Diagnostic tools in the follow-up and monitoring of congenital heart disease and pulmonary hypertension

Meijer, F.M.M.

DIAGNOSTIC TOOLS IN THE FOLLOW-UP AND MONITORING OF CONGENITAL HEART DISEASE AND PULMONARY HYPERTENSION

Fleur M.M. Meijer

DIAGNOSTIC TOOLS IN THE FOLLOW-UP AND MONITORING OF CONGENITAL HEART DISEASE AND PULMONARY HYPERTENSION

Fleur M.M. Meijer

Colofon
Cover: Liselotte Meijer
Layout: Liselotte Meijer
Printing: Gildeprint
ISBN: 978-94-6419-789-1
Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Proefschrift

ter verkrijging van

de graad doctor aan de Universiteit Leiden,

op gezag van rector magnificus prof.dr.ir. H. Bijl,

volgens besluit van het college voor promoties

te verdedigen op woensdag 17 Mei 2023

klokke 13:45 uur

door

Fleur Mathilde Margaux Meijer

geboren te Amsterdam

in 1988

PROMOTIECOMMISSIE

Promotor

Prof. Dr. M.J. Schalij

Copromotoren

Dr. H.W. Vliegen

Dr. P. Kiès

Overige leden

Prof. Dr. M.V. Huisman

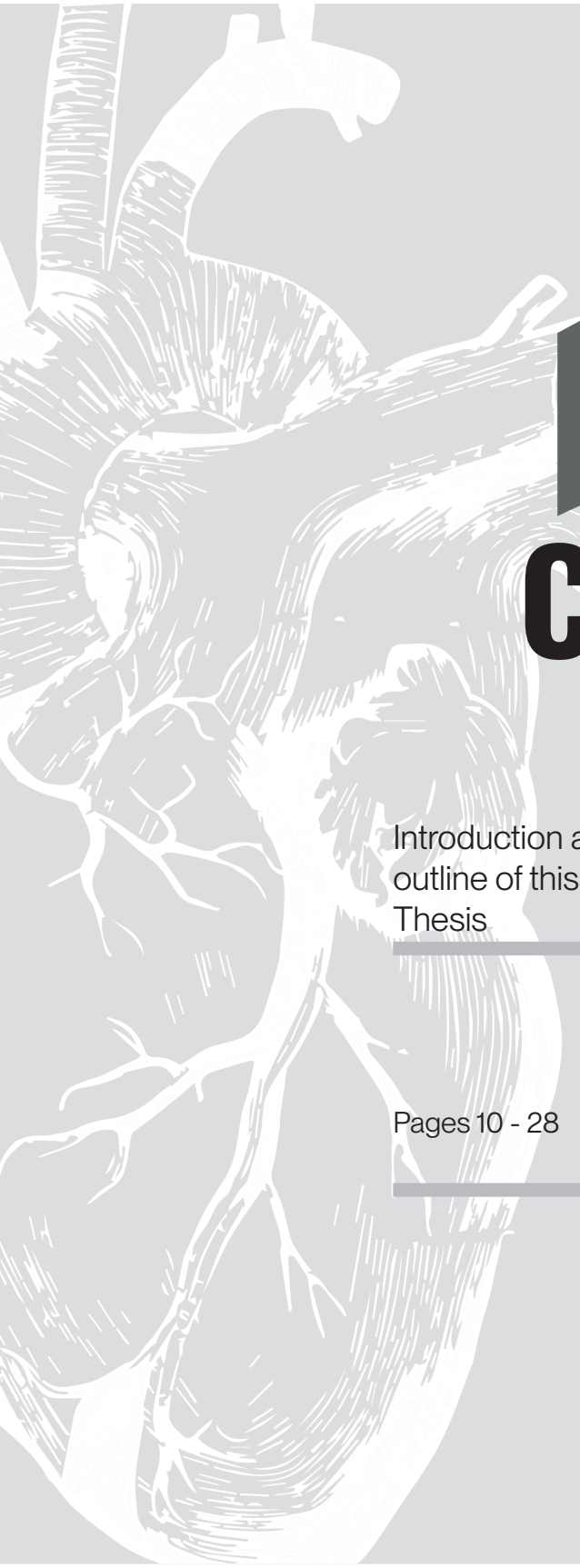
Prof. Dr. A. Vonk Noordegraaf
(Amsterdam UMC)

Prof. Dr. B.J.M. Mulder
(Amsterdam UMC)

Prof. Dr. H.J. Lamb

Dr. J. K. de Vries-Bouwstra

TABLE OF CONTENTS



1 CHAPTER

Introduction and outline of this Thesis

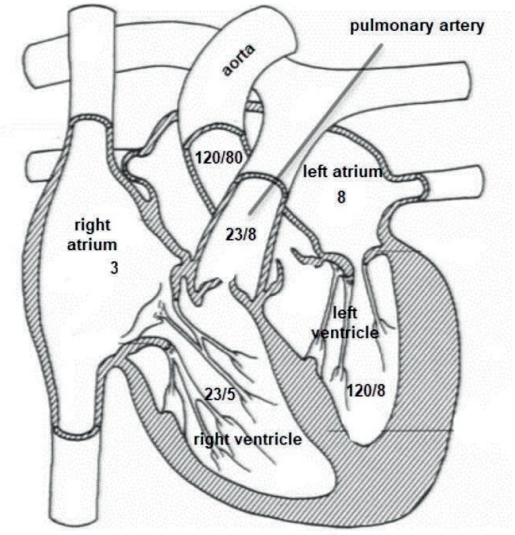
Pages 10 - 28

Part 1: Pulmonary Hypertension

In patients with pulmonary hypertension (PH) the pressure measured in the pulmonary artery by right heart catheterization (mean pulmonary arterial pressure mPAP) is elevated. The right ventricle (RV) has to overcome this higher pressure during the ejection of blood into the pulmonary circulation. The RV has to adapt to manage these elevated pressures and this will eventually lead to RV remodeling: the RV initially becomes hypertrophic, in a later stage systolic function decreases, RV dilatation progresses resulting in RV dysfunction 1. A mPAP of 20mmHg should be considered as the upper limit of the normal value [2]. An elevated mPAP alone is not accurate enough to characterize a clinical condition or pathological process. PH may be pre-capillary, post-capillary or combined pre- and post-capillary (Table 1). In patients with pre-capillary PH an increase in pulmonary vascular resistance is caused by pulmonary vascular remodeling due to pulmonary vascular disease (PVD). PVD is associated with structural changes of small pulmonary arteries. Examples are patients with connective tissue disease, drug- and toxin- induced PH, obstructive- and restrictive lung disease and patients with chronic thromboembolic PH. In both pre- and postcapillary PH there is an elevation of mPAP. In pre-capillary PH concomitant presence of mPAP > 20 mmHg, a pulmonary artery wedge pressure (PAWP) < 15mmHg and a pulmonary vascular resistance (PVR) > 2 woods units (WU) should be present [2]. These pressures are measured with right heart catheterization. **Figure 1** shows an overview of the average normal values measured during a right heart catheterization.
PH cannot be considered to be a specific "disease" [3]. Many clinical conditions manifest in PH, therefore the World Health Organization classified 32 clinical conditions with PH, into five groups according to pathological, pathophysiological and therapeutic characteristics stated in **Table 2** [2]. Pre-capillary PH concerns patients from group 1, 3 and 4 and in some cases from group 5. And as mentioned earlier there are patients from group 2 with combined pre- and post-capillary PH. Despite possible comparable elevations of pulmonary arterial pressure in the different clinical groups, the underlying mechanisms, diagnostic approaches, and prognostic and therapeutic implications are completely different.

PAH (group 1) comprises a clinical group of rare conditions with pre-capillary PH, in which other causes of pre-capillary PH are excluded, such as pulmonary embolisms, or interstitial lung disease [3]. Examples are patients with systemic sclerosis (SSc) and congenital heart disease (CHD). PAH is a well-known complication of CHD, especially in patients with uncorrected systemic-to-pulmonary shunts [5]. A systemic-to-pulmonary shunt gives rise to volume and pressure overload of the pulmonary circulation, leading to an increased pulmonary vascular resistance, which above > 20mmHg is described as PAH[4]. In

Figure 1. normal values of mean pressures during right heart catheterization



Mean pulmonary arterial pressure = (systolic + 2x diastolic)/3. Pulmonary vascular resistance is mean pulmonary arterial pressure – pulmonary arterial wedge pressure/cardiac output)

Figure 2 the pathophysiologic response of PAH is explained. There is destruction of the pulmonary vasculature due to underlying disease, which increases pulmonary vascular resistance. This causes an increase in pulmonary arterial pressure. The overall 5 year survival rate in untreated patients is 57%. Important is that the longitudinal trends suggest survival in patients has improved, mainly since the introduction of new pharmacotherapies [6]. In patients with PAH, specific treatment is available. This treatment has evolved over the past years, examples are endothelin receptor antagonists and prostacyclin receptor agonists [7].

Group 2, PH due to left sided heart disease is the most common cause of PH. In this group of patients, an elevation in left atrial or ventricular filling pressures due to for example mitral valve disease, causes elevation in mean pulmonary arterial pressures, and can be considered as a manifestation of heart failure (**Figure 3**). It is a form of post capillary pulmonary hypertension and diagnosed with right heart catheterization. The hemodynamic definition of group 2 PH consists of a mPAP of > 20mmHg, a pulmonary arterial wedge pressure of > 15mmHg and a PVR of < 2 Woods units. The prognosis for patients with pulmonary hypertension and heart failure with preserved ejection fraction (HFpEF) has not been well studied. The combination of heart failure (with reduced ejection fraction) with

Table 1. Haemodynamic definitions of pulmonary hypertension[4]

Definitions	Characteristics	Clinical groups#
Pre-capillary PH	mPAP >20 mmHg	1, 3, 4 and 5
	PAWP ≤15 mmHg	
	PVR ≥2 WU	
Isolated post-capillary PH (IpcPH)	mPAP >20 mmHg	2 and 5
	PAWP >15 mmHg	
	PVR <2 WU	
Combined pre- and post-capillary PH (CpcPH)	mPAP >20 mmHg	2 and 5
	PAWP >15 mmHg	
	PVR ≥2 WU	

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood Units. #: group 1: PAH; group 2: PH due to left heart disease; group 3: PH due to lung diseases and/or hypoxia; group 4: PH due to pulmonary artery obstructions; group 5: PH with unclear and/or multifactorial mechanisms.

Table 2. Clinical Classification of Pulmonary Hypertension

Group 1 – Pulmonary Arterial Hypertension (PAH)
Group 2 – Pulmonary hypertension due to left side heart disease
Group 3 – Pulmonary hypertension associated with lung diseases and/or hypoxemia
Group 4 – Pulmonary hypertension associated with pulmonary artery obstruction
Group 5 – Pulmonary hypertension due to unclear and/or multifactorial mechanisms

PH is associated with a poor prognosis, these patients have a higher mortality rate (28%) in comparison with patients from the same group without PH 8. The treatment consists of optimization of the treatment of the underlying left heart disease to reduce left sided filling pressures and subsequently reduce pulmonary pressures [7].

Group 3 PH comprises patients with lung diseases, obstructive pulmonary disease,

Figure 2. pathophysiologic response in patients with PAH (Group 1)

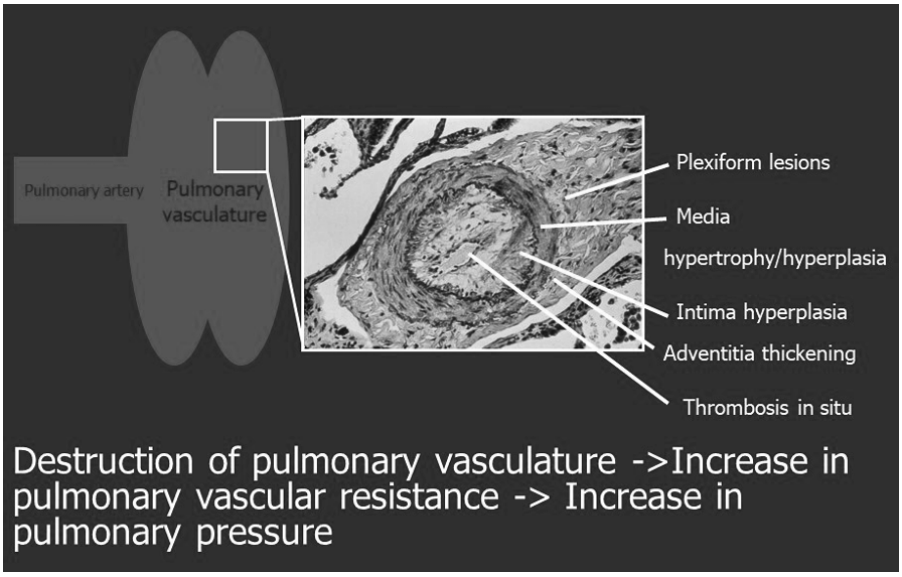
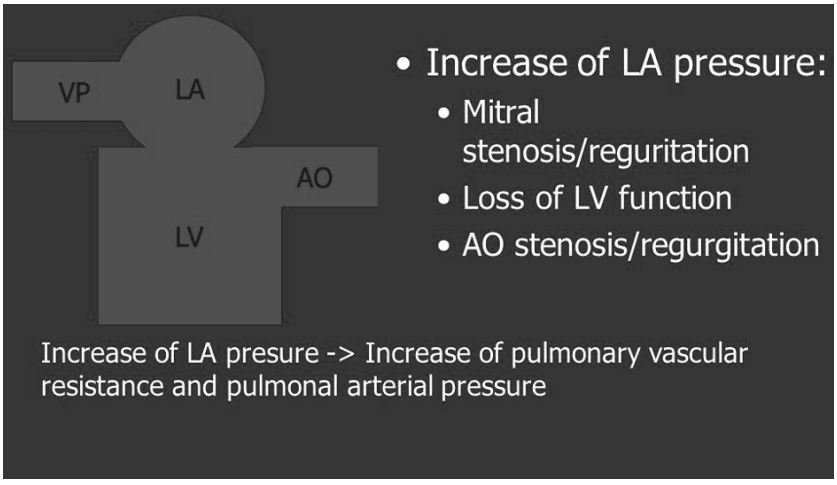


