR's *Acute presentation	*All PHV's *Adequate INR's *Non-acute presentation	*All PHV's *Adequate INR's *Non-acute presentation
Fluoroscopy	*Leaflet restriction	*Leaflet restriction common, but may be absent	*No leaflet restriction
Echocardiography	*Sudden increase in gradient compared to baseline *Mass detected by TEE *In case of mass detection: large mass (>2.0 cm) with low echo density	*Gradual increase of gradient compared to baseline *Small or absent mass *In case of mass detection: small mass with high echo density	*High baseline gradient for the type of PHV *Low baseline EOA for the type of PHV *Absent increase of gradient compared to baseline post-operative TTE *Absent mass
CTA	*Irregular shaped mass *Mass attached to leaflet/ hingepoint *Sub- and supravalvular mass location *Leaflet restriction	*(Semi) circular mass curved along ring *Subvalvular mass *Attachment of mass to PHV ring/hinge points *Leaflet restriction common, but may be absent	*Absent mass *No leaflet restricion

EOA= effective orifice area, Baseline = first postoperative TTE

Although TTE is an excellent diagnostic tool for determination of the severity of obstruction, in most cases it is not able to detect masses interfering with PHV opening. TEE can detect masses obstructing PHV's in mitral position, but is less suitable for PHV's in aortic position due to acoustic shadowing, especially if the mass is localized at the anterior side of the aortic PHV [16,20.] This conclusion may be confounded as the incidence of pannus (smaller masses) in the included *aortic* PHV's is much higher compared to included *mitral* PHV's (Table 4). This observation however reflects our daily clinical experience as it is known that mitral PHV's are more prone to thrombosis and aortic PHV more to obstructive pannus.

In theory, three-dimensional TEE might increase diagnostic accuracy, but studies are still lacking and also 3D-TEE is hampered by acoustic shadowing by the PHV. Only one reliable study on (2D TEE) differentiation between pannus and thrombus in 20 obstructed PHV's has been reported [5]. All the echocardiographic evidence for pannus and thrombus differentiation is based on this small study, which reported that large mass length and low echo density are associated with thrombus (Table 5). However, these parameters have not been confirmed by other studies.

As aortic PHV's MDCT seems to be a promising imaging modality to differentiate pannus formation based on anatomical configuration of the perivalvular masses [5,18,20,21,24,32,33]. Pannus is attached subvalvular to the PHV ring, imaged as a hypodense mass with a (semi)circular ana-

tomical configuration curved along the valve ring (Figure 3, case 1c/2c). In contrast, obstructive thrombi are imaged as supra- and subvalvular hypodense masses with irregular anatomy directly attached to the leaflets and hingepoints causing mechanical obstruction by leaflet restriction (Figure 3, table 5, case 3). Theoretically also mass differentiation (thrombus versus pannus) should be possible by determining the Houndsfield units, though no evidence is available.

Limitations

First, the majority of the included studies dealt with thrombosis patients with PHV's in mitral position and pannus patients with mainly aortic PHV's. Second, only surgically explored or thrombolysed patients were included. This has resulted in a major selection bias. Third, obstructed PHV's with leaflet obstruction at fluoroscopy and mass detection at TEE possibly underwent surgery/thrombolysis more easily. This also resulted in selection bias in favour of thrombosis. Fourth, methodological quality of the studies was generally moderate. This could have influenced our conclusions. Fifth, data on novel imaging techniques (3D-TEE and MDCT) are preliminary. Sixth, studies concern mainly left sided PHV's, therefore no conclusions can be drawn for right sided PHV's.

CONCLUSION

This review shows that studies on acquired mechanical PHV obstruction are scarce and have a varying (moderate) methodological quality. Based on this review and our opinion, in acquired mechanical PHV obstruction without leaflet restriction at fluoroscopy and/or absent TEE mass, thrombosis cannot be confirmed and fibrinolysis is not advised. In contrast, the presence of leaflet restriction and/or TEE mass detection can be caused by either thrombus and/or pannus masses. Evidence for reliable echocardiographic thrombus and pannus mass differentiation is limited. In situation of a diagnostic impasse MDCT might be a promising complementary imaging modality for correct thrombus/pannus differentiation. Well-designed large prospective cross sectional studies are needed to determine the additional value of MDCT and 3D-TEE for determination of the cause of acquired PHV obstruction.

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CHAPTER 7

IMAGING OF PROSTHETIC HEART VALVE DYSFUNCTION: COMPLEMENTARY DIAGNOSTIC VALUE OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY AND MULTIDETECTOR COMPUTED TOMOGRAPHY

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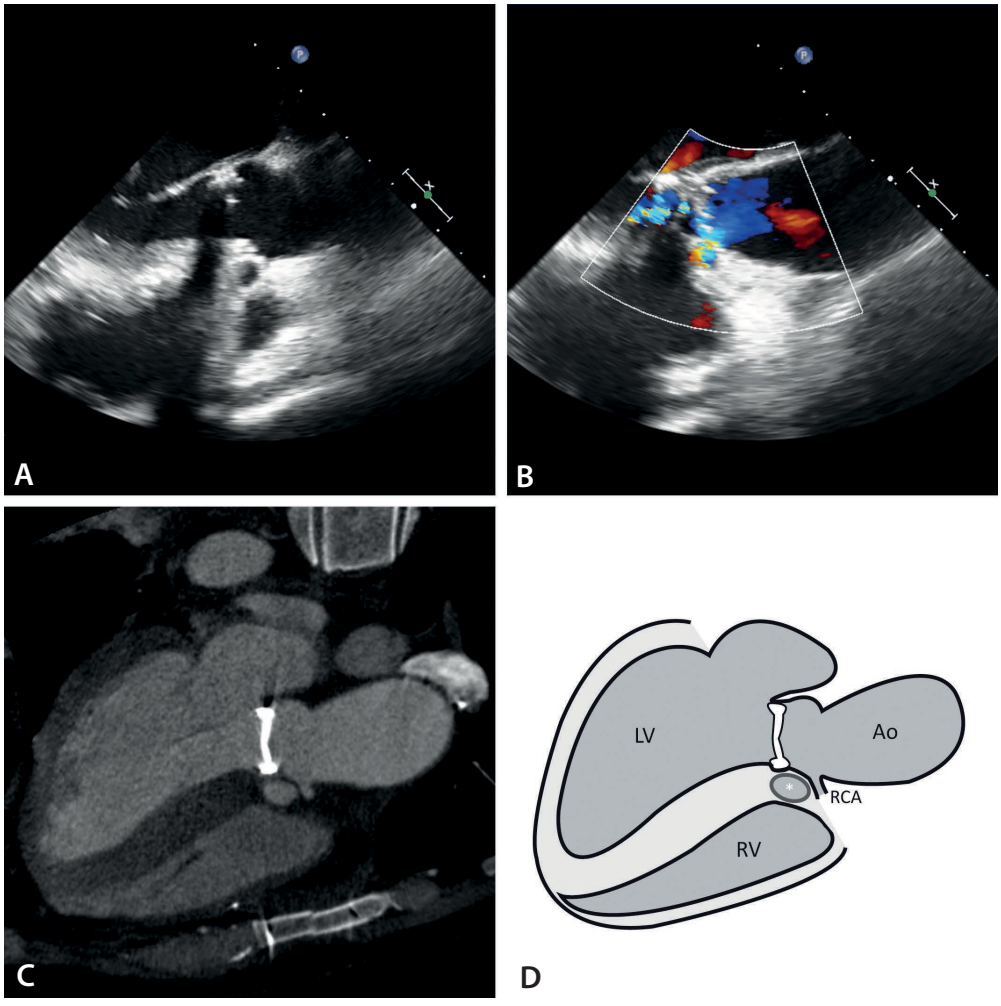
INTRODUCTION

Prosthetic heart valves are increasingly implanted worldwide to replace diseased native valves. Prosthetic heart valve (PHV) dysfunction is rare but potentially life-threatening. In clinical practice, transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and fluoroscopy for mechanical valves, are the routine imaging modalities to evaluate suspected PHV dysfunction [1]. Establishing the exact cause of PHV dysfunction is important to determine the appropriate treatment strategy but can be difficult. Multidetector computed tomography (MDCT) may have complementary diagnostic value to the routine imaging modalities in these patients [1]. In this paper we present the spectrum of findings with echocardiography, fluoroscopy and computed tomography for a variety of PHV dysfunction aetiologies that includes endocarditis, thrombus and pannus formation.

Abbreviation list

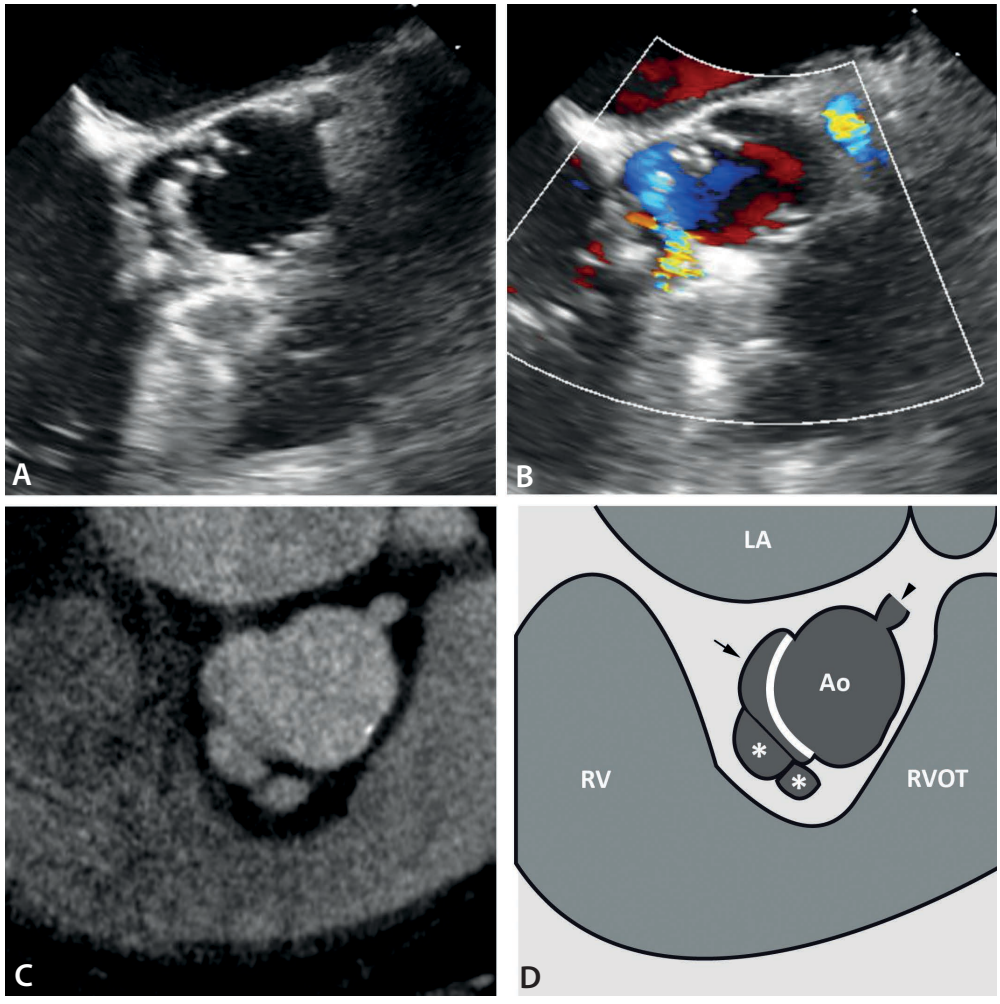
Ao = Aorta
AMVL = Anterior Mitral Valve Leaflet
IVS = Interventricular Septum
LA = Left Atrium
LAA = Left Atrial Appendage
LM = Left Main
LV = Left Ventricle
MDCT = Multidetector Computed Tomography
PHV = Prosthetic Heart Valve
RV = Right Ventricle
RVOT = Right Ventricular Outflow Tract
TTE = Transthoracic Echocardiography
TEE = Transesophageal Echocardiography

Figure 1: PHV endocarditis: 120 degree TEE view and matching MDCT reconstruction



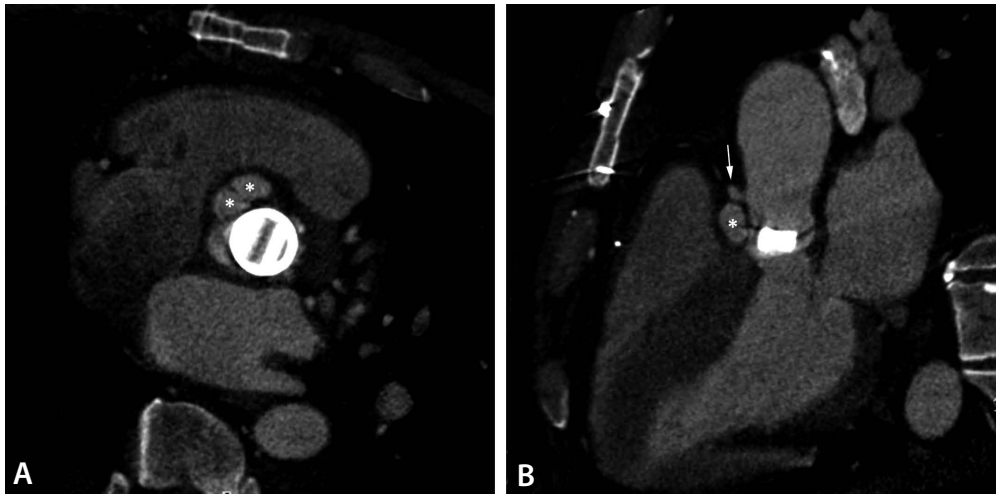
Definite or possible diagnosis of PHV endocarditis is based on the modified Duke criteria in which non-invasive imaging plays a key role [2]. A low threshold for performing TEE after TTE is advisable because of the low sensitivity of TTE for the detection of signs of PHV endocarditis. In this patient with a Carbomedics bileaflet PHV in the aortic position, TTE demonstrates severe aortic regurgitation. In addition, TEE and MDCT reveales a mycotic aortic root aneurysm directly underneath the right coronary artery (RCA) origin (**A**,**C**) with diastolic paravalvular leakage as seen on color Doppler imaging (**B**). Acoustic shadowing on the TEE images (**A**) hampers complete and accurate assessment of the PHV. MDCT however does not show any vegetations (**C**). MDCT nicely demonstrates the close relationship of the mycotic aneurysm and the RCA (**C**, **D**). The location of the mycotic aneurysm is indicated by an asterisk on the schematic drawing (**D**). MDCT images can be reconstructed in any desired imaging plane after acquisition and allow for a one on one comparison with every echocardiographic view.

Figure 2: PHV endocarditis: short axis TEE view and matching MDCT reconstruction



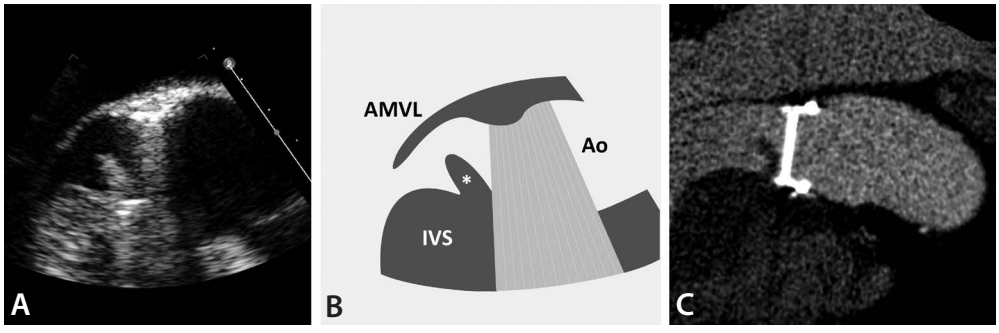
In the same patient as presented in Figure 1, short axis TEE images demonstrates the mycotic aneurysm (**A**) and the diastolic paravalvular leakage on color Doppler (**B**). MDCT also demonstrates the mycotic aneurysm. It allows detailed delineation of its contours (**C**) due to lack of acoustic shadowing, which was present on TEE images (**A**). However, TEE provides additional hemodynamic information by color Doppler flow demonstrating the diastolic flow paravalvular leakage (**B**). Although MDCT confirms the paravalvular route by showing contrast outside the valve it cannot determine the diastolic and systolic flow direction. The illustration (**D**) illustrates the partition of the mycotic aneurysm on MDCT images (**D**; *) and the close relationship of the aneurysm with the right sinus of Vasalva (arrow). The arrowhead indicates the orifice of the left main branch.

Figure 3: PHV endocarditis: MDCT short axis and parallel view



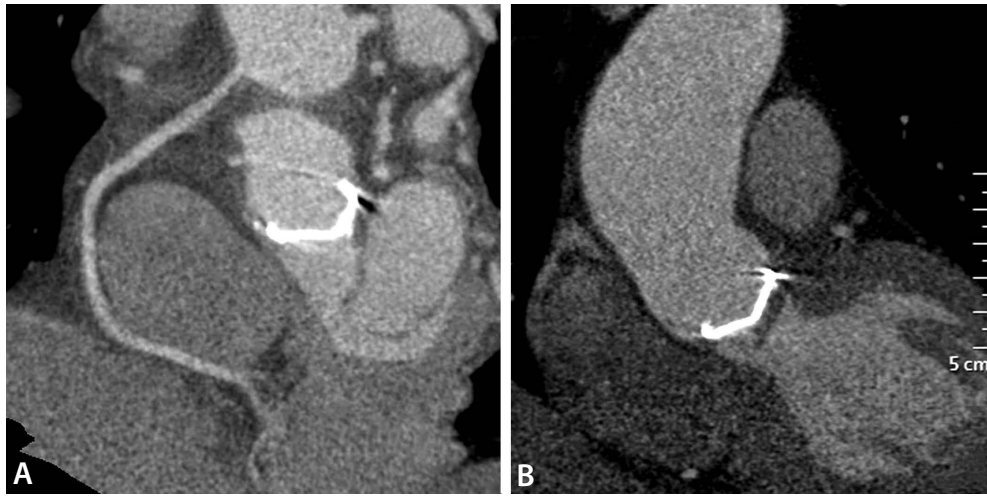
In the same patient as Figures 1 and 2, MDCT images demonstrates the extent of the mycotic aneurysm (**A/B**; *) and the close relationship with the right coronary artery (RCA) (**B**; **arrow**). This anatomical information is of high clinical importance for the preoperative surgical guidance in case of re-operation (prosthetic heart valve replacement with/without pericardial patch or homograft implantation with coronary re-implantation). In this case, the extent of the mycotic aneurysm and the close relationship with the RCA resulted in a successful homograft implantation with re-implantation of the coronary arteries.

Figure 4: PHV endocarditis: 120 degree TEE view and corresponding MDCT reconstruction



This patient with a St. Jude bileaflet PHV in the aortic position presented with suspected PHV endocarditis (fever and multiple positive blood cultures with streptococcus). Both TTE and TEE (**A**) revealed a large (11x14mm) mobile echodense mass indicating the presence of a vegetation. The potential presence of an abscess or mycotic aneurysm on the septal side of the PHV was difficult to assess due to acoustic shadowing (**A/B**). The illustration demonstrates the relation of the vegetation (*) with the interventricular septum (IVS) and the anterior mitral valve leaflet (AMVL). MDCT confirmed the presence of the vegetation underneath the PHV (**C**) and definitely excluded the presence of an abscess or mycotic aneurysm.

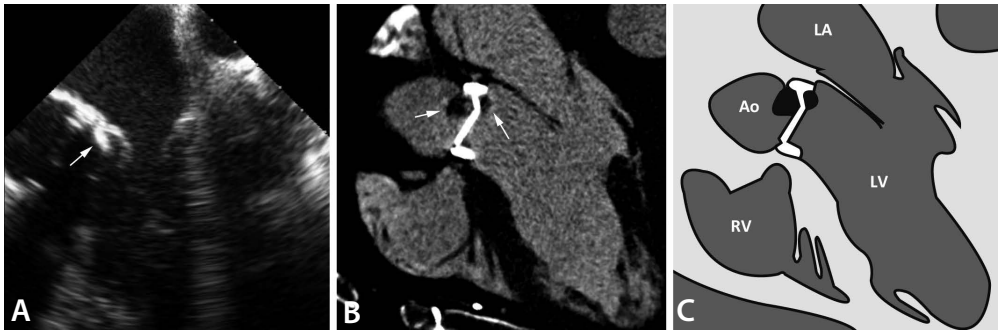
Figure 5: PHV endocarditis: simultaneous coronary artery obstruction and aortic dimension assessment by MDCT



The presence of a large vegetation is an indication for urgent reoperation. For appropriate preoperative assessment, the cardiothoracic surgeon needs to be informed on the presence of coronary artery disease (CAD). Invasive coronary angiography is the gold standard for coronary assessment. However, the presence of a large vegetation is associated with an increased risk of distal embolization by catheter manipulation. Therefore, non-invasive evaluation of the coronary arteries is preferred. Figure **5A** demonstrates the ability of MDCT to evaluate coronary arteries (i.e. RCA) simultaneously with PHV assessment. MDCT excluded coronary artery disease and given the high negative predictive value of MDCT for the presence of coronary artery disease, invasive coronary angiography was omitted (same patient as in Figure 4). Although MDCT is a suitable technique to exclude coronary artery disease, in patients with severe coronary calcifications it is difficult to identify significant coronary stenosis.

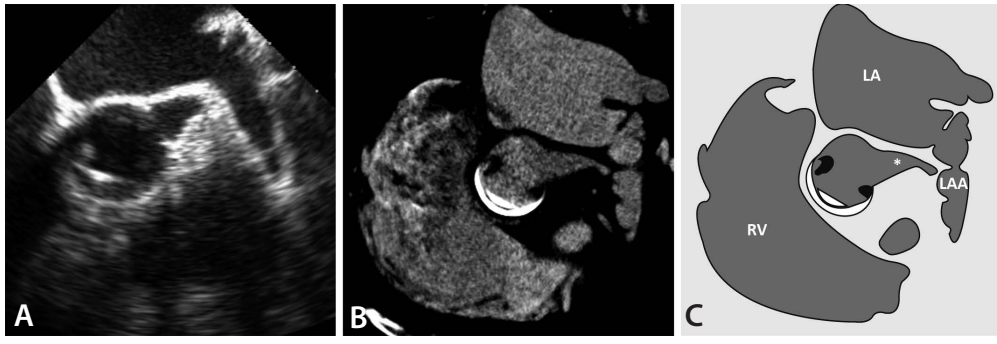
Proximal aortic assessment is important because of possible therapeutic consequences (aortic root and/or arch replacement). In this case, MDCT (Figure **5B**) revealed an aneurysm of the ascending aorta (diameter 50mm) which was missed with TEE because of focusing on PHV assessment. Although TEE is able to detect aneurysms of the ascending aorta, it is inferior to MDCT for diameter measurements. The presence of a large vegetation and the dilated ascending aorta resulted in the choice for replacement of both the PHV and ascending aorta (Bentall procedure). Surgical inspection confirmed the presence of a large vegetation and the absence of a mycotic aneurysm in the aortic root. Surgery also confirmed the dilated ascending aorta.

Figure 6: PHV thrombosis: 0 degree TEE view and corresponding MDCT reconstruction



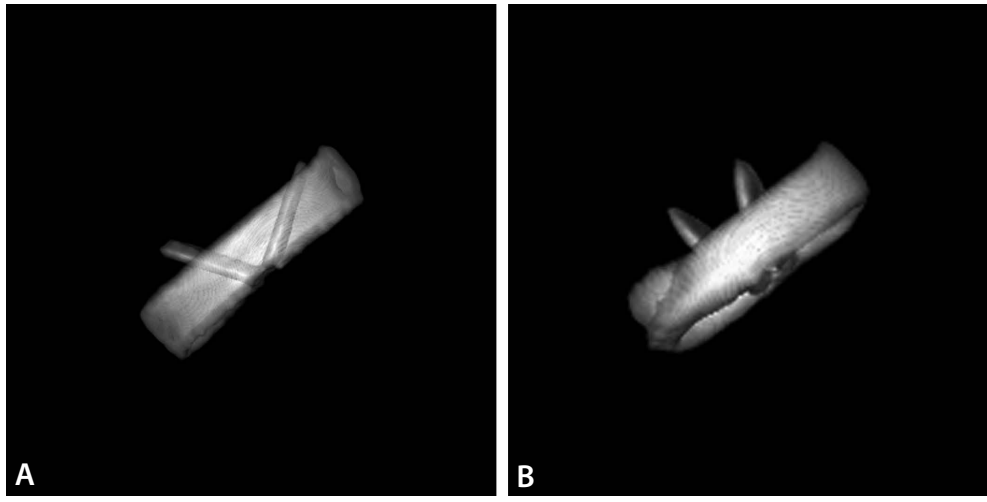
Patients with PHV obstruction presents with an increased pressure gradient and/or decreased prosthetic orifice area on TTE. The exact cause of PHV obstruction is often not detected with TTE. In this patient with a Carbomedics bileaflet PHV in the aortic position, additional TEE, fluoroscopy and MDCT was performed. TEE demonstrates a subvalvular echodense mass located between the septal side of the PHV and the anterior mitral valve leaflet (**A**, **arrow**). MDCT confirmed the presence of this mass on the ventricular side of the PHV. Moreover, an additional hypodense mass was seen on the aortic side of the PHV (**B**, **arrows**). The irregular shape and the location on both the aortic and ventricular side of the PHV (**C**) favours the diagnosis of PHV thrombosis over pannus formation.

Figure 7: PHV thrombosis: short axis TEE view and corresponding MDCT reconstruction



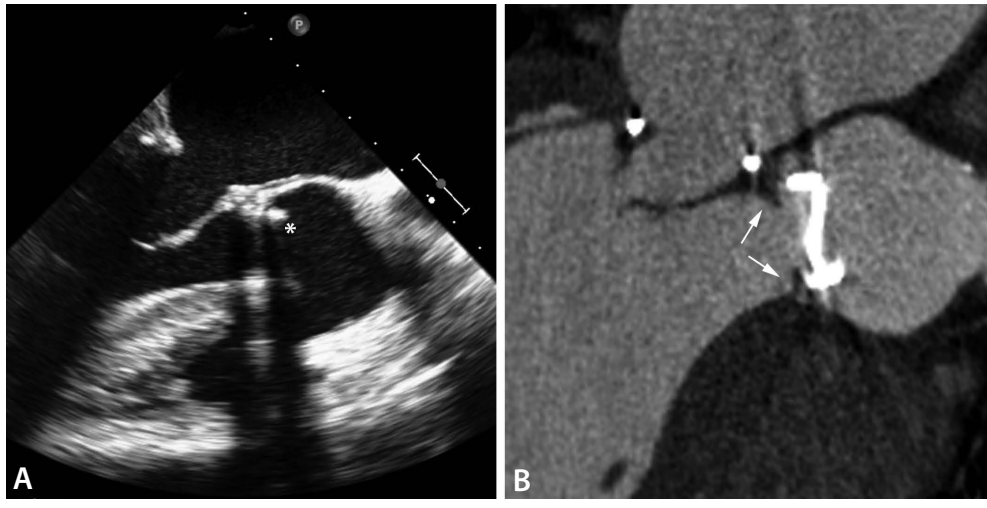
In the same patient as Figure 6, diastolic TEE short axis images demonstrate two possible echodense masses on the aortic side at the level of the origin of the aneurysmatic left coronary artery (**A**). These possible lesions were missed at the initial TEE interpretation. MDCT was performed for determination of the exact cause of the PHV obstruction, and nicely delineated two hypodense irregular shaped lesions on the aortic side of the PHV which are compatible with PHV thrombosis (**B**). After this observation, two possible echodense masses were identified on TEE images. The illustration (**C**) demonstrates the two irregular shaped lesions (black) and their relationship with the PHV and aneurysmatic left main branch (*).

Figure 8: PHV thrombosis: 3D volume rendered MDCT images



In the same patient as Figure 7, both fluoroscopy and MDCT (**A**) demonstrated restricted leaflet opening, more pronounced on one side but also present on the other side. Asymmetric leaflet restriction is often present in PHV thrombosis, but also seen in patients with pannus formation. Comprehensive imaging evaluation resulted in the diagnosis of PHV thrombosis which was treated with additional anticoagulation therapy (warfarin plus low-molecular weight heparins) and antiplatelet therapy (aspirin). After two months, TTE showed normalization of maximum pressure gradient over the aortic PHV. MDCT confirmed this by showing normal leaflet opening of both leaflets (**B**), and the hypodense irregular shaped mass disappeared. This confirmed the correct diagnosis and treatment of PHV thrombosis.

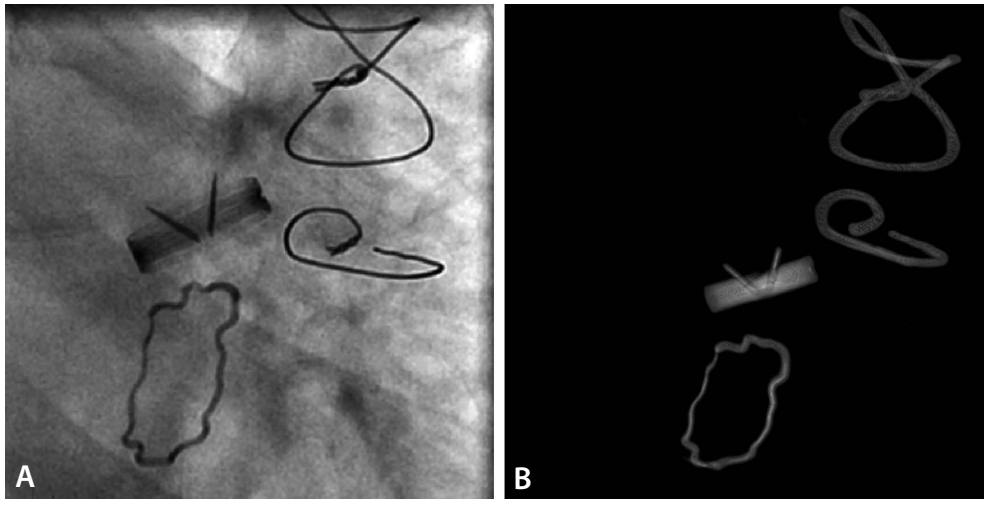
Figure 9: PHV pannus formation: 120 degree TEE view and corresponding MDCT reconstruction



This patient presented with a gradual increase of maximum pressure gradient over the aortic

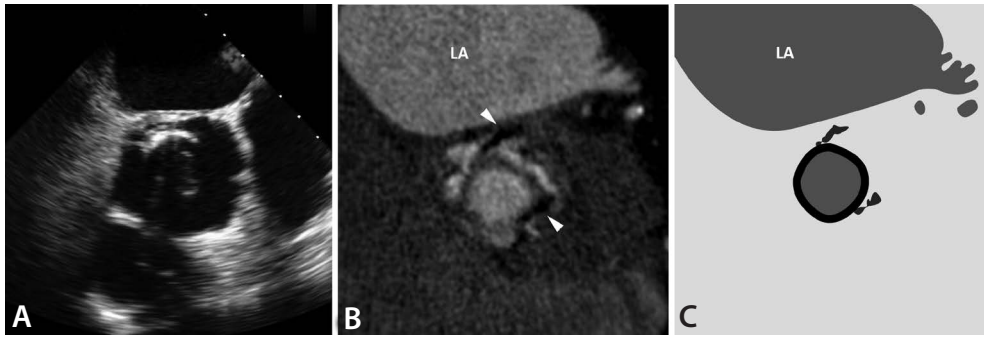
PHV (Carbomedics Tophat bileaflet) and complaints of dyspnea (NYHA class II). TTE did show an increased pressure gradient but could not determine its exact cause. The assessment of the PHV especially the subvalvular area on TEE images was hampered by acoustic shadowing. No echodense masses were seen on the subvalvular side, but a possible supravalvular echodense mass (*) was identified. This contour is however typical for this specific PHV type that is implanted in supra-annular position. MDCT did not show any supravalvular mass. However, MDCT identified a semicircular hypodense mass on the ventricular side of the PHV ring (**arrows**) which is compatible with pannus formation. Pannus formation is a known cause for PHV obstruction leading to a gradual increase of the pressure gradient over the PHV.

Figure 10: PHV pannus formation: Fluoroscopy and MDCT fluoroscopy



Same patient as in Figure 9. PHV leaflet assessment was hampered by acoustic shadowing on TEE. Fluoroscopy was performed to assess leaflet motion. Normal manufacturer leaflet opening angles of this PHV are 78 degrees. Fluoroscopy (**A**) revealed decreased leaflet opening of both leaflets (49 degrees at posterior side and 54 degrees at septal side, respectively). MDCT confirmed this leaflet restriction (**B**). Furthermore, notice the presence of a mitral annuloplasty ring.

Figure 11: PHV pannus formation: short axis TEE and MDCT view



TEE images did not show a subvalvular mass (**A**, same patient as in Figure 9). However, MDCT demonstrated a circular hypodense mass in the subvalvular region (**B**). Hypodense PHV-related artifacts are indicated with arrowheads. The illustration (**C**) emphasizes the circular pattern en the PHV-related artifacts (black) This circular hypodense mass is more suggestive for pannus formation. Therefore, thrombolysis was not considered and the patient was referred for surgery. Surgical inspection confirmed pannus formation as the cause of PHV dysfunction.

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CHAPTER 8

THE DETECTION OF PROSTHETIC HEART VALVE THROMBOSIS BY COMPUTED TOMOGRAPHY ANGIOGRAPHY

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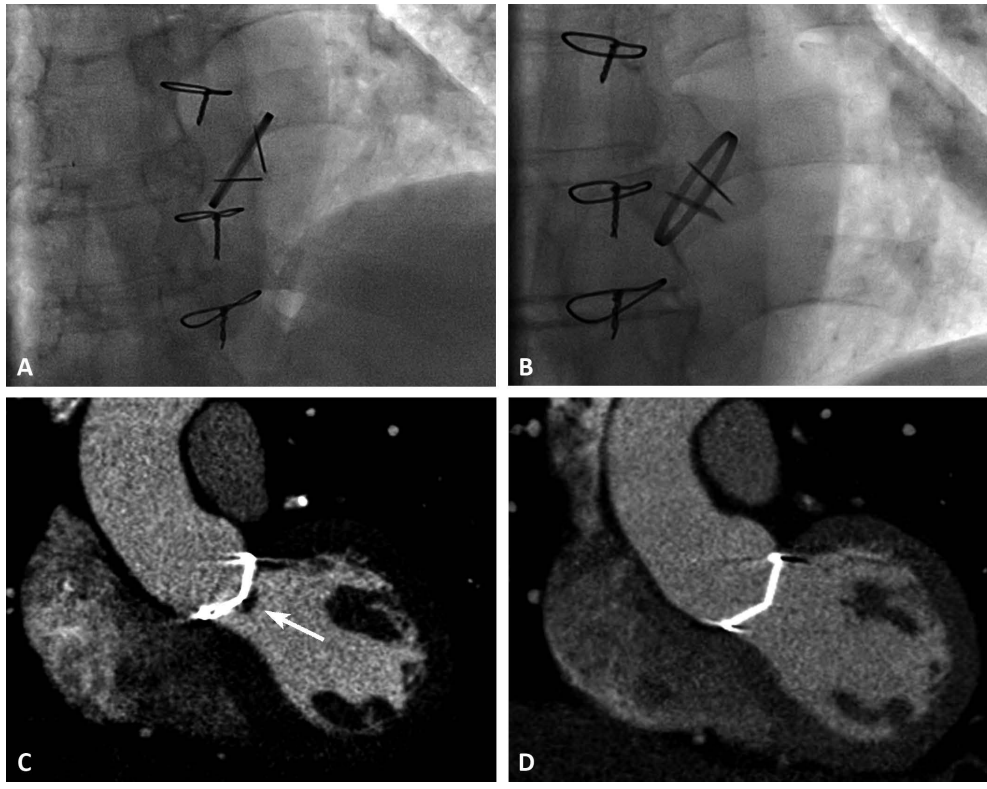
THE SILENCE OF THE LEAFLETS



A 63-year-old man with a bileaflet mechanical aortic-valve replacement presented with a 3-week history of no audible leaflet clicks. Since he had undergone valve placement 6 years earlier for endocarditis, the clicks had always been clearly audible. The physical examination revealed a new systolic murmur and confirmed the absence of leaflet clicks. Transthoracic echocardiography showed a severely increased peak gradient (75 mm Hg, as compared with 32 mm Hg at baseline) over the mechanical aortic valve, and diminished opening of both leaflets was detected on fluoroscopy (**Panel A**). Cardiac computed tomographic angiography (CTA) revealed a hypodense mass on the leaflets that was suggestive of thrombus, although a vegetation could not be ruled out (**Panel C**, **arrow**). Target values for the international normalized ratio were increased from 3.0 to 4.0, and aspirin was administered. The patient was scheduled to undergo repeat aortic valve replacement in 12 weeks. However, when he was subsequently admitted for surgery, he reported hearing the leaflet clicks again. The patient reported having had no symptoms of embolic events during this period. Transthoracic echocardiography showed normalization of the pressure gradient, and fluoroscopy showed normal opening of both leaflets (**Panel B**), which was suggestive of thrombus resolution, as confirmed on CTA (**Panel D**). These images illustrate that the absence of clicks from a prosthetic heart valve requires urgent evaluation. Furthermore it shows that echocardiography and fluoroscopy may not detect the exact cause of the PHV obstruction, CTA however can be of additional help.

CHAPTER 9

NON-INVASIVE CORONARY ANGIOGRAPHY WITH MULTIDETECTOR-ROW COMPUTED TOMOGRAPHY IN PROSTHETIC HEART VALVE DYSFUNCTION

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ABSTRACT

Background and objectives: Retrospectively ECG-gated multidetector-row computed tomography (MDCT) is increasingly used for the assessment of prosthetic heart valve (PHV) dysfunction. In case of PHV reoperation, invasive coronary angiography (CAG) is usually required to determine the need for concomitant bypass surgery. However, indwelling coronary catheters may create an unacceptable risk of distal embolization of aortic PHV vegetations or thrombi. MDCT has the potential to replace CAG. The purpose of this explorative study is to determine whether non-invasive angiography with MDCT can replace CAG in the preoperative diagnostic work-up of PHV patients.

Methods: All PHV patients were identified who underwent retrospectively ECG-gated MDCT and CAG in a university hospital center in The Netherlands from January 2009 until June 2013. MDCT was primarily performed for PHV dysfunction analysis. Based on their medical history, patients were divided into two groups; previously unknown with coronary artery disease (CAD; group I) and previously known with CAD (group II). MDCT images were scored for the presence or absence of significant (>50%) coronary artery or bypass graft stenosis. CAG was used as reference standard.

Results: Fifty-one patients (53 left sided PHV's) were available for analysis; 38 in group I and 13 in group II, including 19 bypass grafts. In group I MDCT accurately ruled out significant stenosis in 19/38 (50%) patients, but was unable to replace CAG in the other 19/38 (50%) patients due to non-diagnostic image quality in 16 or detection of significant stenoses in 3 patients. In group II, MDCT correctly showed at least one significant stenosis in all patients. In addition, MDCT accurately identified 3/3 (100%) obstructed and 13/16 (81%) patent bypass grafts. The remaining 3/16 (19%) patent grafts showed non-diagnostic MDCT image quality.

Conclusion: In patients previously unknown with CAD, MDCT primarily performed to assess PHV dysfunction, may replace invasive angiography in 50% of patients. CAG remains required in all patients known with CAD, however MDCT appeared to be effective in assessing the patency of bypass grafts.