Figure 3. Pathophysiologic response in patients with PH group 2 and in certain cases group 5



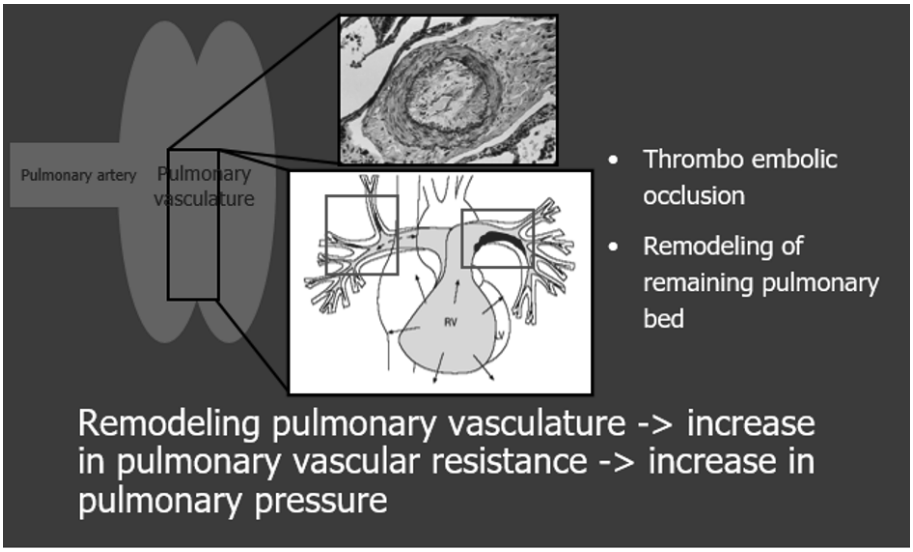
Abbreviations: LA, left atrium; VP, pulmonary veins; LV, left ventricle; Ao, aorta

interstitial lung disease or patients with hypoventilation syndromes and/or hypoxia. It is a form of pre-capillary PH, the lungs become stiffer, and therefore the pressure in the lungs rises (**Figure 4**). Gas exchange becomes more difficult due to ventilation and perfusion mismatch, which results in chronic hypoxia and vasoconstriction. PH has been found to be a poor prognostic indicator in chronic lung disease. In general it is accepted that the worse

the pulmonary hypertension, the higher the mortality [6]. Treatment is primarily directed at the treatment of the underlying disease, examples are oxygen therapy or continuous positive airway pressure [7].

In group 4 PH occurs due to pulmonary artery obstruction from unresolved chronic thromboembolic disease. This chronic thromboembolic pulmonary hypertension (CTEPH) causes remodeling of the remaining pulmonary bed, pulmonary vascular resistance increases and therefore pulmonary arterial pressure rises. Some patients with acute pulmonary embolism develop CTEPH and others don't, there is no clear explanation for this yet. It is hypothesized that patients in which CTEPH develops, have an underlying hypercoagulable state. In the past the survival rate of untreated patients (which received no operation or medication) with CTEPH is very poor, with a 5 year survival rate of 10%. The first step in the management is anticoagulant therapy. Pulmonary endarterectomy is the only definitive and potentially curative therapy for CTEPH and can be performed in

Figure 5. Pathophysiologic response in patients with PH group 4



a selected subgroup in a highly specialized center. Operated patients have better long-term survival than not-operated patients. An international prospective registry from 27 European centers showed that not-operated patients had a significantly worse prognosis, with a 3-year survival rate of 70%, whereas that of patients undergoing surgery was 89%[9].

Group 5 comprises a heterogeneous group of diseases that encompass PH secondary to multifactorial mechanisms. These include hematological disorders, systemic disorders

such as sarcoidosis, metabolic disorders and others. Incidence and prevalence of PH in most of these disorders are unknown [2]. Treatment consists also in this group of treatment of the underlying disease [7].

Given the infaust nature of the disease, a timely correct diagnosis is of the utmost importance. The diagnostic approach in patients with a clinical suspicion for PH starts in the majority of cases with echocardiography. It remains the most important non-invasive screening tool. Right heart catheterisation is ultimately the golden standard and is mandatory to establish the diagnosis [10]. Electrocardiography in patients with a clinical suspicion may provide supportive evidence of PH, however as a screening tool in complicated patients or in patients in the early course of their disease its role has yet to be explored [7]. It is known that a normal electrocardiogram (ECG) does not exclude PH [11]. Previous studies show that the ECG in patients with advance disease and known PAH reflect physiologic and anatomic abnormalities in the right ventricle due to right ventricular (RV) pressure overload [12]. Other researchers have demonstrated that the ECG derived ventricular gradient (VG), when projected on the optimal direction for detection of RV pressure overload (VG-RVPO), can detect PH in a heterogeneous population suspected of PH [13-15].
Patients with SSc are at high risk of developing PAH, and this is a major cause of death in this patient group. However PAH is relatively late diagnosed in routine clinical practice [16]. Systematic screening and early treatment of PAH can significantly improve survival in this patient population and early treatment with PAH specific therapy is beneficial [17, 18]. This underlines the need for better screening tools.
PH in every form often remains a difficult diagnosis due to the non-specific clinical signs and symptoms. Currently there are diagnostic algorithms and decision rules available to improve the decision making of the clinician [19-24]. However only roughly one third of the patients are safely excluded which means there is an opportunity for improving the specificity of these diagnostic algorithms using PH as a diagnostic parameter [23].
The first part of this thesis focuses on the VG-RVPO which is a measure of right ventricular pressure overload, in **Chapter 2** we assess the use of the VG-RVPO as a screening and monitoring tool of early PH in patients with SSc. In **Chapter 3** we investigate the role of the VG-RVPO to improve the efficiency of the YEARS algorithm, an already validated decision tool to diagnose PE. In **Chapter 4** we investigated if the VG-RVPO is an accurate diagnostic tool for estimating presence and severity of acute right ventricular pressure overload, and if it can be used for the risk stratification of patients with PE.

Part 2: Congenital Heart Disease

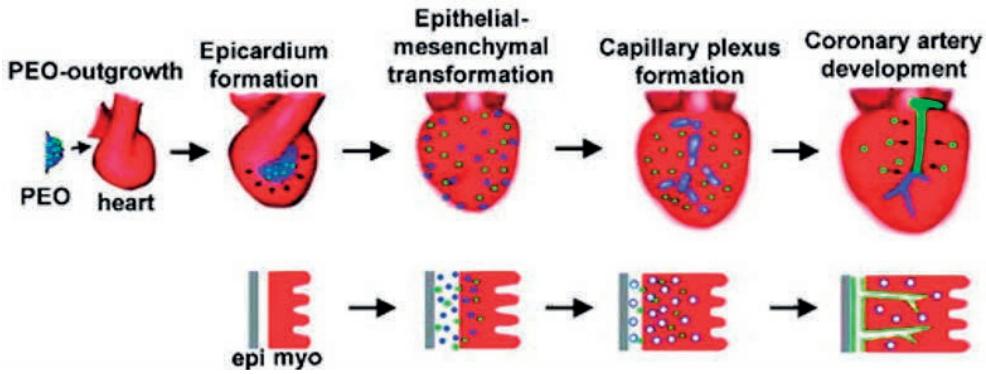
The survival of patients with congenital heart disease (CHD) has markedly improved,

resulting in a continuously growing population of adults with CHD. More than 90% of patients born with CHD now survive into adulthood [25].

Coronary Artery Anomalies

Coronary artery anomalies represent a group of congenital disorders with an anomalous location of a coronary ostium, an anomalous course or an anomalous termination (coronary arterio-venous fistula) of a coronary artery. The prevalence of coronary artery anomalies in the general population is estimated to be around 1% [26, 27]. Although most individuals with coronary artery anomalies remain undetected as their disease course is clinically insignificant, some may become symptomatic and experience adverse cardiac events. Several anatomic high-risk features have been described in patients with anomalous aortic origin of the coronary arteries (AAOCA). These include an inter-arterial course (IAC) between the aorta and pulmonary artery, an intramural course, a slit-like ostium, an acute take-off angle or a proximal narrowing of the anomalous vessel and are considered to

Figure 1. Movement of the pro-epicardial organ (PEO) to and over the heart is shown in the top panel, and mesenchymal migration and differentiation are shown in the bottom panel. The PEO (blue) is an outgrowth from the dorsal body wall that moves to the looping heart (red). Next, migrating epithelium is seen spreading over the heart. In cross section, the epithelium is a single cell layer. Epithelial/mesenchymal transition provides cells that migrate into the myocardium. Vasculogenic cells differentiate and link to form plexi that induce other mesenchymal cells to become smooth muscle. These plexi are remodelled into definitive arteries, and the most proximal points of the major coronaries finally link up with the aorta. (Adapted from Reese DE et al. Development of the coronary vessel system. Circ Res. 2002 Nov 1;91(9):761-8)



be of special interest due to their predisposition to myocardial ischemia, heart failure, ventricular arrhythmias, and sudden cardiac death (SCD) [28-30]. Other coronary artery anomalies include high take-off from the aorta, duplication of coronary arteries or absent left main stem with separate ostium for left anterior descending coronary artery and left circumflex coronary artery, which are rather normal variations without clinical significance in the majority [29].

Considering anatomy: previously, the coronary arteries were thought to be aortic root outgrowths. However, evidence has emerged that coronary endothelial precursors self-organize in the subepicardial space (**Figure 1**) and form a vascular plexus that connects to the aorta only later in embryological development [31]. Different genes, the availability of vascular endothelial growth factor, coronary arterio-venous growth coordination, and the vascular density around the aortic trunk, which is modulated by hypoxic domains, all play a role in the correct connection between the distal coronary artery parts and the proximal aortic root parts [32].

Clinically significant AAOCA variants include AAORCA (anomalous aortic origin of a right coronary artery) and AAOLCA (anomalous aortic origin of a left coronary artery. Although AAORCA is more common than AAOLCA [33], it was previously thought that AAOLCA was the sole cause of SCD because a greater amount of myocardium is potentially at risk for ischemia [34]. However, several studies have found that SCD also occurs in patients with underlying AAORCA [35, 36]. The processes causing AAOCA that contribute to unfavourable cardiac events are not well understood. It has been postulated that the high-risk anatomic characteristics may lead to recurrent coronary ischemia during vigorous physical exercise, scarring, and ventricular arrhythmia. The pathophysiology of high-risk anatomic features during physical exercise (when tachycardia and hemodynamic overload increase myocardial demand while decreasing coronary flow) includes kinking of the acute take-off angled anomalous vessel, lateral compression of the aorta on the intramural segment, intermittent closure of the slit-like orifice, and compression of the interarterial segment by the aorta and pulmonary artery. Probably the most dangerous aspect is the intramural course's length [29, 35, 37 28, 30].

The decision to operate on these patients is partly made on clinical presentation and is not unambiguous [32, 38, 39]. Other factors that are taken into account are age, anatomy and the presence of ischemia in the matching area [32].

There are several surgical options for treating AAOCA, including: unroofing of the intramural

segment, reimplantation to the original sinus, pericardial patch plasty of the aorta and proximal anomalous coronary artery, either alone or in combination with pulmonary artery translocation. Coronary bypass is used infrequently to provide an extra-anatomic source of blood flow to the myocardium, but it is not generally recommended because the anomalous vessel is only compromised during stress or exercise. As a result, most of the time, there will be significant competitive flow, which may result in low graft patency or subclavian steal.

With unroofing, the procedure involves incising the common wall between the aorta and the intramural segment of the anomalous coronary artery via an anterior aortotomy. This incision has several beneficial effects, including relocating the functional orifice to the appropriate sinus, significantly enlarging the orifice, removing the intramural component of the artery, and removing the portion of the vessel that lies between the great arteries. According to Cubero et al [40], the major limitation of unroofing is that it does not eliminate the interarterial segment of the coronary artery with anomalous origin. Unroofing may still leave the coronary artery origin in the "wrong sinus" in cases with only a short intramural segment, with persistence of an interarterial segment. Additional pulmonary artery relocation may be required in such cases. Furthermore, even if the commissure is resuspended at the time of repair, unroofing may necessitate manipulation of the inter-coronary commissure, which may predispose to aortic regurgitation.