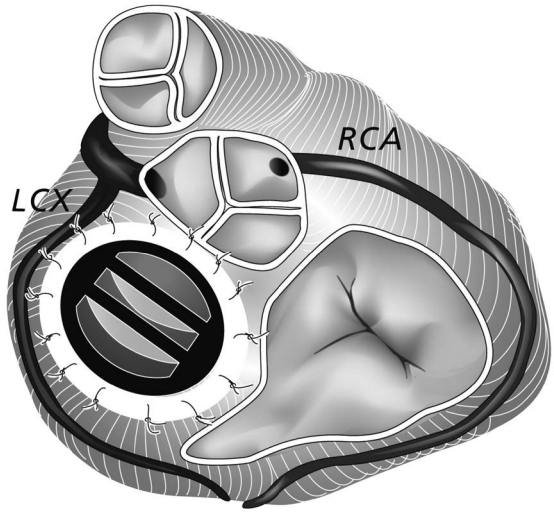
INTRODUCTION

Recently retrospectively ECG-gated multidetector-row computed tomography (MDCT) has shown additional diagnostic value (compared to echocardiography) for the evaluation of prosthetic heart valve (PHV) dysfunction and detection of PHV endocarditis [1-8]. In addition, MDCT may be required before PHV reoperation to assess dilatation or calcifications of the ascending aorta and the relation of bypass grafts to the sternum [9]. According to the guidelines, preoperative invasive coronary angiography (CAG) is often required to detect significant coronary obstructions which may require concomitant bypass surgery. Although, MDCT may provide all aforementioned preoperative required information including coronary artery assessment, CAG is the reference standard for this indication [10]. In case of a vegetation or thrombus on an aortic PHV, however, mechanical manipulation by an invasive catheter may be undesirable since it can be complicated by distal embolization [10]. Furthermore, impaired renal function may be a relative contraindication for performing both MDCT and CAG imaging. As MDCT has a high negative predictive value for coronary artery obstructions in patients with a low or intermediate risk of coronary artery disease, it may replace CAG in patients previously not known with ischemic heart disease [11,12]. Unfortunately, coronary artery assessment by MDCT in PHV patients may be hampered by metallic artifacts or motion artifacts due to elevated or irregular heart rates which are frequently present in PHV dysfunction patients [13]. Moreover, beta-blockers are not routinely administered before PHV assessment by MDCT. Also, MDCT images for PHV assessment are acquired with retrospectively ECG-gating, in contrast to MDCT images for coronary artery assessment, which are preferably acquired using prospective ECG-triggering [9,12]. For the above-mentioned reasons MDCT performed for PHV dysfunction assessment could result in non-diagnostic results for coronary assessment [13]. Although clinically relevant, to our best knowledge no studies have been published that investigated the diagnostic role of MDCT in PHV patients for the exclusion of significant coronary artery disease. Therefore, the purpose of this explorative study is to determine whether non-invasive angiography with retrospectively ECG-gated MDCT can replace CAG in the preoperative diagnostic work-up of PHV patients.

METHODS

Patient selection: We reviewed all patients with a left-sided mechanical or biological PHV who underwent CAG and retrospectively ECG-gated MDCT primarily performed for PHV dysfunction assessment. Patients were selected from the database of the Department of Radiology of the University Medical Center Utrecht, the Netherlands. The search was performed from January 2009 until June 2013 with a maximum allowed interval of six months between CAG and MDCT. Patients who underwent coronary revascularization between CAG and MDCT were excluded. Additional patient information was retrieved from the patient medical records. Informed consent was waived by the local Medical Ethical Committee. Patients were divided in two groups. Group I consisted of patients not known with coronary artery disease (CAD) defined by an absent medical history of: (a) myocardial ischemia due to known coronary artery obstructions, (b) percutaneous coronary intervention (PCI) or (c) coronary artery bypass grafting (CABG). Group II consisted of patients known with CAD defined by a positive medical history of (a) myocardial ischemia due to known coronary artery obstructions, (b) PCI or (c) CABG.

Figure 1: Close relation of an aortic PHV and the proximal coronary arteries



MDCT acquisition: Retrospectively ECG-gated MDCT images were acquired using scan parameters as applied with PHV patients in our daily practice. A comprehensive description of our standard clinical protocol has been presented previously [4]. In short, our most recent clinical 256-slice MDCT acquisition protocol consisted of a scout view and unenhanced prospectively ECG-triggered acquisition of the PHV region followed by the contrast-enhanced retrospectively ECG-gated acquisition with the following parameters: 120 kV, 600-700 mAs, collimation 128 x 0.625, gantry rotation time 270-330 ms and pitch 0.16-0.18. Gantry rotation time and pitch were dependent on the heart rate. For contrast-enhanced imaging our clinical triphasic contrast administration protocol was applied, as described previously [4]. In brief, this usually comprised contrast medium, a mixture of 30% contrast medium and 70% saline and a saline flush, respectively. Images were reconstructed at each 10% of the RR-interval.

Invasive coronary angiography and image analysis: CAG was performed according to currently available guidelines via radial or femoral access [14,15]. Flow fractional reserve (FFR) was occasionally performed if visual assessment of an obstruction was inconclusive [16]. Coronary arteries were scored as: (1) present significant stenosis (>50 %) or FFR < 0.80, (2) absent stenosis or non-significant stenosis (<50 %) or FFR > 0.80 [10,15]. When coronary arteries were judged as requiring a bypass, the location of the stenosis was documented and divided in proximal or distal coronary stenosis of the right coronary artery (RCA), left main (LM), left descending artery (LDA) or left circumflex artery (LCx). Bypass grafts were assessed as patent or significantly obstructed/occluded as well. CAG's were reviewed by the cardiologist who performed the CAG and an independent observer (WT). Both observers were not aware of the MDCT results for coronary artery obstructions. In case of incongruent results, a consensus was reached. Based on this procedure the reference standard result was defined.

MDCT image analysis: Assessment of the MDCT images was performed on a dedicated workstation (Extended Brilliance Workstation, Philips Healthcare, Best, the Netherlands). The best systolic and diastolic image phase for coronary assessment was selected for each coronary artery segment. All coronary artery segments were assessed and scored as present or absent [17]. Present coronary artery segments were scored as: 1. non-diagnostic (not sufficiently visualized to perform diagnostic assessment) or 2. diagnostic (stenosis grade of the segment can be assessed). Reasons for non-diagnostic segments were classified as: PHV-related artifacts, low contrast enhancement, pacemaker lead artifacts, technical failure, superimposing vein, motion artifacts and noise. Very small coronary segments are clinically not relevant as these segments are not eligible for concomitant bypass grafting. Therefore segments that were too small (< 1mm) for MDCT intraluminal evaluation, and thus for grafting, were excluded from analysis. Only if a MDCT acquisition was diagnostic for all present coronary artery segments larger than 1 mm, the MDCT images were used for the detection of: 1. presence of significant stenosis (>50 %) or 2. absence of stenosis or non-significant stenosis (<50 %). For stenosed coronary arteries the location of the stenosis was documented and divided into proximal or distal coronary stenosis of the RCA, LM, LDA or LCx. The main reason for non-diagnostic MDCT was determined per patient. In case of multiple non-diagnostic reasons, the reviewers chose the artifact which was mainly responsible for hampered coronary visualization. Since no full cardiac unenhanced acquisitions were performed the Agatston calcium score could not be assessed. As calcified plaques may interfere with the correct interpretation of coronary artery obstructions, the amount of calcium was scored on a qualitative visual calcium score per coronary artery (LM/LAD/RCA/LCx) as follows; 0. absent (no calcium), 1. mild (small and few calcium spots), 2. moderate (extended and larger calcified plaques) or 3. severe (extremely calcified). For analysis, per patient overall calcium score was calculated by adding the visual calcium scores of the individual four coronary arteries. As a result, the total score varied between 0 as minimum and 12 as maximum per patient.
For coronary bypasses, the graft patency was scored even when MDCT scans were non-diagnostic for the native coronary arteries. Bypasses were scored as: 1. non-diagnostic, 2. patent or 3. occluded/significantly obstructed (>50%). All MDCT scoring was performed independently by two reviewers (DS and EL). Reviewers were blinded for CAG results. A consensus was reached for discordant MDCT results. The data analysis was based on the consensus score.

Data analysis: Data analysis was restricted to descriptive statistics. Categorical data were presented in total numbers or percentages. Based on the data distribution, continuous data were reported as mean ± standard deviation (SD) or median and interquartile range (IQR). Only diagnostic MDCT scans were compared with the reference standard; CAG ± FFR. In group II, coronary bypass patency assessment on MDCT was compared to CAG results even when MDCT scans were non-diagnostic for the native coronary arteries.

RESULTS

We identified 51 patients with 53 left sided PHV's; 45 aortic and eight mitral valves. Thirty-eight patients were not known with CAD (group I) and 13 patients were known with CAD (group II; 12 coronary bypass surgery and one PCI). Median time between CAG and MDCT was 86 days (IQR 22-129 days). Other baseline characteristics are shown in Table 1. The mean heart rate

Table 1: Patient characteristics

	Unknown CAD N = 38	**Known CAD N = 13**
Age, mean ±SD	62.9 ± 12.2	70.9 ± 7.8
Male (%)	29 (76%)	9 (69%)
CABG (grafts)	0	12 (19)
PCI	0	1
Time (days) CAG-MDCT, median (IQR)	99 (43-134)	27 (9-95)
Valve position (%)		
Aortic	32 (84%)	11 (85%)
Mitral	4 (11%)	2 (15%)
Aortic and Mitral	2 (5%)	0
Mechanical valves (%)	29 (71%)	8 (62%)
ATS	1	0
Björk-Shiley	2	0
Carbomedics	12	2
Duromedics	1	0
ON-X	2	1
Sorin bicarbon	2	0
St. Jude	9	5
Biological valves (%)	10 (26%)	5 (39%)
CE Perimount	8	3
Medtronic Mosaic	0	1
Mitroflow	2	1
TAVI valves (%)	1 (3%)	0
Edwards Sapien	1	0

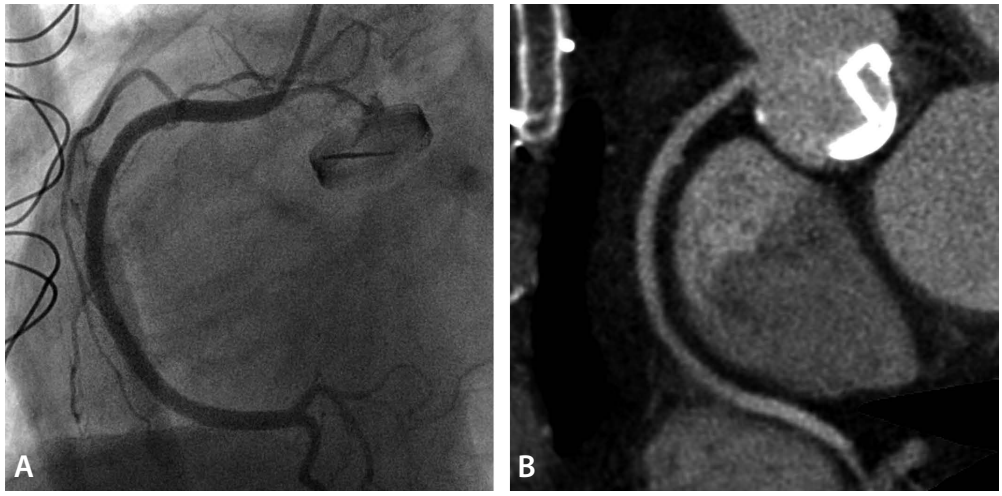
CABG = coronary artery bypass graft; CAD = coronary artery disease; IQR = interquartile range; MDCT = multidetector-row computed tomography; PCI = percutaneous coronary intervention; SD = standard deviation; TAVI = transcatheter aortic valve implantation

during the MDCT acquisition was 71 ± 16 beats per minute (bpm). In 14/51 (27%) patients, the heart rate during the MDCT scan was unknown. Five (14%) patients had an arrhythmia during MDCT acquisition. A flowchart of the results is provided in Figure 4.

Group one

CAG images identified 36/38 patients without significant coronary artery stenosis. In two of these patients FFR was required to exclude a significant obstruction. Two patients revealed significant

Figure 2: Invasive versus non-invasive coronary angiography in a PHV patient



*Invasive angiography (**A**) and computed tomography angiography (**B**) image showing the patent right coronary artery in a patient with a prosthetic aortic valve.*

stenoses on CAG: one patient with distal RCA and distal LAD stenosis, the other with a LM and proximal and distal RCA stenosis. An example of a CAG versus a MDCT image is presented in Figure 2.

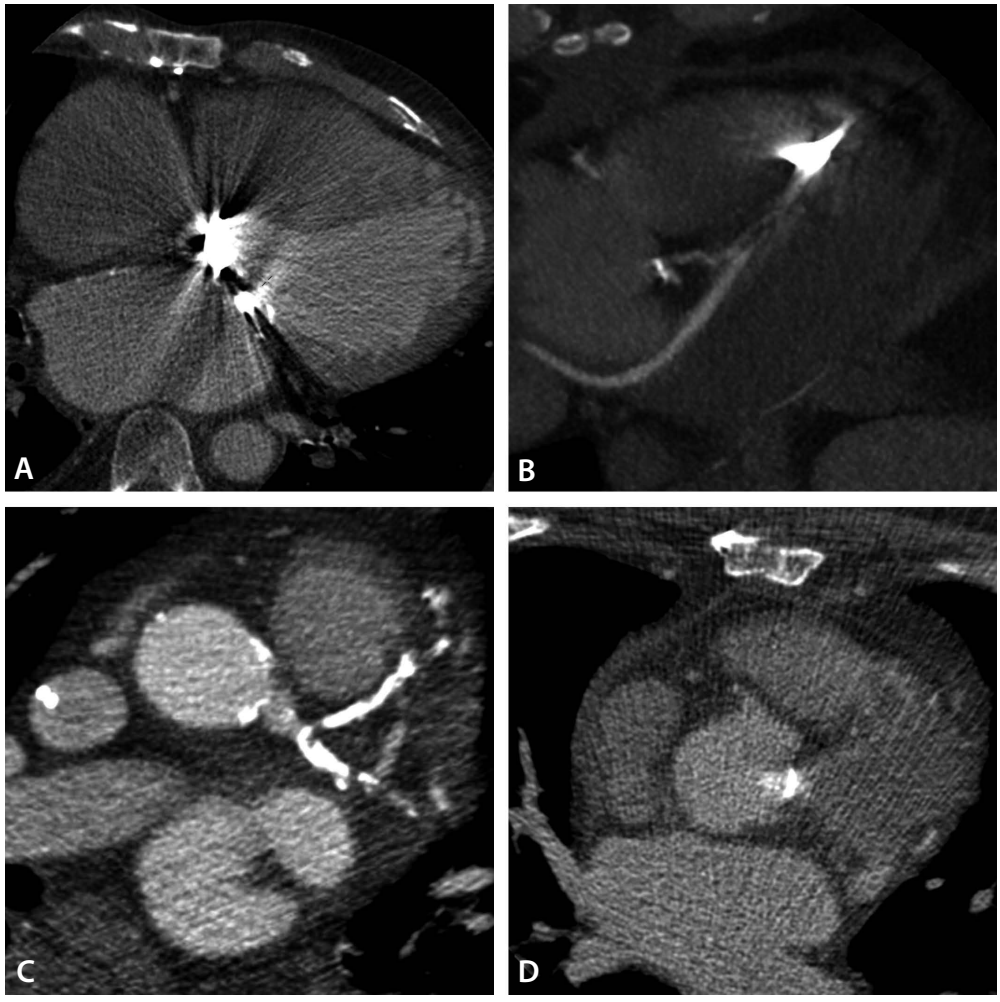
Mean heart rate during MDCT examinations was 70 ± 16 bpm. The calcium score analyzed per patient was overall 3 ± 3 (mild). MDCT accurately ruled out significant obstructions requiring bypass surgery in 19/38 patients (50%). In the remaining 19/38 patients (50%) MDCT could not replace CAG as MDCT was non-diagnostic (n=16) or revealed a coronary obstruction (n=3). In one patient in the latter group MDCT correctly detected significant distal RCA and LAD stenoses. The other two patients with significant obstructions on MDCT proved to be false positive. In the first false positive case MDCT revealed a stenosis in the proximal LAD in which the calcium score was judged as severe. In the other false positive case MDCT revealed proximal LAD and LCx stenoses with calcium scored as moderate and mild, respectively.

Main reasons for non-diagnostic MDCT (n=16) were: PHV artifacts (n=5), noise artifacts (n=5), motion artifacts (n=5) and technical failure (n=1). Mean heart rate during MDCT was 67 ± 11 bpm for patients with a diagnostic MDCT compared to 76 ± 20 bpm for patients with a non-diagnostic MDCT. Mean calcium score analysed per patient was overall 2 ± 2 (mild) for patients with a diagnostic MDCT and 3 ± 4 (mild) for patients with a non-diagnostic MDCT.

Group two

CAG showed one or more significant obstruction of the native coronary arteries in all patients (n=13). In this group mean heart rate during MDCT examinations was 72 bpm ± 16. The calcium score per patient was 9 ± 3 (moderate-severe). In 9/13 patients (69%) the MDCT scan was non-diagnostic for evaluation of native coronary arteries. Main reasons for non-diagnostic MDCT for evaluation of native coronary arteries were: PHV artifacts (n=1), noise artifacts (n=3), motion artifacts (n=3), superimposing vein (n=1) and pacemaker artifacts (n=1) (Figure 3). MDCT was

Figure 3: Artifacts encountered in non-invasive angiography by MDCT



A. *Computed tomography (CT) image of a patient showing prosthetic heart valve artifacts due to the Björk-Shiley valve.* ***B.*** *Pacemaker artifact hampering assessment of the right posterior descending artery.* ***C.*** *Calcifications in the left coronary system with blooming artifacts impairing adequate stenosis evaluation.* ***D.*** *Non-diagnostic CT image due to image noise.*

diagnostic in the other four patients and revealed significant coronary artery stenoses in all. Of note, besides these correctly diagnosed stenoses, MDCT also revealed false positive stenoses in other severely calcified segments in all these four patients.

In total 19 bypass grafts were present in 12 CABG patients. CAG revealed 3/19 non-patent and 16/19 patent grafts. All patent bypass grafts were free of calcifications. MDCT correctly identified all 3/3 (100%) non-patent grafts. Furthermore, 13/16 (81%) patent bypass grafts were correctly identified. In the other 3/16 (19%) patent bypass grafts (LIMA) MDCT was non-diagnostic for graft analysis because of small vessel size. Thus, bypass graft patency was correctly identified in 16/19 (84%) bypass grafts by MDCT.

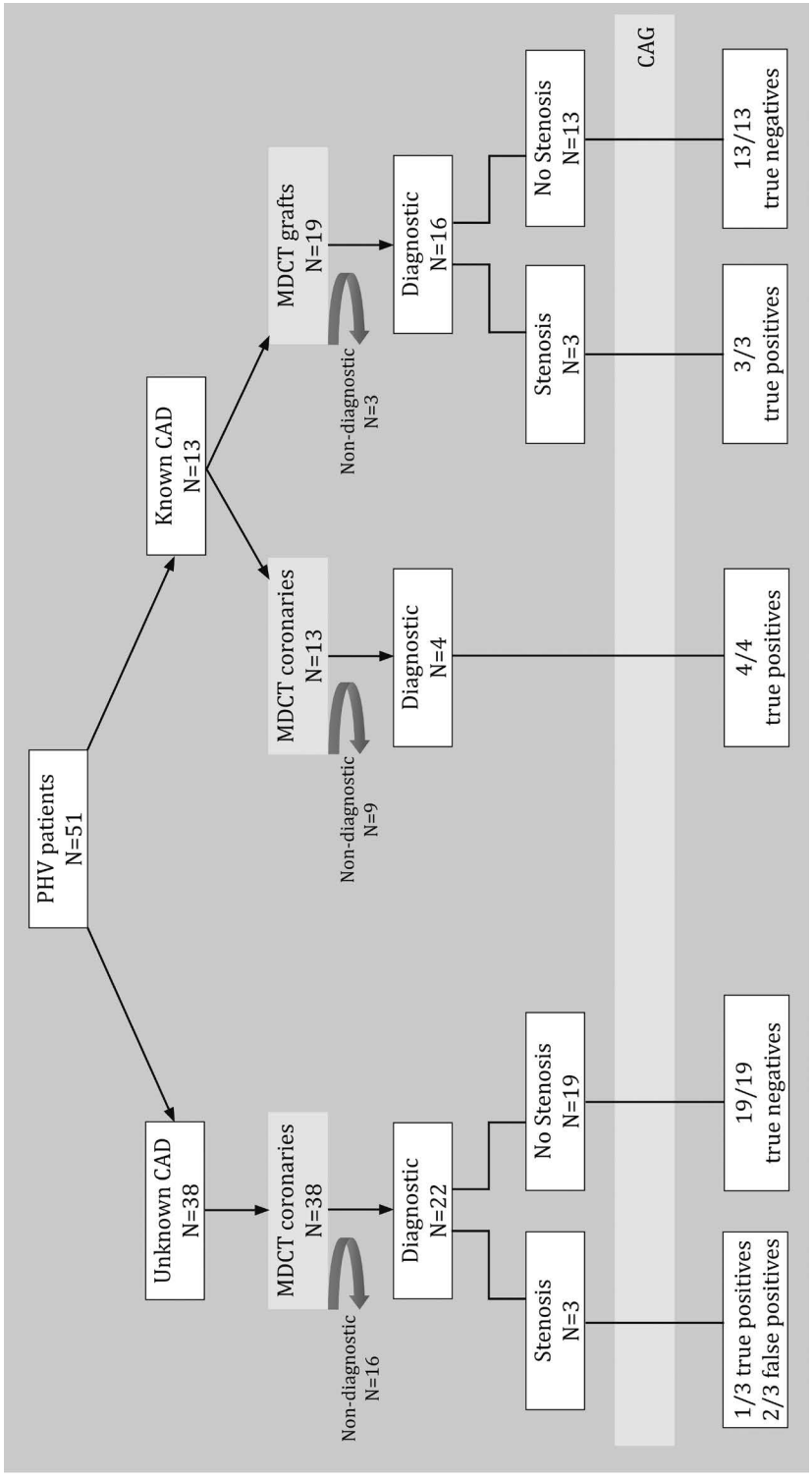


Figure 4: Flowchart of the results

DISCUSSION

The main findings of this study were twofold. First, retrospectively ECG-gated MDCT primarily performed for the detection of PHV dysfunction may replace invasive coronary artery assessment to rule out coronary artery disease in a substantial part (50%) of patients previously not known with coronary artery disease. Second, in patients known with CAD, MDCT appeared to be effective in assessing the patency of bypass grafts, but CAG is still required for native coronary artery assessment in this group.