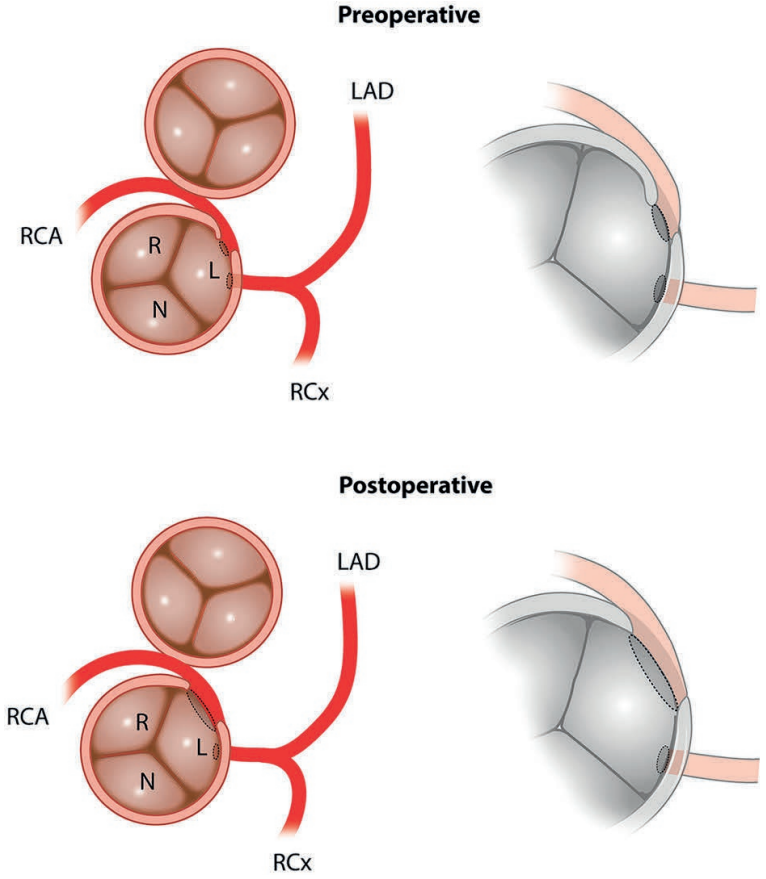
Reimplantation, as in the case of AAORCA from the left coronary sinus with inter-arterial course and intramural segment, is possible41. The RCA is divided immediately distal to the intramural segment and reimplanted end-to-side into the right sinus of Valsalva without a button [42].

An anatomical surgical repair in which the aorta and pulmonary trunk are transected to expose the course of the anomalous left main coronary artery, may also be performed [43]. The anomalous left artery proximal epicardial course is incised, and a patch of pericardium or saphenous vein is used to make a neo-ostium in the appropriate sinus, with the patch incorporated into the aortic suture line. The abnormal interarterial and/or intramural segment is left intact but bypassed, according to proponents of this technique. In the appropriate sinus, a new, enlarged coronary ostium is formed, restoring a normal angle of take-off.

Translocating the PA away from the aorta and leaving the coronary vessels untouched is an alternative method of treating AAOCA. The idea of the PA translocation, whether anterior or lateral, is to shift the PA away from the aorta and increase the space between the major arteries to lessen the likelihood that the anomalous coronary artery will be compressed as it passes through those vessels [44]. Repairs that rely on extraneous sources of coronary

blood flow, such as coronary artery bypass grafting with saphenous vein grafts or internal mammary artery grafts, are generally not recommended in children and young

Figure 2. Schematic representation of AAORCA anatomy prior to and after surgical correction (unroofing)

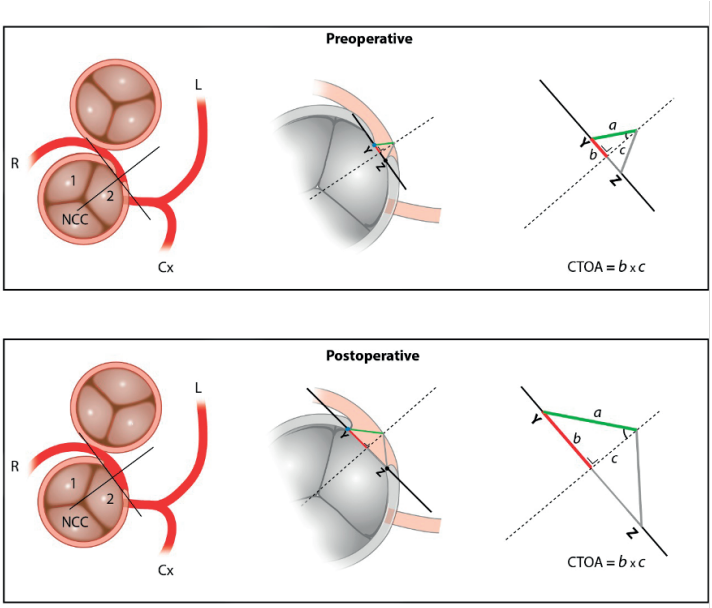


AAORCA, anomalous aortic origin of a right coronary artery; RCA, right coronary artery; LAD, left anterior descending artery; RCx, ramus circumflex artery; R, right coronary cusp; L, left coronary cusp; N, non coronary cusp

adults due to potential long-term graft patency issues, but may be considered in older adults [45]. Patients with AAOCA present with a large range of complaints, from typical to atypical (chest pain, shortness of breath, constricting discomfort in the front of the chest). Limited data is available on follow-up of these operated patients, and how it affected their complaints [27, 28]. All above mentioned techniques are extensively described and depicted in the article of Padalino et al.[46]. In **Chapter 5** the medium term outcomes of patients with

AAOCA are described and related to pre- and postoperative symptoms.

Figure 3. Schematic representation of the of the coronary triangulated orifice area (CTOA) pre- and postoperatively



CTOA = 2 × (½× b × c) = b × c; b = ½ ostial diameter; c = the depth of the triangle measured on CTA. The effective coronary ostial area as measured by the CTOA increases after the surgical correction of the coronary anomaly.

R, right coronary artery; L, left coronary artery; Cx, circumflex coronary artery; NCC, non-coronary cusp; The area of the triangle is formed by 2 equilateral triangles. Y, representing the acute angle the outer edge of the orifice point; Z, representing the end of the ostium of the coronary anomaly; b , the base of the triangle; c, the depth of the triangle

Computed tomography angiography (CTA) is the golden standard in diagnosing AAOCA with high accuracy [47, 48]. It can specifically assess the anomalous coronary artery origin, its course, degree of luminal narrowing, its relationship to surrounding structures and concomitant obstructive coronary artery disease [49]. The full spectrum of application of CTA in the postoperative setting is yet to be explored. In **Chapter 6** we compare the pre- and postoperative CTA features of a series of patients who underwent surgical correction of malignant AAOCA and deduce a new CTA derived parameter, the coronary triangulated orifice area (CTOA) (**Figure 3)**. The origin and course of the anomalous coronary artery and the ostial dimensions were evaluated and correlated with restenosis of the operated

coronary artery during follow-up.

Tetralogy of Fallot

Etienne Fallot described the combination of cardiac abnormalities in tetralogy of Fallot (TOF) in 1888, though Niels Stensen had already described it in 1672. Tetralogy of Fallot is characterized by four cardiac abnormalities, namely 1) (sub)pulmonary stenosis (PS), 2) ventricular septal defect, 3) aortic overriding, and 4) right ventricular hypertrophy. Antero-cephalad deviation of the (muscular) outlet septum of the RV in combination with hypertrophy of the septoparietal trabeculations are the essential features that cause this phenotype. As a result, the muscular orifice leading to the subpulmonary infundibulum becomes narrowed. The severity and extent of right ventricular outflow tract (RVOT) obstruction can differ significantly between patients. The pulmonary valve region, which in the majority of patients has only two leaflets, and the supravalvular region may also be stenotic. Furthermore, at the site of the ductus arteriosus's origin, the branch pulmonary arteries, particularly the left pulmonary artery, may be stenotic. The deviation of the outlet septum also causes a VSD, which is a septal malalignment defect, and aortic overriding. Pressure overload to the RV caused by (sub)pulmonary stenosis causes right ventricular hypertrophy [50-52]. Tetralogy of Fallot accounts for 4% of all congenital heart defects [53]. TOF has been reported to have a birth prevalence of 0.4 per 1.000 liveborn infants, with males and females affected equally [54].

C. Walton Lillehei reported the first total intracardiac repair in 1955 [55]. Total intracardiac repair entails complete VSD closure as well as RVOT obstruction relief. A patch is used to close the VSD, and the RVOT obstruction is relieved by resecting (sub)infundibular muscle bundles and, if necessary, performing pulmonary valvotomy. Furthermore, in many patients, enlargement of the RVOT is required to achieve adequate pulmonary blood flow. Enlargement of the RVOT necessitates the use of a patch, which frequently includes the area of the pulmonary valve annulus (transannular patch). As a result of this procedure, many patients have significant pulmonary regurgitation (PR) after surgery [50-53]. Although pulmonary regurgitation can be tolerated for many years, the right ventricle (RV) compensatory mechanisms will eventually fail, as the incidences of arrhythmias, exercise intolerance, heart failure, and cardiac-related death have been reported to increase with age [55 52, 56 57]. Patients with severe PR and RV dilatation are frequently considered for pulmonary valve replacement (PVR), which is typically performed using a pulmonary homograft. PVR has become more common in TOF patients with severe PR over the last decade, and longer-term follow-up results are now available. However, in asymptomatic patients with severe PR and significant RV dilatation the timing of PVR is still debatable

and should strike a balance between the preservation of RV function and the risk of future surgical or interventional procedures later in life. On the one hand, PVR should not be performed "too soon," because the lifespan of a homograft is limited, which means that patients may require additional interventions later in life [58, 59, 60]. PVR, on the other hand, should not be performed "too late," because irreversible RV dysfunction may have already occurred, and it does not appear to recover completely after PVR [60, 50, 61]. The decisions to perform PVR on individual patients are typically made in multidisciplinary teams and may differ between tertiary referral centers [51]. Recent guidelines state criteria when PVR should be considered in asymptomatic patients with severe PR and/or right ventricular outflow

Table 3

Criteria for pulmonary valve replacement in patients with Tetralogy of Fallot
Decrease in objective exercise capacity
Progressive RV dilation to RVESVi ≥ 80 mL/ m2 , and/or RVEDVi ≥ 160 mL/m2 f, and/or progression of TR to at least moderate
Progressive RV systolic dysfunction.
RVOTO with RVSP >80 mmHg

PVRep = pulmonary valve replacement; RV = right ventricle/ventricular; RVESVi = right ventricular end systolic volume indexed; RVEDVi = right ventricular end diastolic volume indexed; RVOT = right ventricular outflow tract; RVOTO = right ventricular outflow tract obstruction; RVSP = right ventricular systolic pressure

tract obstruction (RVOTO) [25]. Today, there is a large group of patients with a repaired TOF who underwent PVR, and more clinical data are available. In **Chapter 7** the objective was to evaluate the late hemodynamic and clinical outcomes in this patient group.

The main objective of this thesis was to obtain more insight in diagnosis and follow-up of patients with systemic sclerosis, pulmonary embolisms, Tetralogy of Fallot and anomalous aortic origin of the coronary arteries in order to prevent further disease progression and complications, and consequently improve prognosis.

References

1. Guazzi M, Naeije R. Pulmonary hypertension in heart failure: pathophysiology, pathobiology, and emerging clinical perspectives. Journal of the American College of Cardiology. 2017;69(13):1718-34.

2. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). European Heart Journal. 2022;43(38):3618-731.

3. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery J, Barbera J, et al. Task force for diagnosis and treatment of pulmonary hypertension of European Society of Cardiology (ESC); European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT). Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2009;34(6):1219-63.

4. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. European Respiratory Journal. 2019;53(1).

5. D'Alto M, Merola A, Dimopoulos K. Pulmonary hypertension related to congenital heart disease: A comprehensive review. Global Cardiology Science and Practice. 2015;2015(3):42.

6. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest. 2012;142(2):448-56.

7. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Revista espanola de cardiologia (English ed). 2016;69(2):177.

8. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. Journal of the American College of Cardiology. 2001;37(1):183-8.

9. Taniguchi Y, Jaïs X, Jevnikar M, Boucly A, Weatherald J, Brenot P, et al. Predictors of survival in patients with not-operated chronic thromboembolic pulmonary hypertension. The Journal of Heart and Lung Transplantation. 2019;38(8):833-42.

10. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography: endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. Journal of the American society of echocardiography. 2010;23(7):685-713.

11. Frost A, Badesch D, Gibbs JSR, Gopalan D, Khanna D, Manes A, et al. Diagnosis of pulmonary hypertension. European Respiratory Journal. 2019;53(1).

12. Bossone E, Paciocco G, Iarussi D, Agretto A, Iacono A, Gillespie BW, et al. The prognostic role of the ECG in primary pulmonary hypertension. Chest. 2002;121(2):513-8.

13. Henkens IR, Mouchaers KT, Vonk-Noordegraaf A, Boonstra A, Swenne CA, Maan AC, et al. Improved ECG detection of presence and severity of right ventricular pressure load validated with cardiac magnetic resonance imaging. American Journal of Physiology-Heart and Circulatory Physiology. 2008;294(5):H2150-H7.

14. Draisma HH, Schalij MJ, van der Wall EE, Swenne CA. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006;3(9):1092-9.

15. Kamphuis VP, Haeck ML, Wagner GS, Maan AC, Maynard C, Delgado V, et al. Electrocardiographic detection of right ventricular pressure overload in patients with suspected pulmonary hypertension. Journal of electrocardiology. 2014;47(2):175-82.

16. Mathai SC, Hassoun PM. Pulmonary arterial hypertension in connective tissue diseases. Heart failure clinics. 2012;8(3):413-25.

17. Hachulla E, Gressin V, Guillevin L, Carpentier P, Diot E, Sibilia J, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis & Rheumatism. 2005;52(12):3792-800.

18. Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Annals of the rheumatic diseases. 2017:annrheumdis-2017-211448.

19. van Belle A, Buller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. Jama. 2006;295(2):172-9.

20. Douma RA, Mos IC, Erkens PM, Nizet TA, Durian MF, Hovens MM, et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. Ann Intern Med. 2011;154(11):709-18.

21. Mos IC, Douma RA, Erkens PM, Kruip MJ, Hovens MM, van Houten AA, et al. Diagnostic outcome management study in patients with clinically suspected recurrent acute pulmonary embolism with a structured algorithm. Thrombosis research. 2014;133(6):1039-44.