The results of our study may be of significant clinical impact as MDCT is increasingly performed for the detection of PHV endocarditis or the morphological cause of PHV obstruction (thrombus and pannus) [1-4]. In case of PHV replacement, MDCT may also replace preoperative invasive angiography. This would save patient radiation dose, contrast exposure, costs and exposure to risk of invasive catheterization. For patients with thrombi or vegetations attached to aortic PHV's, a CAG may be relatively contraindicated as manipulation with invasive catheters may result in distal embolization [10]. In these specific cases, non-invasive coronary assessment is of even more clinical value. We previously assessed the effect of PHV's on coronary image quality on MDCT examinations. However, the MDCT results of this study were not compared to invasive angiography, which is the reference standard for the heart team to decide whether obstructed coronary arteries need bypass grafting in case of PHV reoperation [13]. Furthermore, the former study performed a per segment analysis instead of a per patient analysis, the latter seems more relevant for clinical implementation. One of the main results of our previous study was that in most commonly implanted PHV's no artifacts were encountered, despite the close anatomical relationship of the PHV and proximal coronary arteries (Figure 1) [13]. However, imaging cobalt-chrome containing PHV's (Björk-Shiley, Sorin tilting disc and Duromedics bileaflet) encountered major artifacts hampering coronary assessment [13]. According to these results, we also found that in a small percentage PHV-related artifacts resulted in non-diagnostic images (12%; 6/51). The main reason for this is probably the inclusion of small amounts of cobalt-chrome PHV's. However, nowadays most implanted bileaflet PHV's do not contain cobalt-chrome.

In agreement with studies investigating non-invasive identification of coronary artery lesions by MDCT in non-PHV patients, MDCT is also of limited value in PHV patients with known CAD. It has the tendency to overestimate the significance of stenosis and therefore a CAG is required when a significant stenosis is observed by MDCT [11,18]. As a consequence, native coronary artery assessment by MDCT is not advised in patients already known with ischemic heart disease.

However, MDCT may have additional value for the surgeon and the candidates for cardiac reoperation after CABG. In agreement with the study of Weustink et al. which investigated non-PHV patients, our study showed good diagnostic accuracy for MDCT in the assessment of bypass grafts and their patency [18]. This finding may be of additional clinical value before a CAG is performed. For example, in case of graft obstruction already detected by MDCT, attempts to find the graft during invasive CAG can be omitted, which saves catheter manipulations in the aorta, procedure time and contrast exposure. Furthermore, details on the position of the graft in relation to other anatomical landmarks may help the surgeon to avoid injuring a graft during a reoperation.

Compared to standard coronary MDCT studies in non-PHV patients with a prospective scan protocol and beta-blockers/nitroglycerine administration, the present study showed a relative high

percentage of non-diagnostic scans. This was also observed in the group of patients previously not known with coronary artery disease (n=38) with relatively low calcium score and low incidence of coronary artery obstructions (2/38). As already known, prospectively triggered scanning results in less PHV artifacts compared to retrospectively gated MDCT acquisitions [19]. Retrospectively gated cardiac MDCT has a higher total radiation dose compared to prospectively triggered acquisitions, but the relative radiation dose per cardiac phase is lower compared to prospective triggering in which one cardiac phase receives the full dose. However retrospectively ECR gated acquisition allows reconstruction of ten cardiac phases and provides for dynamic imaging of the PHV. In contrast, with retrospective gating the full dose is spread over ten cardiac phases which is important for dynamic imaging of the PHV. Related to this, our study showed a high percentage of non-diagnostic scans as a result of motion artifacts, noise/calcium and PHV-related artifacts. The high percentage of non-diagnostic coronary arteries on MDCT is probably also caused by relative higher heart rates during scanning as beta-blockers usually are not given and a large number of patients with PHV dysfunction have arrhythmias. Close collaboration between the radiologist and cardiologist is essential to optimize heart rate before acquisition.

Limitations

This study has several limitations. First, our study concerns a retrospective analysis containing various PHV types represented in only small numbers and mainly placed in the aortic position. Second, objective calcium scoring according to Agatston was not possible. As a result a visual calcium score was provided. Third, beta-blockers were not routinely administered before MDCT. This may have reduced the image quality of the depicted coronary segments. However, beta-blockers could be contraindicated in patients with PHV dysfunction because of possible hemodynamic deterioration and conduction disturbances.

CONCLUSION

In conclusion, in PHV patients previously not known with coronary artery disease MDCT primarily performed to diagnose PHV dysfunction can replace invasive angiography for the exclusion of significant coronary artery disease in approximately half of these patients. In PHV patients known with coronary artery disease MDCT is not able to replace CAG reliably for the assessment of the native coronary artery system. However, coronary artery bypass graft patency can be reliably determined in the majority of patients.

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CHAPTER 10

GENERAL DISCUSSION AND CONCLUSIONS

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INTRODUCTION

In this thesis the diagnostic value of the routine diagnostics for prosthetic heart valve (PHV) endocarditis (part 1) and obstruction (part 2) were investigated. Furthermore, the additional value of novel imaging techniques on top of the routine diagnostics were evaluated. **Part 1** of this thesis did elaborate on routine and novel imaging techniques for PHV *endocarditis.* A meta-analysis was performed (chapter 2) to assess the diagnostic accuracy of 2-dimensional transthoracic and transesophageal echocardiography (TTE and TEE) for signs of PHV endocarditis. Furthermore the first studies on multidetector computed tomography (MDCT) were analyzed for the additional diagnostic value of MDCT on top of TTE/TEE. In the following chapters (3-5)**,** the diagnostic accuracy/role of novel imaging modalities for the detection of PHV endocarditis were compared to the diagnostic accuracy of the routine imaging modalities (TTE and TEE). Firstly, the additional value of MDCT was investigated (chapter 3), secondly the complementary value of hybrid/combined imaging by 18F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) *and/or* MDCT (chapter 4) and finally the additional value of three dimensional TEE (3D-TEE) was studied (chapter5). **Part 2** of this thesis concerned acquired PHV obstruction. Firstly, a systematic review was performed to assess the diagnostic role of TTE, TEE, fluoroscopy and MDCT in PHV obstruction (chapter 6). Subsequently, in the following chapters (7-9) the additional value of MDCT was further demonstrated.

PART 1: RESULTS IN PHV ENDOCARDITIS

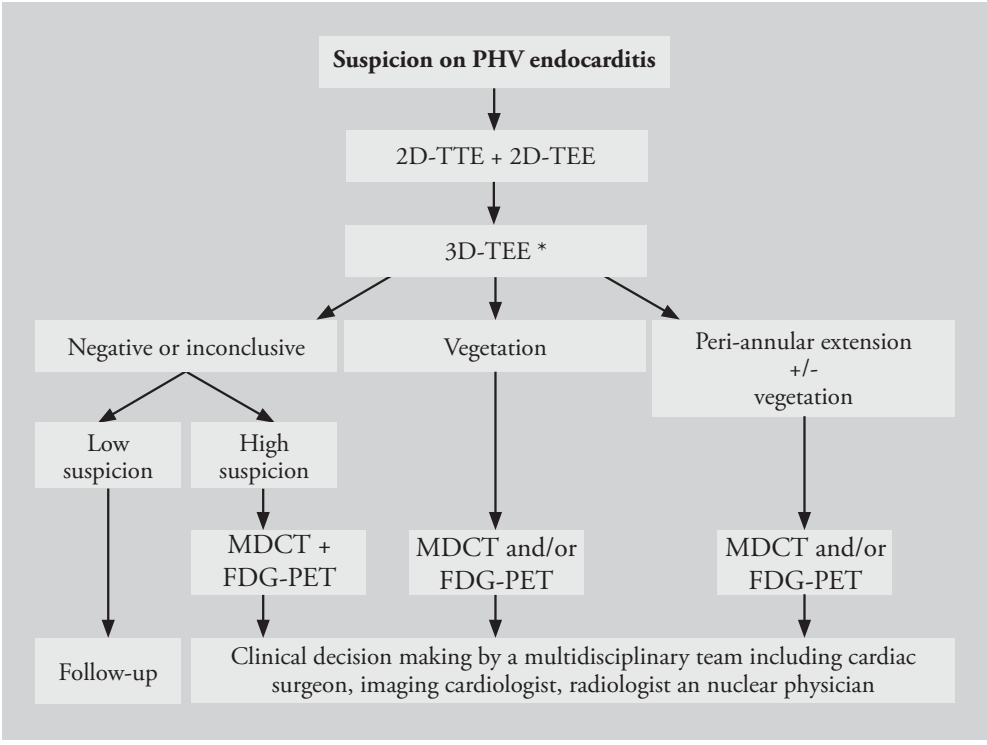
In chapter 2 the currently available literature on the diagnostic value of different imaging modalities (TTE/TEE/MDCT) was systematically reviewed and meta-analysed. TEE was significantly more sensitive (but not specific) compared to TTE for the detection of vegetations (82% versus 29%) and peri-annular extensions (86 % versus 36%). Although TEE detects the majority of signs of PHV endocarditis, the main finding of this study was that TEE still misses a substantial number of vegetations (18%) and peri-annular extensions (14%) as compared to the reference standard (i.e. surgical inspection/autopsy or clinical follow-up). The incorrect diagnostic assessment of PHV endocarditis patients may result in incorrect treatment strategies, therefore additional imaging techniques are required. The meta-analysis provides a strong indication that the diagnostic accuracy improves when MDCT is added to TEE . However this statement is premature as MDCT studies were scarce and included only a limited number of patients resulting in broad confidence intervals. Therefore more and larger prospective studies are required. Such a study is presented in **chapter 3**, it includes a prospective cross-sectional investigation on the additional value of MDCT (on top of the routine clinical work-up including TTE/TEE) for the detection of signs of PHV endocarditis. MDCT was not only performed to assess its diagnostic accuracy, but also its complementary diagnostic *and* therapeutic value compared to echocardiography. For the diagnostic accuracy, the reference standard was surgical findings or clinical follow-up. To determine the complementary diagnostic/therapeutic value an expert-panel (multidisciplinary heart team consisting of cardiologists, radiologists and surgeons) was used as reference standard. In this study, twenty-eight patients were included, and it was found that the diagnostic accuracy of routine clinical workup plus MDCT was superior to clinical routine workup alone. MDCT resulted in a major diagnostic changes in 6/28 patients (21%), mainly

driven by the novel detection of mycotic aneurysms. More importantly, compared to the routine clinical work-up, addition of MDCT resulted in a treatment change in seven patients (25%). Consequently, this study demonstrates that MDCT on top of TTE/TEE is of additional value in patients with suspected PHV endocarditis. Therefore, MDCT imaging has to be considered after clinical routine workup in patients with a high suspicion on PHV endocarditis (figure 1). Two other studies with a total of 22 PHV patients support this statement [1, 2]. In these studies MDCT also resulted in superior diagnostic accuracy (on top of TEE) for signs of PHV endocarditis.

18F-Fluorodesoxyglucose Positron Emission Tomography (FDG-PET) including low dose Computed Tomography (CT) is another imaging technique which is potentially useful in the diagnostic workup of these patients, since it provides metabolic instead of detailed anatomical information. Therefore, in **chapter 4** we presented a study with PHV patients (n=33) in which a FDG-PET combined with a localizing low dose CT (also for attenuation correction) was performed in addition to routine TTE/TEE. Included PHV patients consisted of endocarditis free controls (n=18) and surgically proven PHV endocarditis cases (n=15) with mainly negative/inconclusive echocardiography findings. In the PHV endocarditis cases FDG-PET/CT detected all peri-annular PHV abscesses and mycotic aneurysms correctly, but missed all PHV vegetations. Vegetations did not show FDG uptake, probably due to the large amount of motion of the valve leaflets and vegetations resulting in blurring of the PET signal beyond the point of detectability. Other contributing causes of missing vegetations may be the low spatial resolution of PET imaging, the background activity of the bloodpool and/or direct exposure of vegetations to antibiotics in the bloodstream which make them more prone to be sterilized. Therefore FDG-PET combined/fused with an ECG-gated and contrast enhanced MDCT *instead of* only a non-contrast enhanced non-ECG gated localizing CT may result in improved diagnostic accuracy also for vegetations. As combining MDCT and FDG-PET results in state-of-the-art high resolution anatomical and metabolic imaging of the PHV and its surrounding anatomy, this seems *the* desired imaging strategy in patients with high suspicion of PHV endocarditis but negative/inconclusive echocardiography. Our study indeed showed that this strategy (MDCT added to FDG-PET) detected not only all PHV peri-annular extensions but also all vegetations. On the other hand, addition of only MDCT to TTE/TEE (without FDG-PET) resulted in the detection of one false negative and one inconclusive peri-annular extension. Therefore *combining* both modalities is advised when echocardiography findings are inconclusive or negative despite a high suspicion on PHV endocarditis (figure 1). Furthermore, the additional advantage of whole body FDG-PET/CT is the detection of extra cardiac primary foci or metastatic infections. This may have also therapeutic consequences in a substantial part of PHV endocarditis cases.

Knowledge of normal FDG uptake patterns is crucial for the correct interpretation of the FDG-PET scans and SUV values, especially in the early post-operative phase (< 1 year). In this timeframe postoperative inflammation may be a major issue and could result in false positive imaging. However, no data were present in literature until now. Our study (**chapter 4)** presented normal Standardized Uptake Values (SUV) of PHV's imaged not only in the chronic post-operative phase (>12 months), but also in the early post-operative phase (1-4 months). Nearly all controls (except one) were free of significant FDG uptake. The one false positive FDG-PET/CT was observed in a patient with a pericardial patch. Standardized Uptake Ratios (SUV) ratios around the PHV ring were significantly lower ($p<0.001$) in PHV controls: 2.0 (IQR 1.7-2.1)

Figure 1: Diagnostic Flowchart for patients with suspected PHV endocarditis



*If available during 2D-TEE.

versus 4.2 (IQR 3.8-5.1) SUV ratios around the PHV ring in cases with proven endocarditis were all above 2.6, whereas all controls had SUV ratios ≤ 2.5. Therefore a SUV ratio of > 2.5 appears to be a reasonable cut-off value to detect peri-annular extension in PHV endocarditis. These findings suggest that even in the early postoperative phase (from 4 weeks after PHV implantation) FDG-PET can be used as a reliable diagnostic tool to rule out or detect peri-annular extension of PHV endocarditis. As numbers of included PHV patients are low and partly retrospectively included, larger studies with a prospective design are needed to confirm this statement.

A major drawback of additional techniques such as MDCT and FDG-PET/CT is that they are expensive, expose patients to radiation and in case of CTA iodinated contrast is administered. The use of contrast is relatively contra-indicated when PHV endocarditis is complicated by renal failure. In most modern echo laboratories, 3D-TEE is available nowadays as it is of additional value for anatomical valve evaluation and guidance of treatment procedures (TAVI, Mitraclip). This 3D technique may also be beneficial for the detection of PHV endocarditis, however data are very scarce in literature. Therefore, in **chapter 5** we presented an explorative study with PHV patients (n=15) with surgically confirmed and severely complicated aortic PHV endocarditis in which the additional value of 3D-TEE was compared to 2D-TTE+TEE. In two different patients one vegetation and one abscess was additionally detected. Furthermore, in three other patients, 3D-TEE resulted in better delineation of the proximal coronary arteries in relation to peri-annular inflammation, with CTA as the reference standard. This is also important information

for determining the pre-operative strategy and it guides the decision making on requirement of aortic root replacement with coronary artery re-implantation or not. In total, the addition of 3D-TEE resulted in improved diagnostic accuracy in 5/15 patients. As it concerns an explorative and small study, no firm conclusions can be drawn, but these results suggest a potential benefit of 3D-TEE. However, more and larger studies are needed, preferably in patients with suspected and absent PHV endocarditis.

The former results raise the question whether patients with a high suspicion on PHV endocarditis and negative or inconclusive 2D-echocardiography should undergo additional 3D-TEE or MDCT or FDG-PET/CT. One could even argue that combining all techniques is justified in a patient category with such a high in-hospital mortality. In our opinion a tailor-made decision has to be made, on which technique should be added primarily. If 3D-TEE is available when performing 2D-TEE, one should have a low threshold for performing 3D images of the PHV at least for confirmation purposes of the 2D findings (figure 1). In patients with renal failure, an additional FDG-PET/CT may be more favourable compared to MDCT as the latter is contrast enhanced and relatively contra-indicated when the glomerular filtration rate is < 30 ml/min. However, in patients with an aortic PHV vegetation and/or suspected root abscess a MDCT is preferable as it may also provide non-invasive coronary angiography. This may replace pre-operative invasive coronary angiography which is not desirable in a patient with aortic PHV vegetations (chapter 9). Furthermore, in case of PHV re-operation MDCT provides valuable information about the distance between sternum and right ventricle and also the relation to sternum and bypass grafts if present.