22. Pasha SM, Klok FA, Snoep JD, Mos IC, Goekoop RJ, Rodger MA, et al. Safety of excluding acute pulmonary embolism based on an unlikely clinical probability by the Wells rule and normal D-dimer concentration: a meta-analysis. Thrombosis research. 2010;125(4):e123-7.

23. van der Hulle T, Cheung WY, Kooij S, Beenen LF, van Bemmel T, van Es J, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. 2017;390(10091):289-97.

24. van der Pol LM, Tromeur C, Bistervels IM, Ni Ainle F, van Bemmel T, Bertoletti L, et al. Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. The New England journal of medicine. 2019;380(12):1139-49.

25. Baumgartner H, De Backer J. The ESC Clinical Practice Guidelines for the Management of Adult Congenital Heart Disease 2020. Eur Heart J. 2020;41(43):4153-4.

26. Angelini P, Flamm SD. Newer concepts for imaging anomalous aortic origin of the coronary arteries in adults. Catheterization and Cardiovascular Interventions. 2007;69(7):942-54.

27. Angelini P, Velasco JA, Flamm S. Coronary anomalies incidence, pathophysiology, and clinical relevance. Circulation. 2002;105(20):2449-54.

28. Basso C, Maron BJ, Corrado D, Thiene G. Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes. Journal of the American College of Cardiology. 2000;35(6):1493-501.

29. Angelini P. Coronary Artery Anomalies. An Entity in Search of an Identity. 2007;115(10):1296-305.

30. Eckart RE, Scoville SL, Campbell CL, Shry EA, Stajduhar KC, Potter RN, et al. Sudden death in young adults: a 25-year review of autopsies in military recruits. Annals of Internal Medicine. 2004;141(11):829-34.

31. Bogers A, Gittenberger-de Groot A, Poelmann R, Peault B, Huysmans H. Development of the origin of the coronary arteries, a matter of ingrowth or outgrowth? Anatomy and embryology. 1989;180(5):437-41.

32. Brothers JA, Frommelt MA, Jaquiss RDB, Myerburg RJ, Fraser CD, Jr., Tweddell JS. Expert consensus guidelines: Anomalous aortic origin of a coronary artery. J Thorac Cardiovasc Surg. 2017;153(6):1440-57.

33. Angelini P, Uribe C, Monge J, Tobis JM, Elayda MA, Willerson JT. Origin of the right coronary artery from the opposite sinus of Valsalva in adults: characterization by intravascular ultrasonography at baseline and after stent angioplasty. Catheterization and Cardiovascular Interventions. 2015;86(2):199-208.

34. Cheitlin MD, De Castro CM, MCALLISTER HA. Sudden death as a complication of anomalous left coronary origin from the anterior sinus of Valsalva: a not-so-minor congenital anomaly. Circulation. 1974;50(4):780-7.

35. Pérez-Pomares JM, de la Pompa JL, Franco D, Henderson D, Ho SY, Houyel L, et al. Congenital coronary artery anomalies: a bridge from embryology to anatomy and pathophysiology—a position statement of the development, anatomy, and pathology ESC Working Group. Cardiovascular research. 2016;109(2):204-16.

36. Frescura C, Basso C, Thiene G, Corrado D, Pennelli T, Angelini A, et al. Anomalous origin of coronary arteries and risk of sudden death: a study based on an autopsy population of congenital heart disease. Human pathology. 1998;29(7):689-95.

37. Brothers JA, Frommelt MA, Jaquiss RD, Myerburg RJ, Fraser CD, Tweddell JS. Expert consensus guidelines: anomalous aortic origin of a coronary artery. The Journal of thoracic and cardiovascular surgery. 2017;153(6):1440-57.

38. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al. ACC/AHA 2008 Guidelines for the Management of Adults With Congenital Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease) Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Journal of the American College of Cardiology. 2008;52(23):e143-e263.

39. King N-M, Tian DD, Munkholm-Larsen S, Buttar SN, Chow V, Yan T. The Aberrant Coronary Artery–The Management Approach. Heart, Lung and Circulation. 2017.

40. Cubero A, Crespo A, Hamzeh G, Cortes A, Rivas D, Aramendi JI. Anomalous origin of right coronary

artery from left coronary sinus—13 cases treated with the reimplantation technique. World Journal for Pediatric and Congenital Heart Surgery. 2017;8(3):315-20.

41. Gulati R, Reddy VM, Culbertson C, Helton G, Suleman S, Reinhartz O, et al. Surgical management of coronary artery arising from the wrong coronary sinus, using standard and novel approaches. The Journal of Thoracic and Cardiovascular Surgery. 2007;134(5):1171-8. e5.

42. Mery CM, Lawrence SM, Krishnamurthy R, Sexson-Tejtel SK, Carberry KE, McKenzie ED, et al., editors. Anomalous aortic origin of a coronary artery: toward a standardized approach. Seminars in Thoracic and Cardiovascular Surgery; 2014: Elsevier.

43. Gaudin R, Raisky O, Vouhé PR. Anomalous aortic origin of coronary arteries:'anatomical'surgical repair. Multimedia Manual of Cardiothoracic Surgery: MMCTS. 2014;2014:mmt022-mmt.

44. Rado R, Levi N, Hauser H, Witcher J, Alder N, Intrator N, et al. Seismic signalling as a means of communication in a subterranean mammal. Animal Behaviour. 1987;35(4):1249-51.

45. Feins EN, DeFaria Yeh D, Bhatt AB, Stefanescu A, Youniss MA, Ghoshhajra BB, et al. Anomalous Aortic Origin of a Coronary Artery: Surgical Repair With Anatomic- and Function-Based Follow-Up. The Annals of thoracic surgery. 2016;101(1):169-75; discussion 75-6.

46. Padalino MA, Jegatheeswaran A, Blitzer D, Ricciardi G, Guariento A. Surgery for Anomalous Aortic Origin of Coronary Arteries: Technical Safeguards and Pitfalls. Frontiers in Cardiovascular Medicine. 2021;8:626108.

47. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic Performance of 64-Multidetector Row Coronary Computed Tomographic Angiography for Evaluation of Coronary Artery Stenosis in Individuals Without Known Coronary Artery Disease. Results From the Prospective Multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) Trial. 2008;52(21):1724-32.

48. van Ooijen PM, Dorgelo J, Zijlstra F, Oudkerk M. Detection, visualization and evaluation of anomalous coronary anatomy on 16-slice multidetector-row CT. European radiology. 2004;14(12):2163-71.

49. Dodd JD, Ferencik M, Liberthson RR, Cury RC, Hoffmann U, Brady TJ, et al. Congenital anomalies of coronary artery origin in adults: 64-MDCT appearance. American Journal of Roentgenology. 2007;188(2):W138-W46.

50. Therrien J, Siu SC, McLaughlin PR, Liu PP, Williams WG, Webb GD. Pulmonary valve replacement in adults late after repair of tetralogy of Fallot: are we operating too late? Journal of the American College of Cardiology. 2000;36(5):1670-5.

51. Wald RM, Lyseggen E, Oechslin EN, Webb GD, Silversides CK. Variability in surgical referral patterns for pulmonary valve replacement in adults with repaired tetralogy of Fallot. Congenital heart disease. 2009;4(4):231-8.

52. Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. Journal of the American College of Cardiology. 1997;30(5):1374-83.

53. Knauth Meadows A, Ordovas K, Higgins CB, Reddy GP, editors. Magnetic resonance imaging in the adult with congenital heart disease. Seminars in roentgenology; 2008: WB Saunders.

54. Hoffman JI, Kaplan S. The incidence of congenital heart disease. Journal of the American college of cardiology. 2002;39(12):1890-900.

55. Lillehei CW, Cohen M, Warden HE, Read RC, Aust JB, DeWall RA, et al. Direct vision intracardiac surgical correction of the tetralogy of Fallot, pentalogy of Fallot, and pulmonary atresia defects: report of first ten cases. Annals of surgery. 1955;142(3):418.

56. Murphy JG, Gersh BJ, McGoon MD, Mair DD, Porter C-bJ, Ilstrup DM, et al. Long-term outcome after surgical repair of isolated atrial septal defect: follow-up at 27 to 32 years. New England Journal of Medicine. 1990;323(24):1645-50.

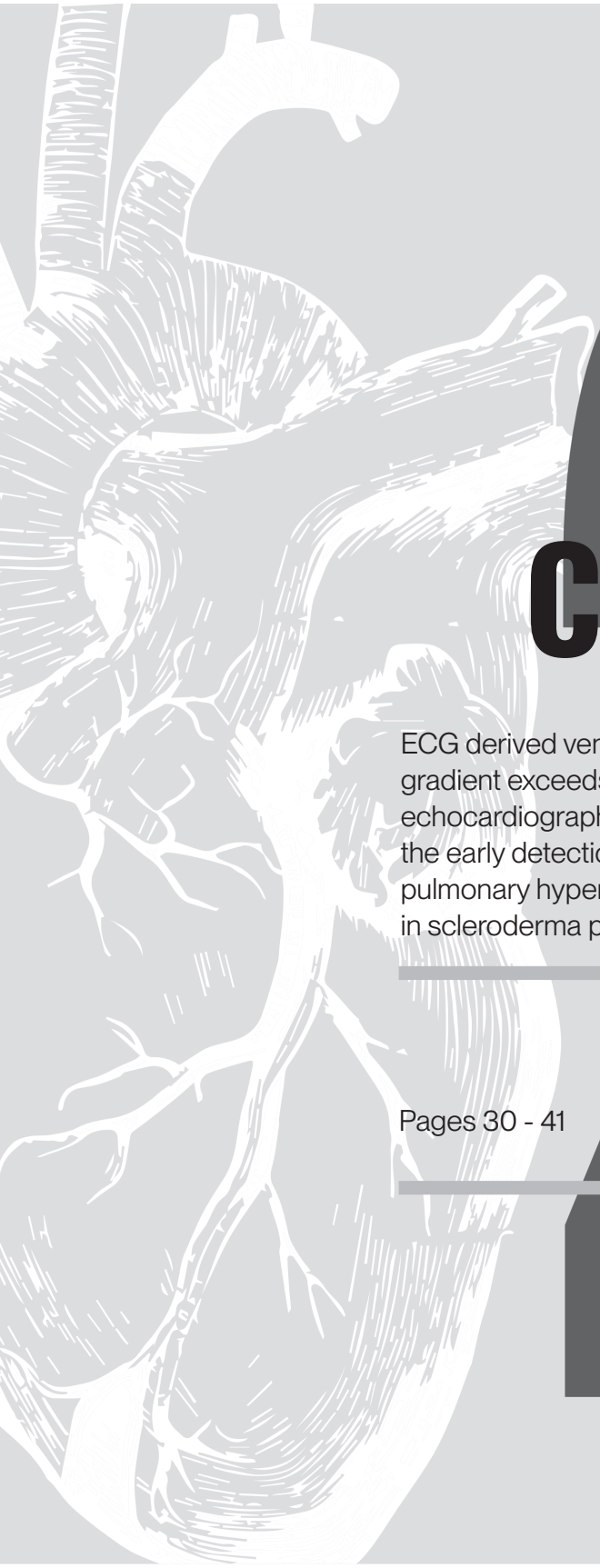
57. Abd El Rahman M, Abdul-Khaliq H, Vogel M, Alexi-Meskishvili V, Gutberlet M, Lange P. Relation between right ventricular enlargement, QRS duration, and right ventricular function in patients with tetralogy of Fallot and pulmonary regurgitation after surgical repair. Heart. 2000;84(4):416-20.

58. Meijboom FJ, Roos-Hesselink JW, McGhie JS, Spitaels SE, van Domburg RT, Utens LM, et al. Consequences of a selective approach toward pulmonary valve replacement in adult patients with tetralogy of Fallot and pulmonary regurgitation. The Journal of Thoracic and Cardiovascular Surgery. 2008;135(1):50-5.

59. Oosterhof T, Meijboom FJ, Vliegen HW, Hazekamp MG, Zwinderman AH, Bouma BJ, et al. Long-term follow-up of homograft function after pulmonary valve replacement in patients with tetralogy of Fallot. European heart journal. 2006;27(12):1478-84.

60. Oosterhof T, van Straten A, Vliegen HW, Meijboom FJ, van Dijk AP, Spijkerboer AM, et al. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation. 2007;116(5):545-51.

61. Frigiola A, Tsang V, Bull C, Coats L, Khambadkone S, Derrick G, et al. Biventricular Response After Pulmonary Valve Replacement for Right Ventricular Outflow Tract Dysfunction Is Age a Predictor of Outcome? Circulation. 2008;118(14 suppl 1):S182-S90.



CHAPTER 2

ECG derived ventricular gradient exceeds echocardiography in the early detection of pulmonary hypertension in scleroderma patients

Pages 30 - 41

ECG DERIVED VENTRICULAR GRADIENT EXCEEDS ECHOCARDIOGRAPHY IN THE EARLY DETECTION OF PULMONARY HYPERTENSION IN SCLERODERMA PATIENTS

F.M.M. Meijer, P. Kiès, M.R.M. Jongbloed, S.E. van Wijngaarden, C.A. Swenne, S. Man, M.J. Schalij, J.K. de Vries-Bouwstra, H.W. Vliegen

International Journal of Cardiology 273 (2018) 203–206

ABSTRACT

Background

Patients with systemic sclerosis (SSc) are at risk for developing pulmonary hypertension (PH) which is a major cause of death in this population. Echocardiographic (TTE) derived pulmonary arterial pressure (PAP) can be unreliable for the early detection of PH. Previous studies demonstrate that the ECG derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO) can detect PH in a heterogeneous population suspected of PH.