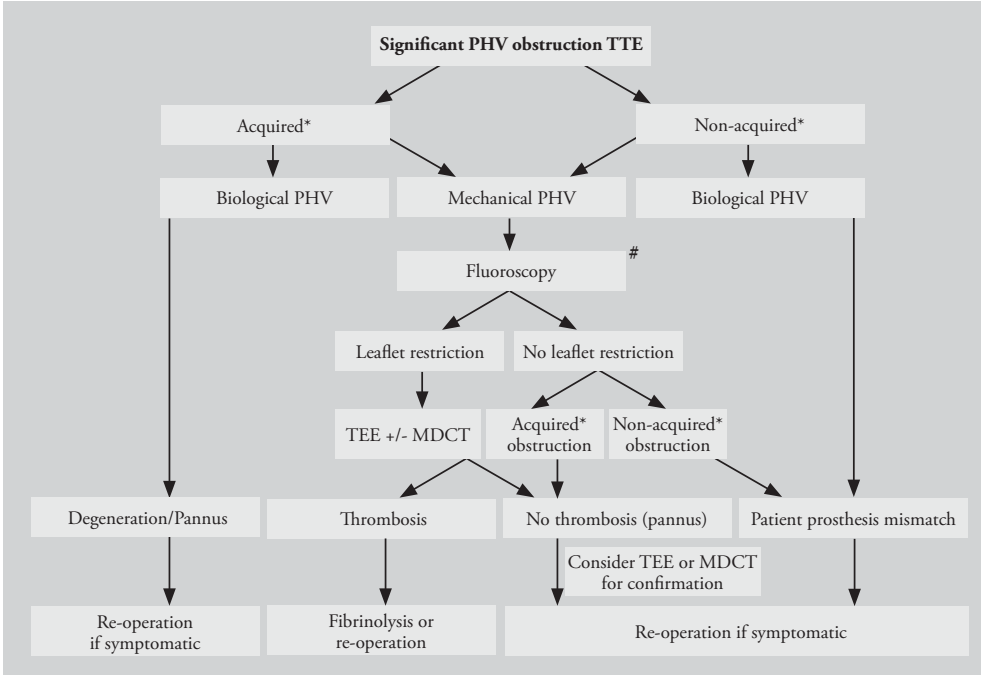
PART 2: RESULTS IN PHV OBSTRUCTION

In **Chapter 6** a systematic review was provided which investigated the diagnostic role of TTE, TEE, fluoroscopy and MDCT for detection of the exact cause of acquired mechanical PHV obstruction. This resulted in an evidence-based imaging strategy for differentiation of obstructive thrombus from pannus. Imaging results have major therapeutic consequences [3], however no evidence based imaging strategy is provided in literature until now. The systematic review revealed that in acquired mechanical PHV obstruction without leaflet restriction detected by fluoroscopy and/or absent mass on TEE examination, obstructive PHV thrombosis cannot be confirmed and consequently fibrinolysis is not advised. In case of present leaflet restriction detected by fluoroscopy *and* mass detection by TEE, both pannus and/or thrombus may still be the underlying mechanism. However, TEE predictors for differentiation of pannus/thrombus are not reliable enough [4,5]. Therefore we suggest to perform MDCT to differentiate pannus from thrombus. MDCT studies reveal that pannus is attached subvalvular to the PHV ring and presents as a hypodense mass with a (semi)circular anatomical configuration curved along the valve ring [6-9]. In contrast, obstructive thrombi are imaged as supra- and subvalvular hypodense masses with irregular anatomy directly attached to the leaflets and hingepoints causing mechanical obstruction by leaflet restriction. Theoretically mass differentiation (thrombus versus pannus) may be possible by determining the Houndsfield units, though no convincing evidence is available yet. In **Chapter 8** a case was presented which supported the data provided in the systematic review of chapter 6 and showed

the additional value of MDCT in acquired mechanical PHV obstruction. Echocardiography was able to detect the severity of acquired PHV obstruction, however not its origin, as pannus could not be differentiated from thrombus. Fluoroscopy detected leaflet restriction which could be caused by both pannus and thrombus. MDCT however was able to differentiate between pannus and thrombus as it revealed an irregular mass attached to the hinge points of the mechanical PHV, anatomically most fitting with thrombosis. Thrombolysis was not given, it was chosen to schedule the patient for re-operation with the addition of aspirin and elevation of INR targets. This treatment regimen confirmed our suspicion on PHV thrombosis as the aforementioned therapeutic strategy resulted in resolving of the detected mass before the re-operation was performed. **Chapter 7** provided more examples of PHV pannus and thrombosis cases, correctly detected by MDCT. In these examples the other imaging modalities were inconclusive for pannus/thrombus differentiation. It was shown that MDCT differentiated more reliably compared to any other imaging modality clinically available at this moment. For this reason more prospective studies are required for the determination of the diagnostic accuracy of MDCT in acquired mechanical PHV obstruction. In case of a thrombosed aortic PHV that needs to be re-operated, pre-operative coronary angiography is required. However, invasive catheters may dislocate thrombus material resulting in distal embolization. For this reason coronary assessment by non-invasive imaging by MDCT is more desirable. In **Chapter 9** we investigated whether MDCT (primarily performed for PHV assessment) was able to replace invasive coronary angiography (CAG) for the detection of significant coronary obstructions in 51 PHV patients. One other study reported on this topic, however the MDCT results of this study were not compared to invasive angiography which is the gold reference standard to decide whether obstructed coronary arteries need bypass grafting in case of PHV re-operation [10]. In contrast to non-PHV cases [11], non-invasive angiography (by MDCT) can be hampered by PHV scattering, especially in cobalt chrome containing PHV's (Bjork Shiley/Sorin tilting disk/Duromedics bileaflet) [10]. In aortic PHV's the assessment of the proximal right coronary artery can be hampered, whereas in mitral PHV's the assessment of the ramus circumflexus can be hampered [10]. This results in less reliable/impossible assessment of these coronary artery segments. Moreover the MDCT scan protocol for PHV assessment uses retrospective gating, whereas MDCT primarily performed for coronary assessment uses prospective gating [11-13]. Retrospectively gated cardiac MDCT has a higher total radiation dose compared to prospectively triggered acquisitions, however the relative radiation dose per cardiac phase is lower compared to prospective triggering in which only one cardiac phase receives the full dose. In contrast, with retrospective gating the full dose is spread over ten cardiac phases. Furthermore, beta-blockers are not routinely given for PHV assessment whereas the majority of PHV dysfunction patients have a hyperdynamic circulation resulting in high and/or irregular heart rates. Despite these considerations, our study (presented in chapter 9) showed that in PHV dysfunction patients formerly *not* known with coronary artery disease, retrospectively gated MDCT was able to reliably replace invasive angiography in 50% of patients. In these patients a pre-operative CAG was not needed anymore as MDCT excluded coronary artery disease. This reduces radiation exposure, contrast use and complications. Namely, in case of aortic vegetations or thrombi mechanical manipulation by an invasive catheter may be complicated by distal embolization. As MDCT is known for its low positive predictive value for significant coronary artery obstuctions, in PHV patients formerly known with coronary artery

disease MDCT was not able to replace CAG. As could be expected in this group, MDCT resulted in non-diagnostic or (false) positive scans in our study, therefore CAG was still required. However in this group of PHV patients (known with severe coronary artery disease), MDCT was helpful in the identification of bypass graft patency, which is clinically relevant as well.
As a result of this thesis and currently available literature an imaging flowchart for patients with PHV obstruction is provided in figure 2.

Figure 2: Diagnostic Flowchart for patients with PHV obstruction.



*Compared to baseline TTE. # by cineradiography or MDCT.

FUTURE PERSPECTIVES

PHV endocarditis

This thesis showed that additional imaging techniques are beneficial for PHV endocarditis patients. Additional 3D-TEE, FDG-PET and MDCT (chapter 2-5) are all of complementary value when performed on top of echocardiography. As almost all studies presented in this thesis are the first clinical implementations of the specific imaging techniques in PHV patients, these results need to be confirmed by other and larger studies. Only then, guidelines will recommend routine additional imaging in the future with level of evidence A or B. Another issue that needs to be resolved is which additional technique needs to be first in line; a new diagnostic algorithm should be developed. Figure 1 shows such a diagnostic algorithm based on current literature and the data presented in this thesis for patients with suspected PHV endocarditis. Prospective

trials need to be started in which all aforementioned additional techniques (3D-TEE, MDCT, FDG-PET) are performed and compared independently to the routine imaging (2D-TTE/TEE). Those trials should add the novel imaging techniques as a new major criterion to the modified Duke criteria to investigate their beneficial effect on the diagnostic accuracy. Such a study was recently presented by Saby et al.[14]. It was shown that sensitivity and specificity of FDG-PET/CT for PHV endocarditis of 73% and 80 % respectively [14]. When FDG-PET/CT was added as a new major criterion to the modified Duke criteria [15] (which includes TTE/TEE), the sensitivity rose from 70 to 97 %. As previously discussed FDG-PET/CT may be a promising imaging tool for patients with suspected PHV endocarditis. However, the study of Saby et al. also showed that PET/CT alone missed a substantial number of vegetations (9/20,45%) in cases with no other echocardiographic signs of PHV endocarditis. Most probably this is the result of low spatial resolution of FDG-PET/CT to detect highly mobile vegetations. For this reason FDG-PET/CT should always be combined with an imaging tool with better spatial resolution (TEE and/or MDCT) as shown in **chapter 3 and 4**. Furthermore the study of Saby et al. shows that the diagnostic accuracy of the sensitivity of Duke criteria was improved. Improvement of diagnostic accuracy of the modified Duke criteria does not mean that patient treatment will also change. However, therapeutic changes are the most important endpoint of a diagnostic study. The Duke criteria were only developed for diagnostic purposes and do not guide the therapeutic process in terms of re-operation or not [15]. Therefore the study design as shown in **chapter 3** with the reference standard of an expert opinion panel in order to define therapeutic changes caused by additional imaging is advised.

Moreover, in the study of Saby et al. the specificity was a concern as the basal FDG uptake around PHV's are not reported and known yet [14]. For correct interpretation of pathological FDG uptake around PHV's with peri-annular extension, base-line FDG-PET uptake around PHV's without endocarditis should be known. However "normal" FDG-PET uptake around PHV's was not determined. Theoretically chronic inflammation around the PHV and consequently also FDG uptake could be expected and would make this diagnostic tool useless. Therefore a normal FDG uptake pattern in order to define the specificity is crucial to investigate. Only then SUV values/ratios can be interpreted correctly, especially in the early post-operative phase (< 1 year). In this timeframe postoperative inflammation may be a major issue and could result in false positive imaging. In **chapter 4** however we provided the first basic FDG uptake values (n=18) and their SUV ratios around the PHV ring. SUV ratios were significantly lower in PHV controls compared to PHV cases. No significant uptake was observed in controls, except in one patient in which a pericardial patch in the aortic root showed significant FDG uptake. As the number of available and presented PHV patients in chapter 4 are low and cases were pre-dominantly retrospectively included, the Medical Ethical Committee of the University Medical Center Utrecht recently approved to start the PROSPECTA (**PROS**thetic heart valves imaged by fused **P**ositron **E**mission tomography and **C**omputed **T**omography **A**ngiography) study, which has started just recently. This study will include patients prospectively.

PROSPECTA

PROSPECTA study design: This study has the objective to determine normal FDG-uptake around aortic PHV's in patients without any signs of endocarditis. It is a single center study with

a prospective cross sectional design. 18-Fluorine FDG-PET is performed to assess uptake around the PHV after fusion with contrast enhanced MDCT.

Methods: 256-slice ECG triggered MDCT imaging is performed which allows detailed visualization of the valve and surrounding tissue. Images will be reconstructed and are transferred to a workstation and analyzed using dedicated software. *18F-FDG-PET*: After at least 24 hour of low carbohydrate diet (of which the last 12 hours are spent fasting) to induce free fatty acid metabolism and suppress glucose metabolism in the myocardium patients receive an intravenous injection of FDG at 2.0 MBq/kg of body weight. Patients are hydrated with 1000 ml of water 1 hour prior to image acquisition. Blood glucose levels are checked in all patients before FDG injection, and no patients should be found to have blood glucose levels greater than 160 mg/dl. FDG-PET scans of the heart are acquired using a FDG-PET scanner (Siemens Biograph Sensation 16, Germany). Approximately 1 hour after FDG injection, the FDG-PET scan is performed. An emission PET scan of the heart is obtained with 3-minute acquisitions per bed position using a 3-dimensional acquisition mode. After PET scanning a low dose CT is performed for attenuation correction. This low dose CT is not ECG-triggered and for this reason not useful for anatomic evaluation of the PHV and surrounding aortic root. Attenuation corrected PET images are reconstructed with an ordered-subset expectation maximization iterative reconstruction algorithm. After performing the FDG PET scan fusion with MDCT is performed manually in order to assess FDG-PET uptake around the PHV. This MDCT cannot be used for attenuation correction. Uptake is scored by two independent observers and respectively measured by a qualitative and quantitative method: 1. Qualification Visual Score for Hypermetabolism (QVSH). 2. Standardized Uptake Value (SUV) ratio. QVSH is divided in: None (no or less uptake than mediastinum) = 0, Mild (more uptake than in the mediastinum, less than in the liver) = 1, Moderate (more uptake than in the liver) = 2, Severe (extreme uptake) = 3. In case of abnormal uptake QVSH 1-3: location of uptake is described, former LCC/RCC/NCC/Ascending aorta/other. The SUV ratio is defined as the maximum SUV value around the PHV divided by the mean SUV value in the descending aorta.

Study population: consists of a total group of 75 patients after uncomplicated PHV implantation in aortic position. The FDG-PET/MDCT imaging is performed in the early and late and chronic postoperative episode (group 1, 2 and 3 respectively): Early postoperative group 5 (± 1) weeks after PHV implantation (n=25), late postoperative group 12 (± 2) weeks after PHV implantation (n=25) and chronic postoperative group 12 (± 2) months after PHV implantation (n=25). We will only include patients in group 3 in case FDG uptake around the PHV in group 2 results in moderate or severe FDG uptake according to the QVSH score in 1 or more patients. Patients cannot be included in two groups.

Main study parameters: 18F-FDG-PET baseline uptake measured by the QVSH value and the SUV ratios around the PHV in early, late and possibly also in the chronic postoperative phase: 5 (± 1) weeks, 12 (± 2) weeks and 12 (± 2) months respectively.

Inclusion criteria: Age ≥ 50 years, patients after uncomplicated PHV implantation in aortic position (mechanical and biological PHV's), normal routine follow up TTE (standardly performed 5 days after operation) without any signs of obstruction, endocarditis or significant paravalvular leakages, weight < 90 kg

Exclusion criteria: Known contrast allergy, known renal impairment (GFR<60), diabetes mellitus,

mild contractile dysfunction of the left and/or right ventricle (Eyeballing, Ejection fraction <45 %, TAPSE <14 mm), active cardiac decompensation, uncontrolled cardiac arrhythmias, suspicion on active endocarditis, previous participation in scientific studies using radiation, possible pregnancy in pre-menopausal women above 50 years not on reliable birth control therapy, use of pericardial patches and re-operation of aortic PHV in past medical history, any contraindication for MDCT/intravenous contrast, (possible) pregnancy, refusal to be informed about potential additional MDCT or FDG-PET findings.

In conclusion, PROSPECTA will study normal FDG-PET uptake values around aortic PHV's in the early, late and the chronic post-operative phase. PROSPECTA will provide cut off values for normal FDG-PET uptake. This will result in data about the specificity of FDG-PET resulting in more reliable assessment of this imaging strategy in patients with suspected PHV endocarditis.

Acquired PHV obstruction

Biological and mechanical PHV's are susceptible to develop obstruction, however as outlined in **chapter 1** the diagnostic and therapeutic dilemmas are mainly encountered in mechanical PHV's [16]. In contrast to biological PHV's, acquired mechanical PHV obstruction is mainly caused by pannus or thrombosis, which have a different therapeutic strategy [3]. Therefore differentiation is clinically very important. As echocardiography and fluoroscopy are not able to differentiate adequately, MDCT is a promising imaging tool for correct differentiation [9]. However no prospective MDCT studies are present studying obstructed PHV's by pannus and thrombosis. However the IMPACT (**IM**aging of **P**rosthetic he**A**rt valves by **CT**A) study which is a collaboration between the Academic Medical Centre (AMC) in Amsterdam and the UMCU will provide these data soon. The results of this study probably will change the diagnostic algorithm for obstructed PHV's. Based on this thesis and currently available literature the diagnostic algorithm should be as in figure 2.

GENERAL CONCLUSION OF THIS THESIS

PHV endocarditis and the cause of PHV obstruction remains difficult to diagnose correctly by echocardiography alone. As clinical implications may be major, this thesis provides evidence that clinicians should have a low threshold to perform additional imaging by novel techniques in the field of PHV dysfunction such as 3D-TEE, FDG-PET/CT and MDCT. When performed on top of 2D-echocardiography these techniques may improve diagnostic accuracy and optimize patient treatment strategies.

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HOOFDSTUK 10

DISCUSSIE EN CONCLUSIES

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INLEIDING

In dit proefschrift wordt de toegevoegde waarde van nieuwe beeldvormingstechnieken bij kunsthartklep (PHV) infectie (endocarditis) en kunsthartklep obstructie onderzocht en vergeleken met de routinematig verkregen diagnostische gegevens. **Deel 1** van dit proefschrift zal ingaan op nieuwe beeldvormingstechnieken bij PHV *endocarditis.* Een meta-analyse werd uitgevoerd (hoofdstuk 2) naar de diagnostische nauwkeurigheid van transthoracale en slokdarm echocardiografie (TTE en TEE), de huidige standaard uitgevoerde beeldvormingstechnieken om tekenen van PHV endocarditis op te sporen. Bovendien werden de eerste studies over computer tomografie angiografie (CTA) geanalyseerd. In de daarop volgende hoofdstukken (3-5) werd de diagnostische nauwkeurigheid voor het vaststellen van kunsthartklep endocarditis van nieuwe beeldvormende modaliteiten vergeleken met de routinematig gebruikte modaliteiten (TTE en TEE). Ten eerste, werd de meerwaarde bestudeerd van CTA, vervolgens die van hybride/gecombineerde beeldvorming met CTA *en/of* 18F-Fluorodeoxyglucose Positron Emissie Tomografie (FDG-PET) en tenslotte de meerwaarde van drie dimensionale slokdarm echocardiografie (3D-TEE). In **deel 2** van dit proefschrift werden de diagnostische modaliteiten bij verworven kunsthartklep obstructie onderzocht. Ten eerste, werd er een systematische evaluatie uitgevoerd om de diagnostische rol te beoordelen van TTE, TEE, fluoroscopie en CTA (hoofdstuk 6). In de opvolgende hoofdstukken (7-9) werd de toegevoegde waarde van CTA verder aangetoond.

DEEL 1: RESULTATEN IN PHV ENDOCARDITIS

In hoofdstuk 2 werd de momenteel beschikbare literatuur over de diagnostische waarde van verschillende beeldvormende modaliteiten (TTE/TEE/CTA) systematisch geëvalueerd en werd er een meta-analyse uitgevoerd. TEE was aanzienlijk meer gevoelig (maar niet specifiek) vergeleken met TTE voor het opsporen van vegetaties (82% versus 29%) en peri-annulaire uitbreiding (86% versus 36%). Hoewel TEE de meerderheid van de tekenen van PHV endocarditis correct detecteerde, was de belangrijkste conclusie van deze studie dat TEE nog een aanzienlijk aantal vegetaties (18%) en peri-annulaire uitbreidingen (14%) miste in vergelijking tot de referentie standaard (chirurgische inspectie/autopsie of klinische follow-up). De onjuiste detectie van PHV endocarditis kan resulteren in verkeerde behandelingsstrategieën en daarom zijn extra beeldvormingstechnieken vereist. De meta-analyse verschaft een sterke aanwijzing dat de diagnostische nauwkeurigheid verbetert wanneer CTA wordt toegevoegd aan echocardiografie. Deze stelling is echter wel enigszins voorbarig omdat de opgenomen CTA studies en geïncludeerde patiënten in de meta-analyse schaars waren. Daarom zijn meer en grotere studies nodig met een prospectief design. Een dergelijke studie wordt gepresenteerd in **hoofdstuk 3**; het omvat ook een prospectief cross-sectioneel onderzoek naar toegevoegde waarde van CTA (t.o.v. de routine klinische work-up inclusief TTE/TEE) voor het opsporen van tekenen van PHV endocarditis. CTA werd niet alleen vervaardigd om de diagnostische juistheid te onderzoeken, maar ook de complementaire diagnostische en therapeutische waarde t.o.v. echocardiografie te beoordelen. De referentie standaard voor de diagnostische juistheid van CTA waren de chirurgische bevindingen of klinische follow-up. Om de aanvullende diagnostisch/therapeutische meerwaarde van CTA te onderzoeken werd een deskundige-panel (multidisciplinaire hart team bestaande uit cardiologen, radiologen en chirurgen) gebruikt als referentie standaard. In deze studie werden achtentwintig

patiënten geïncludeerd. De diagnostische nauwkeurigheid van routine klinische work-up incluis CTA was superieur t.o.v. de klinische routine work-up zonder CTA. Toevoeging van CTA leidde tot een grote diagnostische veranderingen in 6/28 patiënten (21%), voornamelijk als gevolg van de novo detectie van mycotische aneurysmata. Echter nog veel belangrijker, het resulteerde ook in een verandering van behandeling in zeven patiënten (25%). Deze studie toont aan dat CTA toegevoegd aan TTE/TEE van extra waarde is bij patiënten met verdachte PHV endocarditis. CTA dient daarom laagdrempelig te worden overwogen bij patiënten met een hoge verdenking op PHV endocarditis (Figuur 1). Twee andere studies met in totaal van 22 PHV patiënten ondersteunen deze conclusie [1, 2]. In deze studies resulteerde CTA (bovenop TEE) ook in superieure diagnostische nauwkeurigheid voor het aantonen van PHV endocarditis.

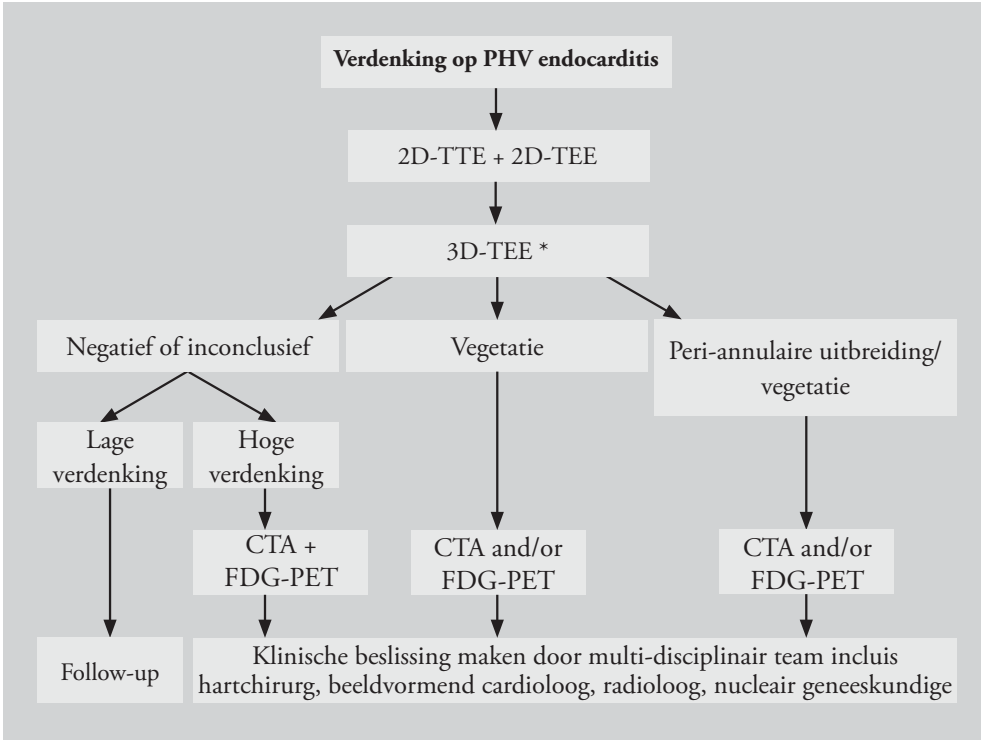
FDG-PET met inbegrip van lage dosis computer tomografie (CT) is een andere beeldvormende techniek die nuttig kan zijn in de diagnostische work-up van deze patiënten. Het detecteert namelijk metabole in plaats van gedetailleerde anatomische informatie. Daarom wordt in **hoofdstuk 4** een studie met PHV patiënten (*n* = 33) gepresenteerd waarbij een FDG-PET gecombineerd met een lage dosis CT (voor verzwakkingscorrectie) werd uitgevoerd naast de routine TTE/TEE. Geïncludeerde PHV patiënten bestonden uit controles zonder endocarditis (*n* = 18) en chirurgisch bewezen PHV endocarditis gevallen (*n* = 15) met voornamelijk negatieve/inconclusieve echocardiografie bevindingen. In de PHV endocarditis patiënten detecteerde FDG-PET/CT alle peri-annulaire abcessen en mycotische aneurysmata correct, maar miste alle PHV vegetaties. Vegetaties tonen waarschijnlijk geen FDG opname vanwege de grote hoeveelheid beweging van de kunstklep bladen resulterend in de vervaging van het PET signaal voorbij het punt van detecteerbaarheid. Andere bijdragende oorzaken zijn mogelijk de lage spatiële resolutie van PET imaging, de achtergronds activiteit van de bloodpool en/of rechtstreekse blootstelling van vegetaties aan antibiotica in de bloedbaan, waardoor ze vergeleken met abcessen meer vatbaar zijn om steriel te worden. Om deze reden kan een FDG-PET gecombineerd/gefuseerd met een ECG-gated CT met contrast *in plaats van* een niet-ECG gated CT zonder contrast, resulteren in verbeterde diagnostische nauwkeurigheid, ook voor vegetaties. Combineren van CTA en FDG-PET resulteert in state-of-the-art hoge resolutie anatomische en metabole beeldvorming van de PHV en haar omringende anatomie. Dit lijkt de gewenste beeldvormingsstrategie bij patiënten met een hoge verdenking van PHV endocarditis maar negatieve/inconclusieve echocardiografie. Uit onze studie bleek inderdaad dat deze strategie (CTA toegevoegd aan FDG-PET) niet alleen alle peri-annulaire uitbreidingen, maar ook alle vegetaties detecteerde. Aan de andere kant, resulteerde toevoeging van alleen CTA aan TTE/TEE (zonder FDG-PET/CT) in 1 vals negatief en 1 inconclusief resultaat voor het detecteren van peri-annulaire uitbreidingen. Daarom wordt het *combineren* van beide modaliteiten aangeraden wanneer de echocardiografie bevindingen onduidelijk of negatief zijn, ondanks een hoge verdenking op PHV endocarditis (figuur 1). Bovendien is het extra voordeel FDG-PET/CT dat het infectie foci in het gehele lichaam kan detecteren en dus primaire of metastatische extra-cardiale infecties kan vaststellen. Dit heeft therapeutische gevolgen in een substantieel deel van de PHV endocarditis gevallen.

Kennis van normale FDG opname patronen is cruciaal voor de correcte interpretatie van de FDG-PET scans en gestandaardiseerde opname waarden (SUV) rond de PHV, met name in de vroeg postoperatieve fase (< 1 jaar). In dit tijdsbestek kan postoperatieve ontsteking een groot diagnostisch probleem geven en leiden tot vals positieve beeldvorming. Echter, er waren in

de literatuur tot nu geen gegevens hierover beschikbaar. Onze studie in **hoofdstuk 4** presenteerde echter ook normale SUV waarden van PHV's niet alleen in de chronisch postoperatieve fase (> 12 maanden), maar ook in de vroeg postoperatieve fase (1-4 maanden). Bijna alle controle patiënten (behalve één) waren vrij van belangrijke FDG opname. De ene vals positieve FDG-PET/CT werd waargenomen bij een patiënt met een pericardiale patch. SUV ratio's rondom de ring in controle PHV waren aanzienlijk lager ($p < 0.001$) dan in PHV endocarditis patiënten met peri-annulaire uitbreiding: respectievelijk 2.0 (IQR 1.7-2.1) versus 4.2 (IQR 3.8-5.1). SUV ratio's rond de PHV ring waren in alle gevallen boven de 2.6 bij patiënten met bewezen peri-annulaire extensie, terwijl alle controle patiënten SUV ratio's ≤ 2.5 hadden. Een SUV ratio van > 2.5 lijkt dus een redelijke afkapwaarde te zijn om peri-annulaire uitbreidingen te detecteren. Deze bevindingen tonen dat zelfs in de vroeg postoperatieve fase (vanaf 4 weken na PHV implantatie) FDG-PET kan worden gebruikt als een betrouwbare diagnostisch hulpmiddel voor het uitsluiten of detecteren van peri-annulaire uitbreidingen van PHV endocarditis. Omdat het aantal bestudeerde PHV patiënten laag en de patienten deels retrospectief geïncludeerd zijn, zijn grotere studies met prospectieve inclusie nodig om deze premature bevindingen te bevestigen.

Een groot nadeel van additionele technieken zoals CTA en FDG-PET/CT is dat ze duur zijn, patiënten onderwerpen aan straling en in het geval van CTA ook aan jodiumhoudend contrast. Het gebruik van jodium houdend contrast is relatief gecontra-indiceerd wanneer PHV endocarditis wordt gecompliceerd door nierfalen. Echter, in de meeste moderne echo laboratoria is 3D-TEE tegenwoordig beschikbaar omdat deze techniek een toegevoegde waarde is voor anatomische klep evaluatie en begeleiding van procedures zoals TAVI en Mitraclip plaatsing. De 3D technieken zijn mogelijk ook gunstig voor de detectie van PHV endocarditis, maar gegevens in de literatuur zijn zeer schaars betreffende dit onderwerp. Daarom wordt in **hoofdstuk 5** een PHV patiënten groep (n = 15) met peroperatief bevestigde en ernstig gecompliceerde aortakunstklep endocarditis gepresenteerd, waarin de meerwaarde van 3D-TEE werd vergeleken met 2D-TTE + TEE. 3D-TEE detecteerde bij twee verschillende patiënten één vegetatie en één abces, die waren gemist door gecombineerd 2D-TTE en 2D-TEE. Bovendien, in drie andere patiënten, resulteerde de toevoeging van 3D-TEE in een betere afbakening van de proximale kransslagaderen in relatie tot de peri-annulaire uitbreiding van de PHV endocarditis in vergelijking met 2D-TEE (met CTA als standaard referentie). Dit is ook belangrijke informatie voor het bepalen van de pre-operatieve strategie met betrekking tot aorta wortel vervanging met coronaire re-implantatie of niet. Dus de toevoeging van 3D-TEE geresulteerd in verbeterde diagnostische nauwkeurigheid in 5/15 patiënten. Omdat het een exploratieve en kleine studie betreft kunnen er geen harde conclusies worden getrokken, maar deze resultaten suggereren wel een mogelijk voordeel van toevoeging van 3D-TEE. Echter, er zijn meer en grotere studies nodig, bij voorkeur bij patiënten met verdachte PHV endocarditis.

Figuur 1: Diagnostische stroomdiagram voor patiënten met verdenking op PHV endocarditis



*Indien beschikbaar tijdens 2D-TEE

De bovenstaande resultaten doen de vraag rijzen of patiënten met een hoge verdenking op PHV endocarditis en negatieve of inconclusieve 2D-echocardiografie uitslag een aanvullende 3D-TEE, MDCT of FDG-PET/CT zou moeten ondergaan. Men kan zelfs stellen dat het combineren van al deze technieken in een patiënten categorie met een dergelijk hoge mortaliteit, gerechtvaardigd is. Volgens ons dient er een op maat gemaakt besluit te worden gemaakt welke nieuwe techniek er dient te worden toegevoegd. Als 3D-TEE beschikbaar is bij het uitvoeren van de 2D-TEE, moet men een lage drempel hebben voor het uitvoeren van 3D-imaging van de PHV, al is het ter bevestiging van de 2D bevindingen (figuur 1). Wanneer de glomerulaire filtratie < 30 ml / min is, kan er beter allereest voor een FDG-PET/CT worden gekozen, CTA is in deze gevallen relatief gecontra-indiceerd. Echter, bij patiënten met een aorta kunstklep vegetatie en/of vermoedelijk wortel abces is een CTA een betere keuze. Dit kan namelijk een eventueel pre-operatief *invasief* coronair angiogram vervangen welke niet wenselijk is in een patiënt met aorta kunstklep vegetatie (hoofdstuk 9). Bovendien, in geval van een re-operatie biedt CTA waardevolle informatie over de afstand tussen het borstbeen en rechterventrikel, alsmede de relatie tot borstbeen en eventueel aanwezige coronaire bypasses.

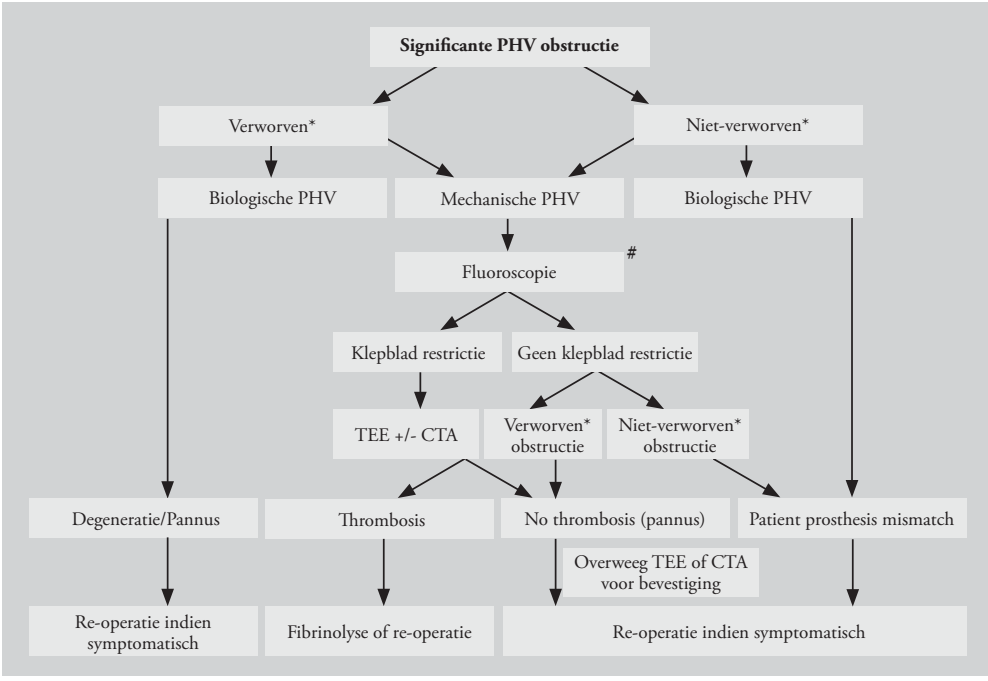
DEEL 2: RESULTATEN IN PHV OBSTRUCTIE

In **hoofdstuk 6** werd een systematische beoordeling verstrekt die de diagnostische rol van TTE, TEE, fluoroscopie en CTA onderzocht voor de detectie van de exacte oorzaak van verworven mechanische kunstklep obstructie. Dit resulteerde in een op wetenschappelijk bewijs gebaseerde imaging strategie voor de differentiatie tussen obstructieve trombose en pannus. De beeldvormingsresultaten hebben grote therapeutische gevolgen [3], maar een op wetenschappelijk bewijs gefundeerde imaging strategie werd tot nu toe in de literatuur niet geleverd. Uit de systematische evaluatie bleek dat in verworven mechanische PHV obstructie zonder klepblad beperking vastgesteld met fluoroscopie en/of afwezige massa bij TEE onderzoek, een obstructieve PHV trombose niet kan worden bevestigd en dientengevolge fibrinolyse niet wordt geadviseerd. In het geval van klepblad restrictie gedetecteerd door fluoroscopie *en* massa detectie door TEE, kan zowel pannus en/of trombus nog steeds het onderliggende mechanisme zijn. TEE voorspellers voor differentiatie van pannus/trombose zijn echter niet betrouwbaar [4, 5]. Wij stellen daarom voor een CTA uit te voeren om pannus van trombose te onderscheiden. CTA studies tonen dat pannus zich subvalvulair van de kunstklep ring bevindt en zich presenteert als een hypodense massa met een (semi) circulaire anatomische configuratie lopend langs de klep ring [6-9]. Obstructieve trombose kan zich echter als een supra- en subvalvulaire hypodense massa presenteren met een onregelmatige anatomie direct verbonden aan de klepbladen en/of scharnierpunten. Theoretisch kan CTA massa differentiatie (trombus versus pannus) mogelijk maken door het bepalen van de Houndsfield eenheden, echter hiervoor is nog geen overtuigend bewijs aanwezig in de literatuur. In **hoofdstuk 8** werd een patiënt gepresenteerd die de bevindingen van hoofdstuk 6 bevestigde en de toegevoegde waarde van CTA toonde in een casus met een verworven mechanische PHV obstructie. Echocardiografie detecteerde de ernst van verworven PHV obstructie, echter niet de origine ervan; pannus kon niet worden onderscheiden van trombose. Fluoroscopie detecteerde kunsklep bewegingsbeperking, maar dit kan zowel worden veroorzaakt door pannus als trombus. CTA kon echter wel het onderscheid tussen pannus en trombose maken; er bleek zich namelijk een onregelmatige massa aan de scharnierpunten van de mechanische kunstklep te bevinden, op anatomisch gronden het meest compatibel met trombose. Trombolyse werd niet gegeven, maar de patiënt werd ingepland voor re-operatie met toevoeging van aspirine en verhoging van de INR targets. Dit behandelingsregime bevestigde onze verdenking op PHV trombose omdat de bovengenoemde medicatie aanpassing resulteerde in het oplossen van de gedetecteerde massa voordat de re-operatie werd uitgevoerd. **Hoofdstuk 7** geeft meer voorbeelden van PHV pannus en trombose gevallen, correct gedetecteerd door CTA. In deze voorbeelden konden de andere beeldvormende modaliteiten met betrekking tot pannus/trombose differentiatie geen uitsluitsel geven. CTA lijkt op dit moment het meest betrouwbaar te zijn voor trombus/pannus differentiatie in vergelijking tot alle andere imaging modaliteiten die op dit moment klinisch beschikbaar zijn. Er zijn wel meer prospectieve studies nodig voor de bepaling van de exacte diagnostische nauwkeurigheid van CTA in verworven mechanische PHV obstructie. In geval van een getromboseerde aorta kunstklep die re-operatie behoeft, is in de meerderheid van de gevallen een pre-operatief coronair angiogram vereist. Echter, invasieve katheters kunnen trombose materiaal ontwrichten wat kan resulteren in distale embolisatie. Om deze reden is een coronaire beoordeling door niet-invasieve imaging middels CTA meer wenselijk. In **hoofdstuk 9** onderzochten we in 51 PHV patiënten of CTA (primair uitgevoerd voor PHV beoordeling) in

staat was een invasief coronair angiogram (CAG) te vervangen voor het opsporen van significante stenoses. Er is één andere studie over dit onderwerp gepubliceerd, maar de CTA resultaten van deze studie werden niet vergeleken met invasieve angiografie wat de gouden standaard is om te beslissen of kransslagaders een bijkomende bypass operatie behoeven in geval van PHV re-operatie [10]. In tegenstelling tot niet-PHV patienten [11], kan non-invasieve coronair angiografie (door CTA) worden belemmerd door PHV scattering, met name in kobalt-chroom bevattende PHV's (Bjork Shiley/Sorin kantelschijf kunstkleppen en Duromedics dubbeldeurs kleppen) [10]. In aorta kunstkleppen kan de beoordeling van de proximale rechter coronair worden belemmerd, terwijl bij kunstkleppen in mitralis positie de beoordeling van de ramus circumflexus kan worden belemmerd [10]. Dit kan resulteren in minder betrouwbare/onmogelijk beoordeling van deze coronaire segmenten. Bovendien wordt bij het CTA scan protocol voor PHV beoordeling retrospectieve gating gebruikt, terwijl CTA primair uitgevoerd voor coronaire beoordeling gebruik maakt van prospectieve gating [11-13]. Retrospectief gated CTA geeft een patient een hogere totale stralingsdosis in vergelijking met een prospectief gated CTA. Echter in een retrospectief gated scan is de relatieve stralingsdosis per cardiale fase lager in vergelijking met prospectieve CTA, waarbij slechts één cardiale fase de volledige dosis ontvangt. Retrospectieve gating geeft de volledige dosis verspreid over meer dan tien cardiale fasen. Bovendien worden beta-blokkers niet routinematig gegeven voor de PHV beoordeling, terwijl de meerderheid van de PHV dysfunctie patiënten een hyperdynamische circulatie en hoge of onregelmatige hartslag heeft. Ondanks deze overwegingen, bleek uit onze studie (gepresenteerd in hoofdstuk 9) dat in PHV dysfunctie patiënten die voorheen *niet* bekend waren met coronaire hartziekten, retrospectief gated CTA in staat was om in 50 % van de patiënten op betrouwbare wijze een invasief coronair angiogram te vervangen. In deze patiënten was een pre-operatief CAG niet meer nodig, wat blootstelling aan straling, jodium houdend contrast en complicaties vermindert. Namelijk, in geval van aorta kunstklep vegetaties of stolsels kan mechanische manipulatie door invasieve katheters gecompliceerd worden door distale embolisatie. Omdat CTA bekend staat om haar laag positief voorspellende waarde voor significante coronaire obstructies, kan in PHV patiënten reeds bekend met coronair lijden een CTA de CAG niet vervangen. Zoals verwacht kon worden resulteerde ook in onze studie de CTA in niet-diagnostische danwel (vals) positieve scanresultaten in alle gevallen en was een CAG nog steeds vereist. CTA was echter in de groep PHV patiënten bekend met coronaire hartziekte toch enigszins behulpzaam, omdat de doorgankelijkheid van bypass grafts wel goed kon worden geïdentificeerd.

Op basis van de resultaten van dit proefschrift alsmede de op dit moment beschikbare literatuur wordt in figuur 2 een imaging stroomdiagram voor PHV obstructie gegeven.

Figuur 2: Diagnostisch stroomdiagram voor patienten met kunsthartklep obstructie.