The aim of this study is to assess the use of the VG-RVPO as a screening and monitoring instrument of early PH in SSc patients.

Methods

Serial ECGs and TTEs from twenty-seven SSc patients who underwent right heart catheterization (RHC) were retrospectively analyzed. The changes in PAP and VG-RVPO over time were studied in patients with and without diagnosed PH.

Results

Twenty-four patients (52.5% female, mean age 58.4 years SD 14.3) were studied. In eleven patients PH was confirmed with RHC. In these patients VG-RVPO was significantly higher -8 ± 19 than in patients without PH -23 ± 10 mV· ms, ($P<0.05$). In addition, in PH patients the VG-RVPO increased over time in contrast to patients without PH ($P<0.01$). The VG was more sensitive to detect disease progression in earlier stages of disease as compared to

echocardiographic derived PAP.

Conclusions
The VG-RVPO is a sensitive, non-invasive and cost effective tool for early detection of PH in SSc patients. Serial measurements indicate that the VG-RVPO can be used as a follow-up instrument and outperforms TTE to detect early changes in right ventricular pressure over time.

Introduction
Patients with systemic sclerosis (SSc) have a high risk on developing pulmonary arterial hypertension (PAH) which is a major cause of death in this patient group. The high mortality rates can be partly explained by disease-related comorbidities but also by a relatively late diagnosis in routine clinical practice [1]. Recent cohorts studies show that PH develops in 5-15% of the patients and that early intervention with PAH-targeted therapy is beneficial in patients who are mildly symptomatic [2, 3]. Current practice in screening for pulmonary hypertension (PH) in this high risk group mainly relies on symptoms and abnormal findings on transthoracic echocardiography (TTE). In a multicenter study aiming at the development of a screening algorithm in SSc patients (DETECT study), TTE at rest using a sPAP cutoff value of 50 mmHg and dyspnea as a prominent symptom of PH were not sensitive enough to detect early forms of SSc PH [4, 5]. This underlines the need for better screening tools. Progressive PH-related pressure overload of the right ventricle (RV) causes by definition an increase in RV wall tension, and often, but not always, it causes RV hypertrophy and RV dilatation over time [6]. Previous studies show that ECG variables in advanced PH reflect physiologic and anatomic abnormalities in the right ventricle [7]. Thus the ECG may be an important non-invasive, low-cost and easy-to-obtain alternative or extra addition to the other screenings methods. However, the standard 12-lead ECG has only limited value to detect early PAH when conventionally interpreted. Other research demonstrates that the ECG derived ventricular gradient (VG), when projected on the optimal direction for detection of RV pressure overload (VG-RVPO), can detect PH in a heterogeneous population suspected of PH and in patient with SSc [8-10]. It is still unknown whether VG-RVPO can be used as a screening instrument for early PH detection, prediction of future PH, and for monitoring its course over time. In this retrospective study the aim is to assess the value of the ECG-derived VG-RVPO as a follow-up instrument in SSc patients.

Methods
The study population consisted of patients with clinically confirmed SSc who underwent

right heart catheterization (RHC) between February 2009 and February 2017. Patients took (and still take) part in a care track protocol specialized for SSc and were annually evaluated in the outpatient clinic by a rheumatologist, a cardiologist and a pulmonologist [11]. This includes a standard 10-second 12-lead resting ECG, cardio-pulmonary imaging and function tests and clinical evaluation. Patients were included in the study if they had at least 2 consecutive ECGs of good quality and corresponding echocardiograms before and after the RHC. Patients who had prior myocardial infarction were excluded. Annual performance of echocardiography and ECG is part of the care track and performed in all patients. All clinical data were prospectively collected. For the current evaluation selected patients were stratified in 2 groups: patients with and patients without RHC-confirmed PH. Included patients provided written informed consent for use of anonymous clinical data as part of the Biobank Systemic Sclerosis of the department Rheumatology of the LUMC which is approved by the Leiden University Medical Center Institutional Review Board.

ECG measurements

Standard 10-second 12-lead ECGs were recorded in the supine position. The dedicated software program LEADS (online service: www.leadsecg.com) [12] was used to measure all ECG variables used in this study. LEADS determines conventional ECG variables but also vectorcardiographic ECG variables, after mathematically synthesizing a vectorcardiogram (VCG) from the ECG. One important VCG variable is the ventricular gradient (VG). The VG is defined as the 3D integral of the heart vector over the QT interval. The VG thus gives an indication of the action potential morphology distribution in the heart [9], that changes, due to mechanic-electrical feedback, with changes in right-ventricular afterload [10, 13]. Previous research has shown that VG can detect right ventricular pressure overload (and, hence, PH) optimally by taking its projection in the 155° azimuth and 27° elevation direction [10, 14]. In the following, this optimized projection of VG is referred to as VG-RVPO (ventricular gradient – right ventricular pressure overload). Within the VCG coordinate system as it has been standardized by the American Heart Association the projection direction of VG-RVPO points to the right, slightly backward, and slightly downward. In normal hearts, VG-RVPO is usually negative, because VG points more in a leftward direction [15]. With increasing right ventricular pressure, the VG turns more rightward, and VG-RVPO becomes less negative, and, for higher degrees of RV pressure overload, even positive. In addition to VG-RVPO, other parameters including heart rate, QTc duration, QRS duration and the heart axis (QRS axis) in the frontal plane were also used in this study.

Echocardiograms

Images were obtained in the left-lateral decubitus position with a commercially available

system (Vivid 7 or E9; General Electric-Vingmed Ultrasound), using a 3.5-MHz transducer, and digitally stored in cine-loop format; offline analysis was performed using EchoPAC version BT 13 (General Electric-Vingmed). Systolic pulmonary pressure (sPAP) was calculated by summation of tricuspid regurgitant gradient (TR) and atrial pressure [16]. sPAP ≥ 34 mmHg was suspected of having PH. Right atrial pressure was estimated based on the diameter and inspiratory collapse of the inferior vena caval vein IVC [16]. The tricuspid regurgitant jet gradient (TR gradient) was calculated using the modified Bernoulli equation on the 4-chamber view [17].

Included patients had two different primary indications for RHC: risk stratification for hematopoietic stem cell transplantation (HSCT) and screening for pulmonary arterial hypertension, respectively. Patients are excluded for stem cell transplantation if they have pulmonary hypertension. Both groups were discussed in a multidisciplinary team evaluating symptoms and diagnostic test results. Indications for and interpretation of the RHC were done according to the guidelines [18]. Pulmonary arterial hypertension (PAH) (WHO group I) was diagnosed when there was an invasively measured mean pulmonary pressure (mPAP) of 25mmHg, a pulmonary arterial wedge pressure of less than15 mmHg and a pulmonary vascular resistance of more than 3 woods units [18].

Statistical Analysis

All data was analyzed using SPSS version 23 (SPSS, Chicago, IL). Continuous variables are presented as mean ± SD. Categorical variables are reported as numbers and percentages. To compare continuous variables the unpaired Student *t*-test and Mann-Whitney U-test were used for respectively normally or non-normally distributed variables. A total of 24 subjects, obtained as 12 in group one and 12 in group two, were each measured at 11 time points. The study achieves 90% power to detect a difference between the (fixed) group means at the last time of 9.00. The standard deviation is 12.00. The correlation between measurements within a subject is 0.500. A test based on a mixed-model analysis is anticipated at a significance level of 0.150.

Linear mixed models analysis was used to assess the differences in change in VG-RVPO and sPAP over time between the two groups [19]. The time points at which ECGs and echocardiograms were made, and at which PH was diagnosed were incorporated in the model as fixed variables. An unstructured covariance matrix was applied. A *P*-value <0.05 was considered statistically significant.

Results

A total of 24 patients (mean age 58±14 years, 62.5% female) were evaluated. PH on RHC was present in 11(45.8%) patients. All patients with the diagnosis PH were classified in

WHO group 1 (pulmonary arterial hypertension). The clinical characteristics of the study population at the time of RHC, are displayed in **Table 1**. The distribution of SSc subtypes in patients with pulmonary hypertension is the same. Among the 24 patients, 12 patients were also known with interstitial lung disease. Patients with PH on RHC had a significantly higher TR gradient and estimated sPAP on echocardiography. Heart rate, QRS duration, QTc duration and the percentage of patients with a right heart axis were not significantly different between the groups. VG-RVPO was significantly higher, less negative or even positive in the PH group.

Table 1. Clinical Characteristics of the study population at the time instant of RHC VG-RVPO and sPAP over 10 years in pulmonary hypertension versus no pulmonary hypertension

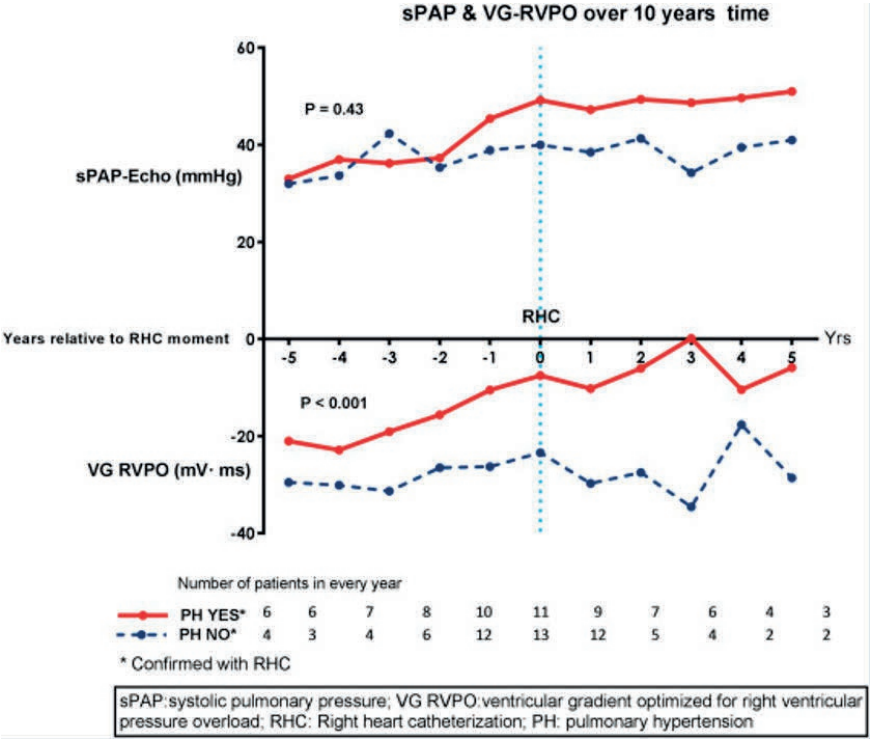
Variable	No Pulmonary Hypertension (N=13)	Pulmonary Hypertension (N=11)	*P*
Age (years)	55.50 ± 16.39	61.88 ± 11.20	0.29
Females (%)	8 (61.5)	7 (63.6)	0.92
Diffuse SSc (%)	9 (69.2)	6(54.5)	0.48
Limited SSc (%)	4 (30.8)	5 (45.5)	0.48
ILD present (%)	5 (38.8)	7 (63.6)	0.23
Echocardiography			
TR Gradient (mmHg)	25.92 ± 7.68	45.45 ± 18.12	**<0.01**
Estimated sPAP (mmHg)	32.31 ± 7.76	49.36 ± 17.37	**0.01**
LV Dysfunction present (%)	0 (0)	1 (9.1)	0.34
ECG			
Heart rate (bpm)	76.11 ± 16.55	81.48 ± 15.08	0.42
QRS duration (ms)	99.85 ± 19.33	100.73 ± 29.03	0.93
QTc duration (ms)	511.10 ± 60.25	477.50 ± 75.14	0.25
Right heart axis (º)	11.66 ± 72.164	21.9 ± 61.3	0.71
VG-RVPO (mV· ms)	-23.02 ± 10.78	-7.94 ± 18.72	**0.02**
RHC			
mPAP (mmHg)	16.85 ± 2.94	28.90 ± 4.70	**<0.01**

TR, maximum tricuspid regurgitant jet; sPAP, systolic pulmonary arterial pressure; VG-RVPO, ventricular gradient – right ventricular pressure overload. RHC, right heart catheterization. ILD; interstitial lung disease; LV dysfunction: Left ventricular ejection fraction < 40%. Data are described as numbers with frequency or mean with SD.

Figure 1 shows the VG-RVPO and sPAP over 10 years' time. The echocardiographic sPAP over time is depicted in the upper panel of fig. 1. In the initial phases of the disease (before

the RHC) the sPAP on echo of both groups did not differ significantly (95% CI -17.6 to 0, *P* = 0.43]. Also after the RHC no significant difference between the PH group and the no PH group were found. The lower panel of the figure contains the VG-RVPO, a more positive VG is associated with higher pulmonary pressures. Overall, the VG-RVPO was significantly higher in patients with PH compared to patients without PH (mean difference -17.3 Mv· ms (95% CI -25.6 to -9.1 Mv· ms, *P*<0.001). Looking closely to the first five years of the disease, that is the years before the RHC, it is noticeable that there is already a significantly higher VG-RVPO in the patients with PH compared to the patients without PH (mean difference -15.0 95% CI -24.0 to -6.2, *P*=0.002).

Figure. 1. sPAP & VG-RVPO over 10 year time



sPAP:systolic pulmonary pressure; VG RVPO:ventricular gradient optimized for right ventricular pressure overload; RHC: Right heart catheterization; PH: pulmonary hypertension

Discussion

The main finding in this study is that in patients with systemic sclerosis the vector ECG derived ventricular gradient optimized for right ventricular pressure overload, can play an important role in the monitoring and detection of PH especially in the early phases of the disease.

Current guidelines suggest that early detection and diagnosis of RV dysfunction may help to identify patients with systemic sclerosis who have subclinical PH and might benefit from early treatment [20-23]. Doppler echocardiography is a widely recognized and available tool for monitoring and screening for pulmonary hypertension in various patient groups [24, 25]. However the experience of the echocardiographer is crucial and assessment of the RV is complicated [26, 27]. The tricuspid gradient may be underestimated if the signal is weak or the regurgitant jet is not fully aligned. This is often the case in early and mild pulmonary hypertension and therefore can be an explanation for the lack of detecting elevated pressures by TTE in our study.

The standard 12 lead electrocardiogram is the most common used non-invasive diagnostic measurement in cardiology. It provides information about frequency, rhythm and conduction disorders. In addition, hypertrophy and fibrosis of both the atria and ventricles can be noticed by changes in depolarization and repolarization. The disadvantage of the standard 12 lead ECG is that it has only a limited value in the early detection of right ventricular overload [28]. One of the reasons is that the conventional ECG criteria are based on detection of right ventricular hypertrophy and this is a late phenomenon of increased pressure overload [29]. In addition, changes in the right ventricle are overshadowed by the much larger left ventricle. Therefore the routine 12-lead ECG is useful for diagnosing left ventricular pathology. A sufficient degree of right ventricular hypertrophy is necessary before the conventional ECG (and QRS) criteria are met, whereas in the early stages of PH the right ventricular wall tension is increased while hypertrophy has not developed yet [30, 31]. There are more ECG-variables to detect increased right ventricular pressure [8, 31, 14, 32-34]. These variables can easily be calculated from a digitally stored 12-lead ECG after transforming them into a VCG. The VCG analysis programs, like our LEADS program, that is available as an online service, can calculate the VG as used in our study. Actually, the VG is a measurement that includes the entire QRST complex. When right-ventricular pressure increases, there is an immediate T-wave change that reflects right-ventricular strain, and this change becomes evident in the ventricular gradient. Previous research has shown that the magnitude and direction of this ventricular gradient when projected in the optimal direction to detect RV overload is a specific marker for the presence and the severity of right ventricular overload. Couperus et al. already stated that also in patients with systemic sclerosis the ventricular gradient optimized for right ventricular pressure overload is significantly elevated when they have pulmonary hypertension [14]. The current study confirms this once more and also makes a distinction in the early phase of the disease between patients who develop PH and who not.

All patients in this study were classified in WHO group 1 (pulmonary arterial hypertension), however pulmonary fibrosis is also a leading cause of death in SSc patients [35, 36]. In our cohort 12 patient presented with interstitial lung disease. There is little literature available on ECG changes in interstitial lung disease. The right side of the heart attempts to deal with the progressive loss of vascular bed, as a result it hypertrophies [37]. Impaired gas exchange in ILD leads to important desaturation and vital organs such as the heart have a decreased oxygen delivery [38]. It is imaginable that those changes influence the ECG (and VG-RVPO). In future research the impact of interstitial lung disease on the electrocardiogram must be taken into account.

Conclusion

The VG-RVPO is a sensitive, non-invasive and cost effective tool for early detection of pulmonary hypertension in SSc patients. Moreover serial measurements indicate that the VG-RVPO can be used as a follow-up instrument and outperforms TTE to detect early changes in right ventricular pressure over time.

Limitations

Due to the retrospective nature of this study, not every ECG or echocardiogram was available at every timepoint. We only have data on a small number of patients; due to low prevalence of the disease and the strict requirements for performing an RHC. Despite these small numbers there still is a significant result which underlines the relevance and additional value of the VCG.

References

1. Mathai SC, Hassoun PM. Pulmonary arterial hypertension in connective tissue diseases. Heart failure clinics. 2012;8(3):413-25.

2. Hachulla E, Gressin V, Guillevin L, Carpentier P, Diot E, Sibilia J, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis & Rheumatism. 2005;52(12):3792-800.

3. Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Annals of the rheumatic diseases. 2017:annrheumdis-2017-211448.

4. Mukerjee D, George DS, Knight C, Davar J, Wells A, Du Bois R, et al. Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis. Rheumatology. 2004;43(4):461-6.

5. Coghlan JG, Denton CP, Grünig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Annals of the rheumatic diseases. 2014;73(7):1340-9.

6. Chemla D, Castelain V, Herve P, Lecarpentier Y, Brimioulle S. Haemodynamic evaluation of pulmonary hypertension. European Respiratory Journal. 2002;20(5):1314-31.

7. Bossone E, Paciocco G, Iarussi D, Agretto A, Iacono A, Gillespie BW, et al. The prognostic role of the ECG in primary pulmonary hypertension. CHEST Journal. 2002;121(2):513-8.

8. Henkens IR, Mouchaers KT, Vonk-Noordegraaf A, Boonstra A, Swenne CA, Maan AC, et al. Improved ECG detection of presence and severity of right ventricular pressure load validated with cardiac magnetic resonance imaging. American Journal of Physiology-Heart and Circulatory Physiology. 2008;294(5):H2150-H7.

9. Draisma HH, Schalij MJ, van der Wall EE, Swenne CA. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006;3(9):1092-9.

10. Kamphuis VP, Haeck ML, Wagner GS, Maan AC, Maynard C, Delgado V, et al. Electrocardiographic detection of right ventricular pressure overload in patients with suspected pulmonary hypertension. Journal of electrocardiology. 2014;47(2):175-82.

11. Meijs J, Schouffoer AA, Marsan NA, Kroft LJ, Stijnen T, Ninaber MK, et al. Therapeutic and diagnostic outcomes of a standardised, comprehensive care pathway for patients with systemic sclerosis. RMD open. 2016;2(1):e000159.

12. Draisma H, Swenne C, Van de Vooren H, Maan A, van Huysduynen BH, Van der Wall E, et al., editors. LEADS: an interactive research oriented ECG/VCG analysis system. Computers in Cardiology, 2005; 2005: IEEE.

13. Greve G, Chen R, Barron D, White PA, Redington AN, Penny DJ. Right ventricular distension alters monophasic action potential duration during pulmonary arterial occlusion in anaesthetised lambs: evidence for arrhythmogenic right ventricular mechanoelectrical feedback. Experimental physiology. 2001;86(5):651-7.

14. Couperus L, Vliegen H, Henkens I, Maan A, Treskes R, de Vries J, et al. Electrocardiographic detection of pulmonary hypertension in patients with systemic sclerosis using the ventricular gradient. Journal of

electrocardiology. 2016;49(1):60-8.

15. Kossmann CE, Brody DA, Burch GE, Hecht HH, Johnston FD, Kay C, et al. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Circulation. 1967;35(3):583-602.

16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification. European journal of echocardiography. 2006;7(2):79-108.

17. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. Journal of the American Society of Echocardiography. 2010;23(7):685-713.

18. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). European heart journal. 2015;37(1):67-119.

19. Verbeke G. Linear mixed models for longitudinal data. Linear mixed models in practice: Springer; 1997. p. 63-153.

20. Humbert M, Yaici A, de Groote P, Montani D, Sitbon O, Launay D, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: Clinical characteristics at diagnosis and long- term survival. Arthritis & Rheumatism. 2011;63(11):3522-30.

21. Humbert M, Sitbon O, Yaici A, Montani D, O'callaghan D, Jaïs X, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. European Respiratory Journal. 2010;36(3):549-55.

22. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JSR, Vrapi F, et al. Connective tissue disease–associated pulmonary arterial hypertension in the modern treatment era. American Journal of Respiratory and Critical Care Medicine. 2009;179(2):151-7.

23. Dimopoulos K, Inuzuka R, Goletto S, Giannakoulas G, Swan L, Wort SJ, et al. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation. 2010;121(1):20-5.

24. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension. Circulation. 2009;119(16):2250-94.

25. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126(1):14S-34S.

26. Greil GF, Beerbaum P, Razavi R, Miller O. Imaging the right ventricle. Heart. 2008;94(6):803-8.

27. Borgeson DD, Seward JB, Miller Jr FA, Oh JK, Tajik AJ. Frequency of Doppler measurable pulmonary artery pressures. Journal of the American Society of Echocardiography. 1996;9(6):832-7.

28. Ahearn GS, Tapson VF, Rebeiz A, Greenfield JC. Electrocardiography to define clinical status in primary pulmonary hypertension and pulmonary arterial hypertension secondary to collagen vascular disease.

Chest. 2002;122(2):524-7.

29. Helm RA. Electrocardiographic cancellation: mathematical basis. American heart journal. 1960;60(2):251-65.

30. Harrigan RA, Jones K. Conditions affecting the right side of the heart.(ABC of Clinical Electrocardiography). British Medical Journal. 2002;324(7347):1201-5.

31. Henkens IR, Mouchaers KT, Vliegen HW, van der Laarse WJ, Swenne CA, Maan AC, et al. Early changes in rat hearts with developing pulmonary arterial hypertension can be detected with three-dimensional electrocardiography. American Journal of Physiology-Heart and Circulatory Physiology. 2007;293(2):H1300-H7.

32. KAWAGUCHI Y. Studies on deflection area vectors of QRS and T and ventricular gradient in right ventricular hypertrophy. Japanese circulation journal. 1985;49(4):395-405.

33. Cowdery CD, Wagner GS, Starr JW, Rogers G, Greenfield JC. New vectorcardiographic criteria for diagnosing right ventricular hypertrophy in mitral stenosis: comparison with electrocardiographic criteria. Circulation. 1980;62(5):1026-32.

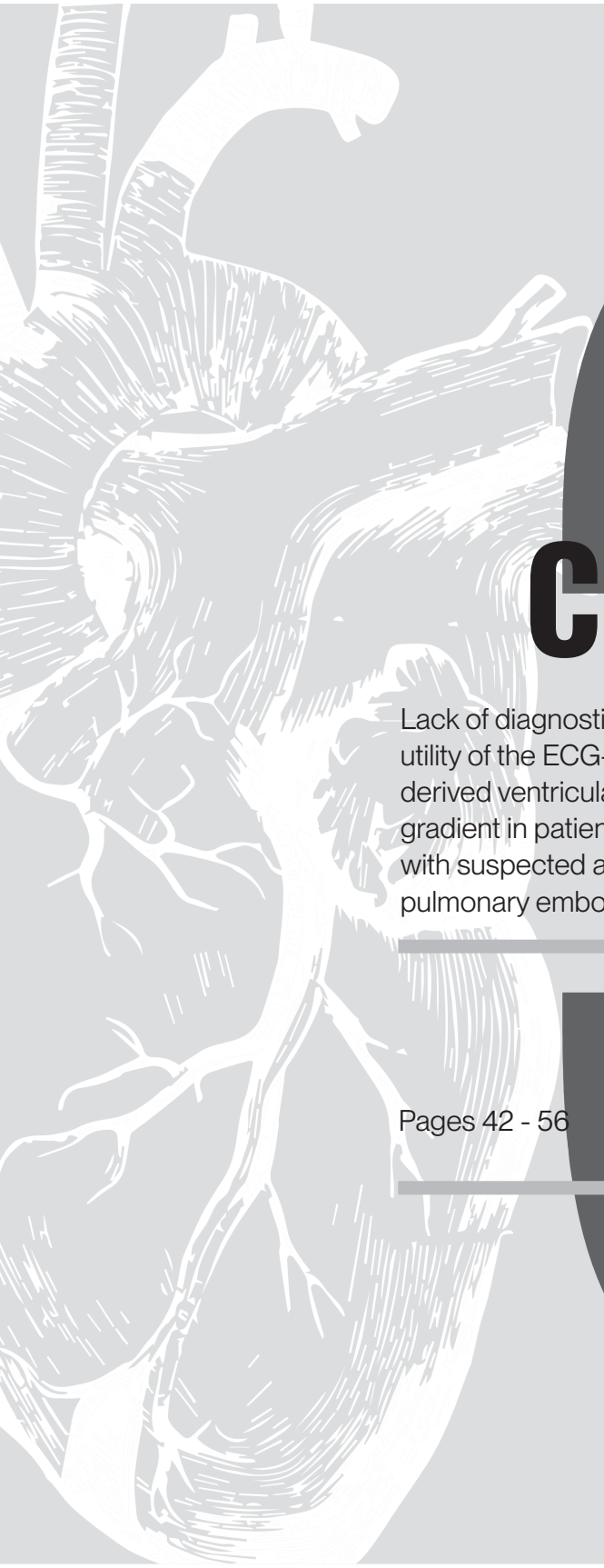
34. Scherptong RW, Henkens IR, Kapel GF, Swenne CA, van Kralingen KW, Huisman MV, et al. Diagnosis and mortality prediction in pulmonary hypertension: the value of the electrocardiogram-derived ventricular gradient. Journal of electrocardiology. 2012;45(3):312-8.

35. Bodolay E, Szekanecz Z, Dévényi K, Galuska L, Csípo I, Vègh J, et al. Evaluation of interstitial lung disease in mixed connective tissue disease (MCTD). Rheumatology. 2005;44(5):656-61.

36. Prakash UB. Respiratory complications in mixed connective tissue disease. Clinics in chest medicine. 1998;19(4):733-46.

37. Crystal RG, Gadek JE, Ferrans VJ, Fulmer JD, Line BR, Hunninghake GW. Interstitial lung disease: current concepts of pathogenesis, staging and therapy. The American journal of medicine. 1981;70(3):542-68.

38. Lama VN, Martinez FJ. Resting and exercise physiology in interstitial lung diseases. Clinics in Chest Medicine. 2004;25(3):435-53.