*Vergeleken met baseline TTE #door cineradiografie of CTA

TOEKOMSTPERSPECTIEVEN

PHV endocarditis

Dit proefschrift toont dat het uitvoeren van nieuwe beeldvormingstechnieken gunstig is voor PHV endocarditis patiënten. 3D-TEE, FDG-PET en MDCT (hoofdstukken 2-5) zijn allemaal van complementaire/toegevoegde waarde wanneer ze uitgevoerd worden naast echocardiografie. Bijna alle studies gepresenteerd in dit proefschrift zijn de eerste klinische implementaties van de specifieke beeldvormingstechnieken in PHV patiënten. De gepresenteerde resultaten dienen bevestigd te worden door andere en grotere studies. Alleen dan zullen de richtlijnen deze beeldvormende technieken als routine gaan aanbevelen met niveau van bewijs A of B. Een andere kwestie die moet worden opgelost is welke extra techniek moet de eerste in lijn dient te zijn na het uitvoeren van 2d-echocardiografie voor het opsporen van tekenen van PHV endocarditis; een nieuwe diagnostische algoritme moet worden ontwikkeld. Figuur 1 toont een diagnostisch algoritme gebaseerd op literatuur tot heden en de gegevens uit dit proefschrift. Prospectieve trials zijn nodig waarin alle bovengenoemde aanvullende technieken (3D-TEE, MDCT, FDG-PET) zijn uitgevoerd en onafhankelijk ten opzichte van de routine imaging (2D-TTE/TEE) en elkaar worden vergeleken. Deze trials moeten de nieuwe beeldvormende technieken als een nieuw belangrijke criterium aan de gemodificeerde Duke criteria toevoegen en hun invloed op de diagnostische nauwkeurigheid onderzoeken. Een dergelijke studie werd onlangs gepresenteerd door Saby et al. [14] . De sensitiviteit en de specificiteit van FDG-PET/CT voor PHV endocarditis bleek respectievelijk 73% en 80% [14]. Wanneer FDG-PET/CT werd toegevoegd als een nieuw

belangrijk criterium aan de gemodificeerde Duke criteria [15] (waaronder TTE/TEE), steeg de sensitiviteit van 70 naar 97%. Zoals eerder besproken is FDG-PET/CT een veelbelovende imaging tool voor patiënten met verdachte PHV endocarditis. Echter, de studie van Saby et al. toonde ook aan dat PET/CT een aanzienlijk aantal vegetaties (9/20,45%) mist in patiënten met geen andere echocardiografische tekenen van PHV endocarditis. Dit is waarschijnlijk het gevolg van lage spatiële resolutie van FDG-PET/CT voor het detecteren van zeer mobiele vegetaties. Om deze reden dient FDG-PET/CT altijd te worden gecombineerd met een imaging tool met betere spatiële resolutie (TEE en/of MDCT) zoals aangegeven in **hoofdstuk 3 en 4**. De studie van Saby et al. toonde bovendien aan dat de diagnostische nauwkeurigheid van de gevoeligheid van Duke criteria werd verbeterd. Dit betekent echter niet dat de patiënten behandeling ook zal veranderen, hoewel therapeutische wijzigingen het belangrijkste eindpunt van een diagnostische studie zijn. De Duke criteria zijn echter alleen ontwikkeld voor diagnostische doeleinden en begeleiden niet het therapeutische proces zoals re-opereren of niet [15]. Daarom is een studie design zoals beschreven in **hoofdstuk 3** met als referentie standaard een deskundig advies panel om therapeutische wijzigingen veroorzaakt door de extra imaging te definiëren, aan te raden.

Bovendien is in de studie van Saby et al. de specificiteit een zorg omdat basale FDG opname rond de PHV bij niet endocarditis patienten niet worden onderzocht [14] . Voor correcte interpretatie van de pathologische FDG opname rond de PHV met peri-annulaire uitbreiding, moet de basale FDG opname rond de PHV bij patiënten zonder endocarditis bekend zijn. “Normale” opname van FDG rond de PHV was echter niet bepaald. Theoretisch kan chronische ontsteking rond de PHV na de operatie worden verwacht en ook FDG opname geven, wat dit diagnostische middel vervolgens nutteloos zou maken. Daarom is bepaling van het normale FDG opname patroon van cruciaal belang voor de interpretatie van de specificiteit en SUV waarden/ ratio’s met name in de vroege postoperatieve fase (< 1 jaar). In dit tijdsbestek kan postoperatieve ontsteking een groot probleem zijn en leiden tot vals positieve beeldvorming. In **hoofdstuk 4** echter rapporteerden wij de eerst FDG opname waarden (n = 18) en hun SUV ratio’s rond de PHV ring. SUV ratio’s waren beduidend lager in PHV controle patiënten in vergelijking met PHV endocarditis gevallen. Er werd geen significante opname waargenomen in controle patienten, behalve in één patiënt met een pericard patch in de aortawortel. Omdat het aantal beschikbare en gepresenteerde PHV patiënten in hoofdstuk 4 laag was en voornamelijk retrospectief werden geïncludeerd, heeft de medisch ethisch comité van het Universitair Medisch Centrum Utrecht onlangs de PROSPECTA (**PROS**thetische hartkleppen afgebeeld door gefuseerde **P**ositron **E**missie tomografie en **C**omputer **T**omografie **A**ngiografie) studie geaccordeerd. Deze studie zal PHV patiënten prospectief includeren als volgt.

PROSPECTA

PROSPECTA studie ontwerp: deze studie heeft tot doel om normale FDG-opname rond aorta kunsthartkleppen in patiënten zonder symptomen van endocarditis. Het is een single centrum studie met een prospectief cross-sectioneel studie ontwerp. 18-fluor FDG-PET wordt uitgevoerd om de opname rond de PHV te beoordelen nadat fusie heeft plaats gevonden met een 256-slice ECG gated jodiumhoudend contrast begeleide CTA.

Methoden: CTA Imaging wordt uitgevoerd op een ECG-gated, 256-slice CT scanner met contrast, voor gedetailleerde visualisatie van de PHV en omliggend weefsel. Beelden worden

gereconstrueerd op een werkstation en geanalyseerd met behulp van speciale software. *18F-FDG-PET*: Na tenminste 24 uur van koolhydraatarm dieet (waarvan de laatste 12 uur vastend worden besteed) om vrij vetzuur metabolisme te stimuleren en het glucose metabolisme in het myocardium te onderdrukken. Patiënten ontvangen vervolgens een intraveneuze injectie van FDG op 2.0 MBq/kg lichaamsgewicht en worden gehydrateerd met 1000 ml water 1 h vóór beeldacquisitie. Glucose waarden van het bloed worden bij alle patiënten vóór FDG injectie gecontroleerd, patiënten dienen geen glucose waarden groter dan 160 mg/dl te hebben. FDG-PET scans worden vervaardigd met behulp van een FDG-PET scanner (Siemens Biograph sensatie 16, Duitsland). Ongeveer 1 uur na FDG injectie, wordt de FDG-PET scan uitgevoerd. Een emissie PET scan van het hart wordt verkregen met 3 minuten durende acquisities per bed positie met behulp van een 3-dimensionale acquisitie-modus. Na de PET scan wordt een lage dosis CT uitgevoerd voor verzwakkingscorrectie. Deze lage dosis CT is niet ECG-getriggered en om deze reden niet nuttig voor anatomische evaluatie van de PHV en omliggende aorta wortel. Verzwakking gecorrigeerde PET beelden worden gereconstrueerd met een tevoren vastgestelde deelverzameling voor maximalisatie met een iteratief reconstructie algoritme. Na het uitvoeren van de FDG-PET scan wordt er handmatig gefuseerd met de CTA om de FDG opname rond de PHV te beoordelen. Deze CTA kan niet worden gebruikt voor verzwakking correctie. Opname wordt gescoord door twee onafhankelijke waarnemers en respectievelijk gemeten door een kwalitatieve en kwantitatieve methode: 1. kwalitieve visuele score voor hypermetabolisme (QVSH). 2. gestandaardiseerde opname waarde (SUV) ratio. QVSH is verdeeld in: geen (geen of minder opname dan mediastinum) = 0, mild (meer opname dan in het mediastinum, minder dan in de lever) = 1, matig (meer opname dan in de lever) = 2, ernstige (extreme opname) = 3. In het geval van abnormale opname QVSH 1-3: wordt de locatie van opname beschreven als: voormalige LCC/RCC/NCC/oplopend aorta /andere structuren. De SUV ratio wordt gedefinieerd als de maximale waarde van de SUV rond de PHV gedeeld door de gemiddelde waarde van de SUV in de descenderende aorta.

Studie populatie: bestaat uit een totale groep van 75 patiënten na ongecompliceerde PHV implantatie in aorta positie. De beeldvorming van FDG-PET/CTA wordt uitgevoerd in de vroege, late en chronische postoperatieve fase (respectievelijk groep 1, 2 en 3): vroeg postoperatieve groep 5 (± 1) weken na PHV implantatie (n = 25), laat postoperatieve groep 12 (± 2) weken na PHV implantatie (n = 25) en chronische postoperatieve groep 12 (± 2) maanden na PHV implantatie (n = 25). We zullen alleen patiënten in groep 3 includeren als er bij 1 of meer patiënten van groep 2 een matige of ernstige FDG opname (QVSH) rond de PHV wordt vastgesteld. Patiënten kunnen niet worden opgenomen in twee groepen.

Belangrijkste studie parameters: 18F-FDG-PET baseline gemeten QVSH-waardes en de SUV ratio's rond de PHV in de vroeg, laat en eventueel ook in de chronische postoperatieve fase: respectievelijk 5 (± 1) weken, 12 (± 2) weken en 12 (± 2) maanden.

Inclusie criteria: Leeftijd ≥ 50 jaar, patiënten na ongecompliceerde PHV implantatie in aorta positie (mechanische en biologische PHV's), normal resultaat van de routine TTE (uitgevoerd ongeveer 5 dagen na de operatie) zonder enige tekenen van obstructie, endocarditis of significante paravalvulaire lekkages, gewicht < 90 kg.

Exclusie criteria: Bekende contrast allergie, bekende nierfunctiestoornis (GFR < 60), diabetes mellitus, milde contractiele dysfunctie van de links en/of rechter ventrikel (Eyeballing, ejectie fractie

< 45%, TAPSE < 14 mm), actieve cardiale decompensatie, ongecontroleerde hartritmestoornissen, verdenking op actieve endocarditis, reeds eerder deelname in wetenschappelijke studies met behulp van straling, mogelijke zwangerschap in pre-menopauzale vrouwen ouder dan 50 jaar die geen betrouwbare anticonceptie middelen gebruiken, gebruik van pericard patches en een operatie van een aorta PHV in de medische voorgeschiedenis, een contra-indicatie voor CTA/ intraveneus contrast, (mogelijke) zwangerschap, weigering om te worden geïnformeerd over eventuele onverwachte bijbevindingen door MDCT of FDG-PET.

Kortom, PROSPECTA zal de normale FDG-PET opname waarden rond aorta kunsthartkleppen bestuderen in de vroeg, laat en indien nodig ook de chronisch postoperatieve fase. PROSPECTA zal afkapwaarden formuleren voor normale FDG opname. Dit zal leiden tot gegevens over de specificiteit van FDG-PET wat resulteert in meer betrouwbare beoordeling van deze imaging strategie bij patiënten met verdachte PHV endocarditis.

Verworven PHV obstructie

Biologische en mechanische PHV zijn onderhevig aan het ontwikkelen van obstructie, maar zoals omschreven in **hoofdstuk 1** zijn de diagnostische en therapeutische dilemma's voornamelijk aanwezig in mechanische PHV's [16] . In tegenstelling tot biologische kunsthartkleppen, wordt verworven mechanische PHV obstructie wordt voornamelijk veroorzaakt door pannus of trombose, welke beiden verschillende therapeutische strategieën hebben [3]. Daarom is de differentiatie klinisch zeer belangrijk. Hoewel echocardiografie en fluoroscopie niet bekwaam zijn om adequaat pannus van trombus te onderscheiden, is MDCT echter een veelbelovende imaging tool voor juiste differentiatie [9]. Echter er zijn geen prospectieve studies aanwezig die de waarde van de CTA bestudeerd voor de differentiatie van pannus en trombus bij geobstrueerde kunsthartkleppen. De impactstudie (**Im**aging van **P**rosthetische kunsth**A**rtkleppen met **CT**A), een samenwerking tussen het academisch medisch centrum (AMC) in Amsterdam en de UMCU zal deze gegevens echter snel leveren. De resultaten van deze studie zullen waarschijnlijk het diagnostische algoritme voor geobstrueerde PHV's veranderen. Op basis van dit proefschrift en op de op dit moment beschikbare literatuur wordt een diagnostisch algoritme zoals in figuur 2 voorgesteld.

ALGEMENE CONCLUSIE VAN DIT PROEFSCHRIFT

Het blijft moeilijk om kunsthartklep endocarditis en obstructie correct te diagnosticeren met echocardiografie alleen. Omdat de klinische implicaties groot zijn, levert dit proefschrift het bewijs dat clinici een lage drempel moeten hebben voor het uitvoeren van additionele imaging met nieuwe technieken op het gebied van kunsthartklep dysfunctie (3D-TEE, FDG-PET/CT en/of CTA). Wanneer deze technieken bovenop 2D-echocardiografie worden verricht kan de diagnostische nauwkeurigheid worden verbeterd en het behandelplan worden geoptimaliseerd.

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DANKWOORD

DANKWOORD

Een week voordat de inhoud van dit boekje naar de drukker ging, diende het dankwoord nog geschreven te worden. Daar zat ik dan, mezelf realiserend dat het belangrijkste hoofdstuk van mijn proefschrift het daglicht nog moest zien. Het zou namelijk volstrekt onmogelijk zijn geweest om als solist in tweeënhalf jaar naast alle klinische werkzaamheden, het resultaat te boeken dat voor u ligt. Zoiets kan alleen maar als er een groep van geweldige mensen om je heen staat, zowel professioneel als privé.

Daarom begin ik bij jou, **Joëlle**, mijn liefste. Jij hebt de afgelopen promotietijd wellicht nog meer moeten inleveren dan ikzelf. Zonder jou had het zeker niet gelukt. We zijn dit traject samen ingegaan, wetend dat het voor ons beiden een grote belasting zou worden, maar ook veel goeds zou brengen. Jij was altijd mijn steun, mijn luisterend oor, mijn klankboord, maar ook mijn rem, ook dat was af en toe broodnodig. Als ik op zaterdagmorgen weer eens de laptop van stal haalde, zei ons Otje zo nu en dan: "Pap, je gaat toch niet weer werken? Ik wil leuke dingen met je doen", dan biggelden de tranen weleens over jouw wangen, mijn liefste, het is klaar……!!! Het leven lacht ons toe, nog steeds zo dol op elkaar, twee schatten van jongens, beiden een mooie baan, we krijgen weer meer tijd voor elkaar, ik heb zo'n zin in de toekomst met jou!!!

Dr. Steven Chamuleau, mijn copromotor. Beste Steven, ook aan jou ben ik ook zoveel dank verschuldigd. Je hebt voor mijn gevoel vanaf het begin een blind vertrouwen in mij gehad. Je liet het me doen, je ondersteunde, sprong voor me in de bres waar nodig, maar was ook kritisch op de juiste momenten. Dit allemaal ondanks dat je al zoveel hooi op je vork had. Je zette me voor een T-splitsing in mijn carrière: interventie of beeldvorming. Ik wilde beiden, jij dwong me te kiezen, beiden is eigenlijk niets zei je, je liet de keuze aan mij. Volledig onbaatzuchtig overigens, want bij de keuze interventie was je mij en onze gezamenlijke projecten kwijt. Ik denk achteraf dat je de T-splitsing terecht en op het juiste moment opwierp. Ik ben uiteindelijk zo blij met de gekozen richting, met jou als mijn leermeester, en huidige baan als gevolg, je bent mijn held, thank you so much!!

Dr. Ricardo Budde, mijn andere copromotor. Beste Ricardo, ook jou wil ik bedanken voor je inzet van de afgelopen jaren. Er meldde zich in 2011 opeens een cardio-assistent die het enthousiaste plan had om naast zijn opleiding te gaan promoveren. Jij keek uiteraard eerst even de kat uit de boom. Jouw vertrouwen kwam echter snel en ik heb ook jouw niet aflatende steun als zeer motiverend ervaren. Hoewel we karakterologisch verschillen, hebben we zeer vruchtbaar, constructief en fijn samengewerkt, misschien juist dankzij het verschil werkte het zo goed. Ik heb veel respect voor jouw ongekende drive en toewijding aan de wetenschap, je laat je vrijwel nooit uit het veld slaan, bent uiterst precies en wat je zegt maak je waar. Ik wens je dan ook veel succes in het Erasmus Medisch Centrum als staflid Radioloog. Het zou mooi zijn, nu we in vrijwel dezelfde regio gaan werken, de handen zowel klinisch als wetenschappelijk opnieuw in elkaar slaan.

Professor Doevendans, mijn promotor. Beste Pieter, in ieder dankwoord van een proefschrift zal wel iets gezegd worden over jouw altijd duidelijke, maar o zo kort en bondige antwoorden op e-mails: “OK, PD”. Uiteindelijk ben ik (na een paar jaar mijmeren) erachter wat je strategie is; je stimuleert de promovendus op deze manier tot het uiterste om hem allereerst zelf met een voorstel te laten komen dat zo goed is, zodat jouw “OK PD” ook echt verdient kan worden. Ik heb de afgelopen jaren jouw onvoorwaardelijke steun op de achtergrond gevoeld. Als ik bij je aan tafel zat, was je altijd laaiend enthousiast over de kunstklep beeldvorming die je op overdrachten en in artikelen/presentaties had voorbij zien komen; uit de mond van een interventiecardioloog kan een beeldvormer niet een groter compliment krijgen. Nadat we de eerste keer een endocarditis patiënt en een controle patiënt met PET + CTA in beeld hadden gebracht, heb je meerdere malen gezegd dat je genoeg wist, geen statistiek meer nodig zei je, voor de vorm nog een paar extra patiënten includeren en klaar. Eén plaatje zegt dus nog steeds meer dan 1000 woorden, het aloude adagium is nog steeds van kracht. Beste Pieter, het ga je goed in het Utrechtse. Je hebt de afgelopen jaren daar een prachtige club ambitieuze mensen bij elkaar gebracht, die je onder jouw Amerikaanse stijl van leiding geven de afdeling Cardiologie tot nog grotere hoogte zal doen laten stijgen!

Professor Mali, mijn andere promotor. Ook zonder uw steun had dit project niet kunnen worden volbracht. Ik dank u voor het strategisch meedenken, de steun op de achtergrond, en uw goedkeuring om samen te werken met de afdeling beeldbewerking/fotografie. Ik hoop dat ik aan uw verwachtingen heb voldaan en wens u een prachtige tijd nu u met emeritaat bent.

Karin van Rijnbach, de lay-out, alle images/tabellen, het boekje etc. etc., allemaal van jouw hand. Je stond altijd voor me klaar, ook zonder jou had het niet gelukt, nogmaals dank daarvoor!

Dr. Jesse Habets, mijn partner in crime! Wat was ik zonder jou geweest man, avonden en avonden met elkaar plannen gemaakt, nieuwe projecten gestart, aan artikelen geschaafd, patiënten geïncludeerd, etc. etc. . Altijd met een tomeloos enthousiasme. Met de “IMPACT bak” gingen we alle ziekenhuizen in de regio af om ons onderzoek voor het voetlicht te brengen en zo meer patiënten geïncludeerd te krijgen. We hebben heel wat flesjes wijn geopend na weer een succesvolle acceptatie, er waren eigenlijk veel pieken en maar weinig dalen, en dat schijnt bijzonder te zijn in de wetenschap, wat een mooie tijd hebben we gehad!! Maar de meeste genoegdoening kregen we toch wel door het optimaliseren van beleid voor de in onze handen gevallen patiënten. De verrichte aanvullende en (op dat moment nog) zeer experimentele beeldvormende technieken hebben voor veel van onze studiepatiënten het verschil gemaakt. Dat wisten we en dat motiveerde ons tot op het bot. Het ga je goed met je opleiding tot radioloog en je wetenschappelijke projecten in het UMC Utrecht, cheerz maatje!

Drs. Ruben Uijlings. Beste Ruben, in 2010 heb jij mij als eerste enthousiast gemaakt voor kunsthartklep beeldvorming. Je vertrok naar Deventer om daar de maatschap cardiologie te gaan versterken als imaging cardioloog. Ik heb altijd zeer gewaardeerd dat je mij als maatje voor Jesse hebt gevraagd. Zie hier het resultaat, dank daarvoor!

Professor van Herwerden, ik wil u ook bedanken voor uw enthousiasme over de in dit proefschrift beschreven nieuwe technieken om kunsthartklep problematiek in beeld te krijgen. In de nadagen van uw carrière heeft u deze technieken volledig omarmd en zag u de meerwaarde van zowel PET en CT snel in. Dit is met alle respect een teken dat u zeer jong van geest bent, anders dan de meesten op het eind van hun carrière, hield u niet vast aan hoe al die jaren daarvoor ging, maar het roer ging om; er kwamen (enigszins chargerend) geen kunstklep endocarditis patiënt zonder CT meer op tafel. Ik heb zeer veel geleerd van de hartteams waarbij u aanzat, altijd kritisch, gedreven, goed luisterend, maar ook vlijmscherp als het moest. Het resultaat was dat uw patiënten de beste zorg kregen. Ik wens u nog vele gezonde en plezierige jaren nu u met emeritaat bent, het ga u goed!

Drs. Dominika Sucha, beste Dominika, als opvolgster van Jesse heb je het best even lastig gehad. Uiteindelijk heb je het roer snel en succesvol overgenomen en ben je ook alweer een heel eind op weg in de voltooiing van een mooi proefschrift. Ik vond de samenwerking bij ons project over non-invasieve imaging van coronairen bij kunsthartklep patiënten zeer prettig. Problemen en meningsverschillen werden zeer openlijk besproken, ik heb dit als ontwapenend ervaren. Ondanks je andere projecten heb je er met overgave de schouders onder gezet en het heeft geleid tot een klinisch zeer relevant stuk. Ik hoop dat ik nog mijn steentje kan bijdragen aan het IMPACT obstructie project, ik wens je veel succes.

Laboranten echolab UMC Utrecht, dames onder jullie leiding hield ik voor het eerst een echoprobe vast, uiteindelijk vond ik die echo toch leuker dan ik dacht, wat heb ik een mooie tijd bij jullie gehad tijdens mijn echostage en aandachtsjaar Imaging. Ik dank jullie voor jullie flexibiliteit en de vele IMPACT echo's die jullie gemaakt hebben.

Maatschap Cardiologie Hagaziekenhuis, beste Arnout, Carl, Hemanth, Joris, Marco, Matthijs, Ramon, en Vincent. Jullie zochten een gepromoveerde cardioloog met veel ervaring en kozen het tegenovergestelde: een cardioloog die net uit de schoolbanken kwam en nog niet gepromoveerd was. Ik voel me nog steeds bijzonder vereerd dat ik nu tot jullie groep mag behoren. Jullie hebben (blijkbaar) veel vertrouwen gehad in de voltooiing van dit proefschrift, dank daarvoor, het is gelukt! De plek die jullie me hebben gegeven, daar heb ik altijd van gedroomd; centrum met A-opleiding, hartchirurgie, elektrofysiologie, PCI, TAVI, vrijwel alles is aan boord. Het allerbelangrijkste echter vind ik de sfeer in de groep, die is ronduit uitstekend; er heerst een "één voor allen, allen voor één" mentaliteit. Het is zelfs leuk om wekelijks te vergaderen, het gaat altijd gepaard met de nodige humor, slagvaardigheid; we zitten op een lijn, het is gezellig! Mijn wens is dat dit zo blijft, laten we dit echt vasthouden (je hoort het vaak anders) en ons centrum uitbouwen tot een nog mooiere tent; sky is the limit, straight to the top, zoals Hemanth dat zo mooi kan roepen!

Dr. Ben Delemarre, beste Ben, hoewel wij qua leeftijd vele jaren schelen voel ik toch een grote verbondenheid met je. Met knikkende knieën ontmoette ik je voor het eerst in het echo lab in het Hagaziekenhuis; dagje meelopen met Delemarre (de nationale echotopper pur sang), was een onderdeel sollicitatie procedure voor de maatschapplek. Ik voelde me echter gelijk om m'n gemak bij je, er ontstonden direct leermomentjes, zelfs over en weer (X-plane LAA, weet je nog).

Ik geniet van je enthousiasme betreffende het onderwerp van deze thesis. We hebben in het Hagaziekenhuis al vaak de aanvullende CT en PET scan uit de kast getrokken, het bracht voor het merendeel van de patiënten de correcte diagnose aan het licht. Je gaat op dit moment echter door een zeer moeilijke fase van je leven, je hebt jouw grote liefde verloren. Ik hoop dat je nog lang aan ons centrum blijft verbonden, om je gedachte op wat anders te zetten en ik wil namelijk nog veel van je leren. Verder hoop ik dat je me volgend jaar begeleidt met het organiseren van de Haagsche echocursus, en dat je jouw voordracht die dit jaar gepland stond, alsnog houdt.

Dr. Maarten-Jan Cramer, beste MJ, ook jij gaat door een zware en heftige tijd in je leven. Ik hoop zo dat je met jouw positivisme en doorzettingsvermogen de strijd tegen je ziekte overwint. Verder dank ik je voor onze mooie tijd samen op het echolab. Jouw hyperdynamische gezelligheid mis ik echt nog weleens. Ook is uiteindelijk zelfs nog gelukt om een stukje samen te publiceren, samen de 3D kast in, dat waren grappige momenten! MJ, het ga je goed, sterkte in jouw strijd!

Dr. Hans van der Heijden en Dr. Henny Peltenburg, beste Hans en Henny, dit hadden jullie nooit meer verwacht, een boekje van collega Tanis. In de functioneringsgesprekken tijdens de vooropleiding Interne werd er steevast gezegd dat het assistent Tanis (lid van de "cardio maffia") allemaal iets te makkelijk afging, er kon wel een tandje worden bijgezet, daarmee doelend op het starten van een promotietraject. Hans probeerde me dan te overtuigen met de one-liner: 'je wilt toch geen ongeletterde boer blijven'. Nou, dat zag ik natuurlijk volstrekt anders; " je wordt echt geen betere arts door een promotie boekje af te leveren", opponeerde ik dan, "integendeel zelfs" nog wat kolen op het vuur gooiend. Toch, schoorvoetend toegegeven, jullie hebben me stiekem een beetje aan het denken gezet, het resultaat ligt voor jullie!

Dr. Hans Kirkels, mijn opleider cardiologie, wat heb ik een groot respect voor jouw kennis en kunde! Dank voor jouw steun tijdens mijn opleiding, ben trots dat ik met je heb mogen werken en onder jouw leiding ben opgeleid.

Drs. Asbjorn Scholtens, nucleair geneeskundige, wat een mooie doorbraak was dat: fusie PET en CT bij een kunstklep endocarditis, the bomb! Ik had het zonder jouw inventiviteit niet gekund. Ik denk dat je op cardiovasculair gebied bij de top van Nederland hoort, wil zeer graag met je blijven samenwerken, ik weet dat je een vaste positie zoekt, men is gek als ze jou niet aannemen.

Beste familie en vrienden, sorry dat ik de afgelopen periode wat "onbereikbaar" ben geweest. Mijn sociale leven heeft er ietwat onder geleden…..Enfin, ik hoop het met jullie allen goed te maken, te beginnen op 20-6-2014!! Toch heb naast het drukke bestaan altijd geprobeerd zoveel mogelijk tijd vrij te maken voor gezellige avonden in het café, terrasje te pakken, wijntje te doen etc. etc. Bedankt voor jullie steun, gezellige avonden en het aanhoren van mijn verhalen……

Ronde Tafel 29 Gouda, mannen wat hebben we het gezellig samen! Toen ik deel van jullie groep werd had ik er natuurlijk helemaal geen tijd voor, was bezig met mijn opleiding en promotie. Ik wilde dus niet……..maar na 1 avond wist ik genoeg……. wat een heerlijke afwisseling, humor, gezelligheid hebben jullie de afgelopen jaren gegeven. Ook jullie tomeloze interesse in het

onderzoek dat ik doe, heb ik zeer gewaardeerd. Ik hoop op een mooi feest in jullie aanwezigheid, het jaarfeest 2014 is door de plee gespoeld, maar ik heb nieuws voor jullie: 20-06-2014 is jullie jaarfeest, komt, drinkt een klein drankje, waagt een klein dansje en toast op het leven!!

De paranimfen, **Drs. Lars Vink en Drs. Martijn Lekx**. Mannen, een hilarisch moment toen ik jullie vroeg om paranimf te worden. Jullie hadden (ik zal het maar netjes zeggen) allerlei seksuele associaties bij het begrip "paranimf" en geen idee wat het werkelijk was. Enigszins teleurgesteld dat het iets met promoveren betrof, kon ik jullie toch zeker over de streep trekken met het woord: feestje. Ik kijk uit naar het moment dat jullie achter me staan (hou het serieus hè, geen gedonder a.u.b), sorry, merk dat ik weer in mijn pastoorsrol schiet, dat heb ik nou werkelijk bij niemand, hoe zal dat nou komen……. nou goed, wat ik wil zeggen; dank voor jullie vriendschap, humor, gezelligheid, openheid, goede gesprekken……..heb ik echt nodig gehad de afgelopen tijd als het me allemaal iets te serieus werd.

Een groot dankwoord aan mijn schoonouders, **Maurits en Marianne Tompot**. Allereerst natuurlijk dank voor het schenken van mijn prachtige vrouw, maar daarnaast ook voor het gevoel dat we altijd op jullie konden bouwen. Jullie rol was zo groot, de kids waren altijd welkom en dat voelde zo fijn. Ik heb nooit het gevoel gehad dat er iets teveel was, verder hadden jullie altijd oprechte interesse in het onderzoek en brachten jullie het positivisme en vertrouwen. En Maurits, ook jij hebt denk ik een zeer belangrijke rol in mijn carrière keuze gespeeld. Je bent (zonder dat je het weet) toch een beetje medeverantwoordelijk voor dit cardiologische boekje. In Australië kreeg je pijn op je borst en ik behandelde je in een verlaten streek met Nitroglycerine, Ascal, verwees je met voorrang naar een PCI centrum etc. etc. Daar werd je met spoed gedotterd in de LAD en liep je een dag later weer fluitend rond. Heb het je het nooit verteld, maar achteraf ben ik toen aan het denken gezet en ervan overtuigd geraakt dat **dr. Mike Scheffer** gelijk had; *Cardiologie is het mooiste vak op aarde!*

Beste **Mike**, jij was het die me de eerste kneepjes van het vak bijbracht. Ik kwam bij je werken, was een ongeleid projectiel en keek alleen maar naar buiten om te zien hoe hard het waaide, en of het de moeite loonde om na het werk naar de Maasvlakte te rijden om een paar goede golven te pakken met de surfplank. Ik ben jouw ongeëvenaarde enthousiasme over de cardiologie nooit vergeten en toen ik een richting in mijn carrière moest kiezen heb ik vaak aan jou en onze werkzaamheden gedacht. Ik vind het machtig gaaf dat ik nu met je mag werken als collega in het Hagaziekenhuis, hoop dit nog vele jaren te doen!

Ot en Abel Tanis. Jullie zijn mijn trots! 2 zonen, wat een rijkdom. Het zit erop, pappa gaat in de weekenden vol overgave kwartetten, puzzelen, fietsen, poffertjes eten, en ja Ot, ik beloof, laptop blijft dicht!

Judith, Martijn, Sam en Max. Ook jullie leefden altijd mee met de kommer en kwel van de promovendus. Er is in ons aller leven de afgelopen jaren veel gebeurd, maar merk dat onze band alleen maar sterker is geworden en hoop dat die trend zich doorzet. Ik geniet van jullie, ik glimlach bij het blijde vooruitzicht dat ons (en al onze boys) streelt!

Mamma, je hebt me het leven geschonken, me met veel liefde opgevoed, je was er altijd. Dit proefschrift komt ook zeker op jouw conto, de basis is eind jaren zeventig gelegd. Daarna heb je me alleen maar moeten afremmen in mijn ambitie, ook dat was nodig. Hoewel je het nooit van de toren blaast, voel ik dat je zo trots bent. Laat 20-6-2014 een dag zijn waarop je straalt, het leven weer een gouden randje heeft, ondanks het grote verlies van 2009. Er komen nog meer mooie momenten, ben ook trots op jou, zoals je het leven oppakt zonder je grote liefde. Love you!

Beste **Pa**, je bent er niet meer, maar toch ook wel, je leeft in me voort. Er zijn de afgelopen jaren zeer veel belangrijke momenten geweest in mijn leven die ik met je had willen delen, dit is er zeker één van. Ik mag in mijn handen knijpen dat jij mijn vader was. Ik heb groot respect voor alle mensen waar ik in mijn dankwoord naar refereer, maar vanuit het diepst van mijn hart wil ik het meest op jou lijken. Jij had zo'n zonnige kijk op het leven, enthousiasme, gezelligheid, doorzettingsvermogen, en een niet aflatend positivisme, jij bent mijn icoon. Je genoot van alle facetten van je leven en veranderde volstrekt niets toen je te horen kreeg dat je ongeneeslijk ziek was, want je leven was namelijk al precies zo ingericht, zoals je het wilde. Je had namelijk altijd al je hart gevolgd. Ook dat is een wijze les, je moet hier en nu het leven inrichten zoals je het ambieert, en anders moet direct het roer om. Je hebt tot 4 weken voor je dood doorgewerkt, het was je hobby, je klanten waren je vrienden. Tussen de chemo therapieën en operaties door stapte je gewoon op de surfplank (foto) en genoot je met volle teugen. Een legendarisch foto voor mij, je trekt je eigen plan, op jouw eigen gereide stijltje, surfend naar het onbekende, ons loslatend, het licht, de zon, de hemel tegemoet, met een brede glimlach, want het was goed geweest.

CURRICULUM VITAE

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Wilco Tanis werd geboren op 7 november 1976 in Gouda, Nederland. Hij groeide op in Waddinxveen als zoon van de lokale groenteman (Willem Tanis). Op zeer jonge leeftijd begon zijn carrière dus met schoonmaken van spruitjes en het snijden van snijbonen. Op zes jarige leeftijd was hij echter al vastberaden om dokter te worden, als eerste stap studeerde hij af op het Driestar College te Gouda (Gymnasium). In 1994 werd hij uitgeloot voor de studie Geneeskunde, derhalve haalde hij in 1995 zijn Propedeuse voor de studie Medische Biologie aan de Vrije Universiteit te Amsterdam. In datzelfde jaar startte hij dan toch met de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam. In 2002 studeerde Wilco af en startte hij als arts-assistent Interne Geneeskunde en Cardiologie in het huidige Maasstad Ziekenhuis te Rotterdam (2003-2004). Vervolgens ging een grote droom in vervulling, namelijk werken (en surfen) als Senior House Officer Emergency Medicine bij het Gold Coast Hospital, Southport, Australia (2004-2005). Alhier werd steeds meer duidelijk dat het specialisme van zijn voorkeur de Cardiologie was. Vandaar dat hij als arts-assistent Cardiologie in het Universitair Medisch Centrum te Utrecht startte (2006). In 2007 werd de opleiding tot Cardioloog aangevangen: allereerst de vooropleiding in het Groene Hart Ziekenhuis in zijn geliefde stad Gouda (2007-2009), daarna het B-jaar Cardiologie in het Meander Medisch Centrum te Amersfoort (2009-2010) en tenslotte de vervolgopleiding in het Universitair Medisch Centrum te Utrecht (2010-2013). Tijdens de vervolgopleiding cardiologie werd hij in 2011 gegrepen door een zeer klinisch onderzoek: aanvullende beeldvormende technieken bij kunsthartklep endocarditis en obstructie. Wilco zag dat het behandelplan van kunsthartklep patiënten door een aanvullende CT of PET scan kon veranderen van een pilletje antibiotica naar een levensreddende spoed hartoperatie. Onder de bezielende leiding van Dr. Steven Chamuleau en Dr. Ricardo Budde startte hij in september 2011 een promotietraject naast de fulltime opleiding tot Cardioloog. Op deze manier hoefde zijn drang om in een topklinische zorgomgeving te praktiseren, niet te wijken voor de wetenschappelijke ambitie, integendeel het onderwerp bracht met zich mee dat het hand in hand kon gaan; het gevolg is het huidige proefschrift. In juli 2013 rondde hij zijn opleiding tot Cardioloog af en in augustus 2013 startte hij als Beeldvormend Cardioloog in de maatschap Cardiologie van het Hagaziekenhuis te Den Haag. Hij is gelukkig getrouwd met Joëlle, heeft 2 zonen (Ot en Abel) en zij wonen in Gouda.

SUPPLEMENTS

Chapter 2 - supplement 1
Chapter 3 - supplement 2 + 3

Supplement 1

Exact search string:

Pubmed:
((“heart valve”[tiab] OR “heart valves”[tiab] OR “prosthetic heart valve”[tiab] OR “prosthetic heart valves”[tiab] OR “PHV”[tiab] OR “biological valve”[tiab] OR “biological valves”[tiab] OR “mechanical valve”[tiab] OR “mechanical valves”[tiab] OR “mechanical prosthesis”[tiab] OR “mechanical prostheses”[tiab] OR “biological prosthesis”[tiab] OR “biological prostheses”[tiab] OR “prosthetic mitral”[tiab] OR “prosthetic aortic”[tiab] OR “prosthetic”[tiab])) AND (“echocardiography”[tiab] OR “transthoracic echocardiography”[tiab] OR “transoesophageal echocardiography”[tiab] OR “ultrasound”[tiab] OR “ultrasonography”[tiab] OR “TTE”[tiab] OR “TEE”[tiab] OR “computed tomography”[tiab] OR “CT”[tiab] OR “multislice computed tomography”[tiab] OR “multidetector-row computed tomography”[tiab] OR “MSCT”[tiab] OR “MDCT”[tiab] OR “computed tomography angiography”[tiab] OR “CTA”[tiab] OR “computed assisted tomography angiography”[tiab] OR “imaging”[tiab])

Embase:
[embase]/lim NOT [medline]/lim AND (‘heart’/exp OR heart AND valve:ab,ti OR (‘heart’/exp OR heart AND valves:ab,ti) OR (prosthetic AND (‘heart’/exp OR heart) AND valves:ab,ti) OR (prosthetic AND (‘heart’/exp OR heart) AND valve:ab,ti) OR phv:ab,ti OR (biological AND valve:ab,ti) OR (biological AND valves:ab,ti) OR (mechanical AND valve:ab,ti) OR (mechanical AND valves:ab,ti) OR (mechanical AND prosthesis:ab,ti) OR (mechanical AND prostheses:ab,ti) OR (biological AND prosthesis:ab,ti) OR (biological AND prostheses:ab,ti) OR (prosthetic AND mitral:ab,ti) OR (prosthetic AND aortic:ab,ti) OR prosthetic:ab,ti) AND (echocardiography:ab,ti OR (transthoracic AND echocardiography:ab,ti) OR (transoesophageal AND echocardiography:ab,ti) OR tee:ab,ti OR (transesophageal AND echocardiography:ab,ti) OR tte:ab,ti OR (computed AND tomography:ab,ti) OR ct:ab,ti OR (multislice AND computed AND tomography:ab,ti) OR (‘multidetector row’ AND computed AND tomography:ab,ti) OR msct:ab,ti OR mdct:ab,ti OR (computed AND (‘tomography’/exp OR tomography) AND angiography:ab,ti) OR cta:ab,ti OR (‘computer’/exp OR computer AND assisted AND (‘tomography’/exp OR tomography) AND angiography:ab,ti) OR imaging:ab,ti)

Supplement 2

2x2 Table

TP	FP
FN	TN

PHV endocarditis in general

Clinical workup (TTE/TEE)	
21	1
1	5

Clinical workup (TTE/TEE/MDCT)	
22	1
0	5

Vegetation

Clinical workup (TTE/TEE)	
5	0
3	20

Clinical workup (TTE/TEE/MDCT)	
8	0
0	20

Mycotic aneurysm/abscess

Clinical workup (TTE/TEE)	
17	1
8	10

Clinical workup (TTE/TEE/MDCT)	
25	1
0	10

FN = false-negative; FP = false-positive; MDCT = multidetector computed tomography; PHV = prosthetic heart valve; TEE = transesophageal echocardiography; TN = true-negative; TP = true-positive; TTE = transthoracic echocardiography

Supplement 3 Diagnostic accuracy measures for PHV endocarditis

Target condition	Modality	Diagnostic accuracy measure (95% CI)	
Vegetation	Clinical workup	Sensitivity	63% (25-91%)
		Specificity	100% (83-100%)
		PPV	100% (48%-100%)
		NPV	87% (66-97%)
	Clinical workup plus CTA	Sensitivity	100% (63-100%)
		Specificity	100% (83-100%)
		PPV	100% (63-100%)
		NPV	100% (83-100%)
Mycotic aneurysms/ abscesses	Clinical workup	Sensitivity	68% (47-85%)
		Specificity	91% (59-98%)
		PPV	94% (73-99%)
		NPV	56% (31-78%)
	Clinical workup plus MDCT	Sensitivity	100% (86-100%)
		Specificity	91% (59-98%)
		PPV	96% (80-99%)
		NPV	100% (69-100%)
PHV endocarditis in general	Clinical workup	Sensitivity	95% (77-99%)
		Specificity	83% (36-97%)
		PPV	95% (77-99%)
		NPV	83% (36-97%)
	Clinical workup plus MDCT	Sensitivity	100% (84-100%)
		Specificity	83% (36-97%)
		PPV	96% (78-99%)
		NPV	100% (48-100%)

CI = confidence interval; CTA = computed tomography angiography; NPV = negative predictive value; PPV = positive predictive value