CHAPTER 3

Lack of diagnostic utility of the ECG-derived ventricular gradient in patients with suspected acute pulmonary embolism

Pages 42 - 56

LACK OF DIAGNOSTIC UTILITY OF THE ECG-DERIVED VENTRICULAR GRADIENT IN PATIENTS WITH SUSPECTED ACUTE PULMONARY EMBOLISM

F.M.M. Meijer, S.V. Hendriks, M.V. Huisman, T. van der Hulle, C.A. Swenne, P. Kiès, M.R.M. Jongbloed, A.D. Egorova, H.W. Vliegen, F.A. Klok

Journal of Electrocardiology 61 (2020) 141–146

ABSTRACT

Background

The YEARS algorithm was successfully developed to reduce the number of computed tomography pulmonary angiography (CTPA) investigations in the diagnostic management of patients with suspected pulmonary embolism (PE), although half of patients still needed to be referred for CTPA. We hypothesized that ECG derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO), an easy to use tool for detecting PE-induced pulmonary hypertension (PH), may further improve the efficiency of the YEARS algorithm.

Methods

In this post-hoc analysis of the Years study, ECGs of 479 patients with suspected PE managed according to the YEARS algorithm were available for analysis. The diagnostic performance of VG-RVPO was assessed and likelihood ratios were calculated.

Results

PE was diagnosed in 88 patients (18%). In patients with confirmed PE, 34% had an abnormal VG-RVPO versus 24% of those without PE (odds ratio 1.6; 95%CI 0.94–2.6). The mean VG-RVPO was -22 ± 13 and did not differ between the two patient groups (-22 versus -20; mean difference -2, 95% CI -4.8 to 1.3). The sensitivity of VG-RVPO for PE was 24% (95%CI 34-45), the specificity 76% (95%CI 71-80) and the c-statistic 0.45 (95% CI 0.38-0.51). When combined with the YEARS algorithm, the likelihood ratios of VG-RVPO

remained close to 1.0. Ruling out PE in patients with an indication for CTPA based on a normal VG-RVPO would have resulted in 58 missed cases.

Conclusions
The VG-RVPO has no diagnostic value for suspected acute PE, either as stand-alone diagnostic test or combined with the YEARS algorithm.

Introduction
The objective of diagnostic algorithms for suspected acute pulmonary embolism (PE) is the fast and efficient identification of patients that benefit from early initiation of anticoagulation, avoiding expensive and potentially harmful imaging tests where possible [1, 2]. Conventional algorithms apply a clinical decision rule and D-dimer tests sequentially to identify approximately one third of all patients in whom PE can be ruled out without imaging, using a fixed D-dimer threshold [3-6]. The YEARS algorithm combines assessment of pre-test probability and D-dimer level in parallel, and applies a pre-test probability dependent D-dimer threshold [7, 8]. This algorithm safely excludes PE in half of the patients without performing computed tomography pulmonary angiography (CTPA). However, even with this contemporary diagnostic approach, only one in roughly three CTPA scans was diagnostic of PE, demonstrating an opportunity for improving the specificity of this algorithm [7]. Recent attempts to improve the specificity of the YEARS algorithm by combinations with chest X-ray or other decision rules did not yield a relevant improvement and/or resulted in an unacceptable number of missed diagnoses [9-11]. The combination of YEARS with electrocardiogram (ECG) reading has not been investigated yet.

It has been long recognized that the diagnostic accuracy of 12-lead ECG reading for acute PE is moderate at best [12, 13]. This is mainly due to the fact that there are different etiologies that can underly the pulmonary pressure elevation observed in patients with acute PE. Left ventricular heart disease and advanced interstitial lung disease are other possible clinical features that may affect pulmonary artery pressure [14]. The vector cardiogram (VCG) is a diagnostic tool in which the ECG-derived ventricular gradient is used to detect patients with increased pulmonary pressure, a prevalent condition in patients with acute PE [2]. Previous studies have shown that the ECG-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO) can detect patients with pulmonary arterial hypertension (PH), with a sensitivity of 62% and specificity of 86% [15-18]. It may be hypothesized that VG-RVPO is a more accurate diagnostic tool for the diagnosis of PE than 'standard' manual ECG reading, and hence, may improve the specificity of the YEARS algorithm.

We therefore set out to measure VG-RVPO in patients with suspected PE managed according to the YEARS algorithm to determine the diagnostic value of VG-RVPO for PE as well as the added diagnostic value of VG-RVPO to the YEARS algorithm.

Methods

Patients and study design

This was a post-hoc analysis of the prospective YEARS study, that included consecutive patients with clinically suspected acute PE between October 2013 and July 2015 [7]. The study design, inclusion and exclusion criteria, outcome measures and baseline population characteristics of the YEARS study have been presented in the original report of the study [7]. Briefly, the attending physician evaluated whether a clinical suspicion of PE was present and if so, the YEARS algorithm was applied (Figure 2). The three criteria from the YEARS algorithm were assessed in all with simultaneous assessment of the D-dimer concentration. According to the algorithm, PE was excluded in patients without YEARS items and D-dimer less than 1000 ng/mL, or in patients with one or more YEARS items and D-dimer less than 500 ng/mL. All other patients were referred for CTPA. Patients in whom PE was ruled out were left untreated and were followed-up for 3 months. Main outcomes of the YEARS study were the number of missed diagnosis and the proportion of patients managed without CTPA.

The current analysis is restricted to patients who were included in our hospital. ECG's were recorded as part of clinical assessment in most of the patients. Patients in whom an ECG could not be retrieved were excluded. Other exclusion criteria were the presence of atrial fibrillation, a pacemaker rhythm, prior myocardial infarction, established severe cardiomyopathy, as these conditions can influence the electrical activity of the ECG. Finally, ECGs that were considered non-interpretable, i.e. with a disrupted electrical signal causing the baselines to shift, were excluded as well. In total 99 (17%) of the originally 578 ECGs that were available were excluded for those reasons. Due to the various aetiologies that can lead to pulmonary pressure elevation, alternative diagnoses were analysed including pulmonary infection (including pneumonia and exacerbation of COPD), decompensated heart failure, acute coronary syndrome, interstitial lung disease, and pulmonary malignancy.

Study objectives

The aim of this study was to investigate the diagnostic accuracy of VG-RVPO for PE in a population of consecutive patients with suspected PE managed according to the YEARS algorithm. Furthermore we aimed to determine the potential incremental diagnostic value of the VG-RVPO to the YEARS algorithm, i.e. whether the posttest probability of PE after an abnormal VG-RVPO would allow for changing the decision to perform CTPA as indicated

by YEARS. Lastly, we evaluated alternative diagnoses than acute PE in patients with abnormal VG-RVPO.
The primary outcome was 1) the mean difference of the VG-RVPO between patients with confirmed PE compared to those in whom the diagnosis PE was rejected and 2) the odds ratio for an abnormal VG-RVPO in patients with PE compared to those without PE and the sensitivity and specificity of VG-RVPO for acute PE.

ECG measurements

Standard 10-second 12-lead ECGs were recorded in the supine position (25mm/second). The first ECG collected within 24 hours after clinical presentation was retrieved from the patient's medical records and analysed. The dedicated software program LEADS (online service: www.leadsecg.com) was used to measure all ECG variables used in this study [19]. The analysis was performed by an independent investigator that was blinded to the patient's identities and clinical course. LEADS not only determines conventional ECG variables (heart rate, heart axis, mean corrected QT interval and QRS duration), which are shown in the results section, but also extracts vector-cardio graphic ECG variables, after mathematically synthesizing a VCG from the ECG. The most relevant VCG variable in the setting of the current study is the ventricular gradient (VG). The VG is defined as the 3D integral of the heart vector over the QT interval. The VG thus gives an indication of the action potential morphology distribution in the heart [16]. With increasing right ventricular pressures this action potential morphology changes, due to mechano-electrical feedback [17, 20]. Previous research has shown that VG can detect right ventricular pressure overload (and, hence, PH) optimally by taking its projection in the 155° azimuth and 27° elevation direction [17, 18, 21]. The projection direction of VG-RVPO points to the right, slightly backward, and slightly downward. In the following, this optimized projection of VG is referred to as VG-RVPO. In normal hearts, VG-RVPO is usually negative, because the VG points more in a leftward direction [22]. With increasing right ventricular pressure, the VG turns more rightward, and VG-RVPO becomes less negative, and, for higher degrees of RV pressure overload, can become even positive. In summary, the more positive the value of the VG-RVPO, the higher and more longstanding the right ventricular pressure overload (Figure 1).

Study definitions

Acute PE was defined as an intraluminal filling defect of the subsegmental or more proximal pulmonary arteries confirmed by CTPA. Recurrent PE during follow-up was defined as a new intraluminal filling defect on CTPA or confirmation of a new PE at autopsy [23]. For the purpose of establishing the diagnostic accuracy of VG-RVPO for PE, patients were considered to have acute PE if the diagnosis was confirmed either at baseline or during

Figure. 1. Change in cardiac vectors from the normal physiologic situation to respectively early stage and chronic PH. Abbreviations: PAH, pulmonary arterial hypertension.

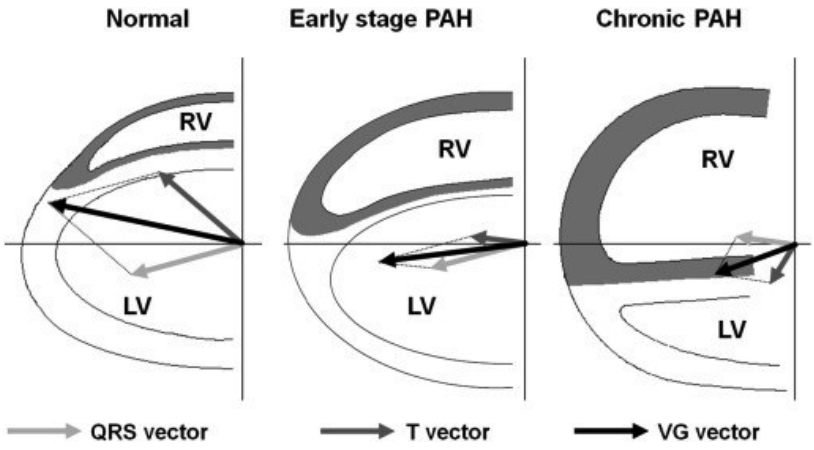
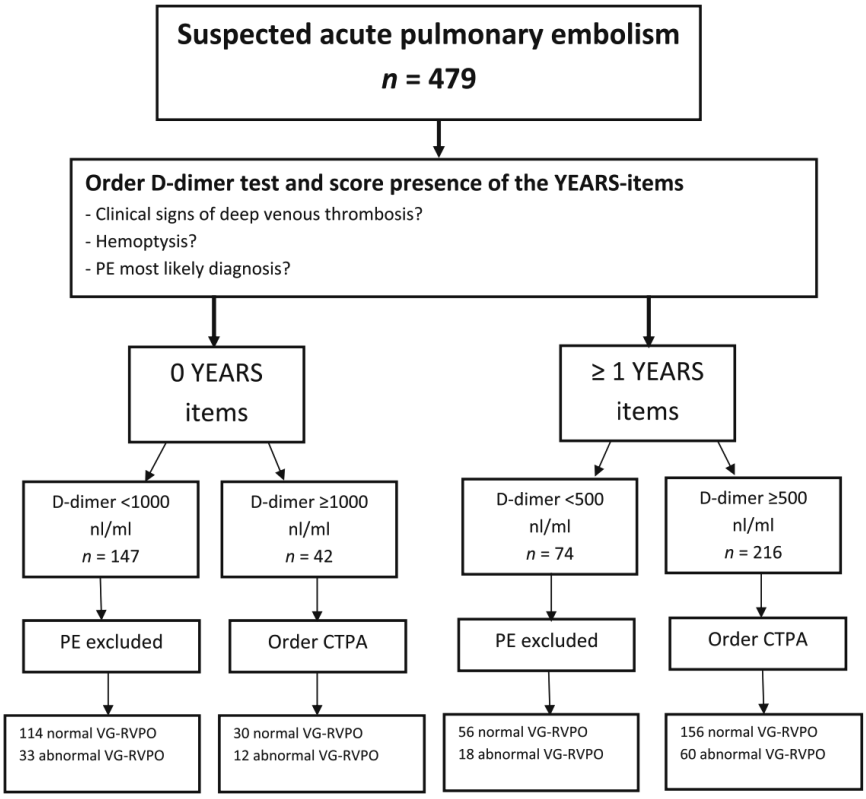


Figure. 2. Study flowchart according to the YEARS Algorithm with additional VG-RVPO analysis.



3-month follow-up. The cut-off value for a normal value of the VG-RVPO was set at -13 mV · ms, with < -13 mV ms being considered normal (PE unlikely) and ≥ -13 mV· ms as abnormal (PE likely). This cut-off value is based on previous research in which the normal value of the ventricular gradient has been published [18, 21, 24-26].

Statistical analysis

Normality of the data was analysed using Kolmogorov-Smirnov test. The results are presented as the mean ± standard deviation (SD) for continuous variables with a normal distribution, as the median (interquartile range) for continuous variables with a non-normal distribution, and as numbers (percentage) for categorical variables. The Mann-Whitney U-test and independent sample t-test were used for comparison of the continuous variables. Measures of OR and of diagnostic performance parameters, e.g. sensitivity and specificity, are reported as point estimates with corresponding 95% confidence intervals (95% CI). Also the area under the curve was estimated with C-statistic. To determine the incremental diagnostic value of VG-RVPO, positive and negative LRs were calculated. From the LRs the posttest probability of an abnormal and a normal VG-RVPO was determined. The pretest probability was dependent on the PE prevalence, which was calculated for the complete cohort as well as for selected patients who were referred for CTPA according to the YEARS algorithm. The LRs indicate by how much the VG-RVPO will change the pretest probability of PE and the indication for CTPA. A LR close to 1 indicates negligible incremental value. Statistical analysis was performed using SPSS version 22.0 (IBM, Chicago, Illinois).

Results

Study Population

Of the 783 YEARS study patients included in our hospital, 578 had an ECG recorded (72%). After exclusion of patients with atrial fibrillation (n=3), pacemaker rhythm (n=4), prior myocardial infarction (n=42), established cardiomyopathy (n=7), complex congenital heart disease (n=5) and non-interpretable ECGs (n=38), 479 patients were included for analysis. Baseline characteristics of the study population are presented in Table 1: their mean age was 51 ±17 years, 287 (60%) were women and 59 (12%) had prior VTE. Details of the diagnostic management of the patients are shown in Figure 2. PE was confirmed by CTPA at baseline in 88 patients (18%), and 2 were diagnosed with VTE during follow-up (0.42%).

ECG Analysis

The results of the ECG analysis are presented in Table 2. During ECG acquisition, the

mean heart rate was 82 ± 17 beats per minute (bpm). The heart rate was higher in patients

Table 1. Baseline characteristics of patients suspected with pulmonary embolism in the Years cohort with ECG availability

	Total Population (n = 479)
Age (years), mean ± SD	51 ± 17
Women, n (%)	287 (60)
Duration of complaints (days), median (IQR)	9
Heart failure with treatment, n (%)	10 (1.8)
Estrogen use, n (%) (% of women)	44 (15.4)
COPD, n (%)	31 (6.5)
Malignancy, n (%)	61 (13.0)
Immobilization or surgery in the past 4 weeks, n (%)	75 (16.0)
Previous VTE, n (%)	59 (12.3)

SD, standard deviation; n, number of patients; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; VTE, venous thromboembolism

Table 2. ECG parameters in the study patients

ECG parameters	All patients (n=479)	No PE (n=391)	PE (n=88)	Mean Difference (95 % CI)
Heart rate (bpm), mean ± SD	82 ± 17	81 ± 17	87 ± 17	-5.2 (-9.3 to -1.2)
QTc duration (ms), mean ± SD	493 ± 81	489 ± 78	515 ± 87	-26 (-46 to -6.2)
QRS duration (ms), mean ± SD	97 ± 17	96 ± 14	100 ± 26	- 3.5 (-7.3 to 0.4)
VG-RVPO (mV · ms), mean ± SD	-22 ± 13	-22 ± 13	-20 ± 14	- 2.0 (-4.8 to 1.3)

ECG, electrocardiogram; PE, pulmonary embolism; bpm, beats per minute; SD, standard deviation; ms, milliseconds; VG-RVPO, ventricular gradient optimized for right ventricular pressure overload

with confirmed PE (87 ± 17 bpm) compared to patients with PE ruled out (81 ± 17 bpm), for an absolute mean difference of 5 bpm (95%CI -9.3 to -1.2). Mean corrected QT interval (QTc) was 493 ms, and also differed between patients with and without PE (absolute mean difference -26, 95%CI -45.9 to -6.2). QRS duration was not significantly different between the patients with and without PE diagnosis.

Primary outcome

The mean VG-RVPO was -22 ± 13 and did not differ between the two patient groups (-22 versus -20; mean difference -2, 95%CI -4.8 to 1.3. For those with confirmed PE (n=88), 34% had an abnormal VG-RVPO versus 24% of those without PE (OR 1.6; 95%CI 0.94–2.6). The sensitivity of VG-RVPO for acute PE was 36% (95% CI 30-43), the specificity was 74% (95% CI 72-76) and the C-statistic was 0.45 (95% CI 0.38-0.51), all indicating insufficient diagnostic accuracy.

Secondary endpoint

Overall, the VG-RVPO was normal in 186 patients (72%) and abnormal in 72 patients (28%) with an indication for CTPA. In the patients were a CTPA was not indicated, 170 patients

Table 3. Distribution of patients in different groups according to the VG-RVPO

ECG results	All Patients (n = 479)	No PE (n = 391)	PE (n = 88)	CTPA indicated (n = 258)	CTPA not indicated (n = 221)
VG-RVPO normal, n (%)	356 (74)	297 (76)	58 (66)	186 (72)	170 (77)
VG-RVPO abnormal, n (%)	123 (26)	94 (24)	30 (34)	72 (28)	51 (23)

ECG, electrocardiogram; n, number of patients; PE, pulmonary embolism; CTPA, computed tomography pulmonary angiography; VG-RVPO, ventricular gradient optimized for right ventricular pressure overload

(77%) had a normal VG-RVPO and 51 patients (23%) an abnormal VG-RVPO (Table 3). Table 4 presents the LR with confidence intervals for the VG-RVPO: all approximated the 1.0, indicating little to no incremental value of VG-RVPO to the YEARS algorithm. If PE would have been considered ruled out in patients with a normal VG-RVPO despite an indication for CTPA according to the YEARS algorithm, 186 CTPA scans would have been additionally saved (38%) at cost of 58 missed cases of PE (65% of all PE cases, failure

Table 4. likelihood ratios and VG-RVPO results in combination with the YEARS algorithm

	All Patients (n= 479)		**Patients in whom CTPA was indicated according to the YEARS algorithm (n=294)**	
Results ECG	Positive LR (95% CI)	Negative L (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
VG-RVPO normal	1.42 (1.01-1.99)	0.87 (0.74-1.02)	1.21 (0.89-1.65)	0.94 (0.84-1.04)

ECG, electrocardiogram; n, number of patients; CTPA, computed tomography pulmonary angiography; LR, likelihood ratio; CI confidence intervals; VG-RVPO, ventricular gradient optimized for right ventricular pressure overload.

Table 5. Alternative diagnosis in patients with abnormal VG-RVPO and pulmonary embolism ruled out

Alternative explanation (n = 94)	**Number of patients n (%)**
Pulmonary infection	6 (6.4)
Acute coronary syndrome	19 (20.1)
Decompensated heart failure	13 (13.8)
Interstitial lung disease	10 (10.6)
Pulmonary malignancy	11 (12)
History of PE	3 (3.2)
Pulmonary Hypertension on echocardiography	2 (2.1)
Obstructive sleep apnea	4 (4.3)
Other: - History of aortic valve replacement - ICD in situ - patent foramen ovale - no alternative explanation	26 (27.6) 1 (1.1) 1 (1.1) 1 (1.1) 23 (24.4)

N, number of patients; SLE, systemic lupus erythematosus; PE, pulmonary embolism

rate 19%, 95%CI 0.15-0.24). If PE would have been considered present in patients with an indication for CTPA according to years and with an abnormal VG-RVPO, 72 CTPA scans would have been avoided but 51 cases (11%) would have been false positive.

The alternative diagnoses in patients with abnormal VG-RVPO but without PE are shown in Table 5: the most frequent alternative explanation was acute coronary syndrome (20%). Previous research stated that the vector and thus VG can change due to ischemia [27, 28]. Other common diagnoses were interstitial lung disease (11%), decompensated heart failure (14%) and lung cancer (12%).

Discussion

In this post hoc analysis of the YEARS study, the diagnostic value of VG-RVPO for PE as stand-alone diagnostic test as well as combined with the YEARS algorithm was very limited. If the VG-RVPO would have been used to rule out acute PE, the failure rate of the algorithm would have been unacceptably high.

Several different ECG abnormalities have been associated with PE. The most frequently mentioned abnormalities are: sinus tachycardia, right bundle branch block, T-wave inversion in leads V1 through V4, S wave in lead I, Q wave in lead III, inverted T in lead III, and S1Q3T3 complex [29, 30]. Notably, many of the described changes are transient and highly prevalent in patients with suspected acute PE. These ECG findings therefore lack sufficient sensitivity and specificity to be of useful diagnostic value [31]. Because of this, ECG findings play no role in the current recommended diagnostic work-up of suspected PE [29, 32]. Their value mainly lies in excluding other causes of dyspnea or chest pain in the initial patient assessment. The QT time was significantly different between the two groups in our study. In both groups the QT interval was also longer compared to the general population. The QT interval is reported to be prolonged in the acute phase of PE, especially in high risk patients due to increased pulmonary pressure, sympathetic nervous system overactivity and myocardial ischemia related to hemodynamic alterations associated with PE [33, 34]. The QT time in general is an important prognostic factor in patients with- and without cardiac diseases [33, 34]. In the patients without PE other factors may be present that prolong the QT interval. Furthermore the end of the T wave is detected at the intersection of the steepest tangent to the descending leg of the T wave with the baseline. Strictly direct comparison of measured QT time with other QT times is therefore not possible [19].

This is the first study investigating the diagnostic value of VG-RVPO in patients with suspected PE. The VG-RVPO specifically measures right ventricular pressure overload,

can be easily made, is inexpensive and immediately available [17]. Moreover, the diagnostic value of ECG-derived VG-RVPO have already been proven in patients with suspected PH. Former studies showed accurate estimation of the mean PAP in patients screened for PH and evaluated with right heart catheterization with the use of ECG-derived VG-RVPO, which also can be used to distinguish between normal RV pressure load, mildly to moderately increased RV pressure load, and severely increased chronic RV pressure load [15,17,18].

Our hypothesis that VG-RVPO would yield a higher specificity than sensitivity was confirmed, However, we found no incremental diagnostic value of the VG-RVPO as stand-alone diagnostic test or combined with the YEARS algorithm for acute PE. The main explanation for this finding is the poor sensitivity of the VG-RVPO, for the detection of PE, which is to be expected, because not all PEs lead to RV pressure overload. For instance, in low risk patients with PE, defined by a sPESI score of 0, acute ventricular overload (RV/LV diameter ratios > 1.0) has been described to only be present in 38% of all patients [35]. The PA pressure increases only if more than 30–50% of the total cross-sectional area of the pulmonary arterial bed is occluded by thromboembolic disease, which explains the normal aspect of the RV in the majority of patients with PE [36,37]. Hence, even despite its accuracy to detect PH, VG-RVPO likely only detects patients with sufficient thromboembolic burden to raise PA pressure. Furthermore 28% of the patients in this cohort with PE excluded had an alternative diagnosis associated with higher PA pressures and therefore abnormal VG-RVPO, e.g. left heart disease, chronic lung disease and hypoxia, resulting in lower specificity. Thus, the incremental diagnostic value of the VG-RVPO for diagnosing PE is limited. Even so, the role of VG-RVPO recorded on admission could potentially be valuable in the risk stratification of PE during hospitalization, although this remains to be studied.

Strong points of our study are the novelty of our data, the prospective design of the YEARS study and the completeness of its follow-up. Furthermore, all endpoints were adjudicated by independent experts. The main limitations are its post-hoc design causing non-availability of ECGs in 205 (28%) study patients, with an additional 38 (4.9%) patients with non-interpretable ECGs. This may have resulted in selection bias. Unfortunately, echocardiography in patients suspected of PE is not routine practice in our hospital. Because of this, no data on pulmonary artery pressure is available. The relatively long duration since symptoms started (9 days), may also have affected our outcomes.
In conclusion, this post-hoc analysis of the YEARS study failed to demonstrate incremental diagnostic value of VG-RVPO for acute PE, either as stand-alone diagnostic test or combined with the YEARS algorithm.

References

1. Huisman MV, Klok FA. How I diagnose acute pulmonary embolism. Blood. 2013;121(22):4443-8.

2. Huisman MV, Barco S, Cannegieter SC, Le Gal G, Konstantinides SV, Reitsma PH, et al. Pulmonary embolism. Nature reviews Disease primers. 2018;4:18028.

3. van Belle A, Buller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. Jama. 2006;295(2):172-9.

4. Douma RA, Mos IC, Erkens PM, Nizet TA, Durian MF, Hovens MM, et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. Ann Intern Med. 2011;154(11):709-18.

5. Mos IC, Douma RA, Erkens PM, Kruip MJ, Hovens MM, van Houten AA, et al. Diagnostic outcome management study in patients with clinically suspected recurrent acute pulmonary embolism with a structured algorithm. Thrombosis research. 2014;133(6):1039-44.

6. Pasha SM, Klok FA, Snoep JD, Mos IC, Goekoop RJ, Rodger MA, et al. Safety of excluding acute pulmonary embolism based on an unlikely clinical probability by the Wells rule and normal D-dimer concentration: a meta-analysis. Thrombosis research. 2010;125(4):e123-7.

7. van der Hulle T, Cheung WY, Kooij S, Beenen LFM, van Bemmel T, van Es J, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet. 2017;390(10091):289-97.

8. van der Pol LM, Tromeur C, Bistervels IM, Ni Ainle F, van Bemmel T, Bertoletti L, et al. Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. The New England journal of medicine. 2019;380(12):1139-49.

9. van der Pol LM, van der Hulle T, Cheung YW, Mairuhu ATA, Schaar CG, Faber LM, et al. No added value of the age-adjusted D-dimer cut-off to the YEARS algorithm in patients with suspected pulmonary embolism. Journal of thrombosis and haemostasis : JTH. 2017;15(12):2317-24.

10. van der Pol LM, van der Hulle T, Mairuhu ATA, Huisman MV, Klok FA. Combination of Pulmonary Embolism Rule-out Criteria and YEARS Algorithm in a European Cohort of Patients with Suspected Pulmonary Embolism. Thrombosis and haemostasis. 2018;118(3):547-52.

11. van der Pol LM, Tromeur C, Faber LM, van der Hulle T, Kroft LJM, Mairuhu ATA, et al. Chest X-Ray Not Routinely Indicated Prior to the YEARS Algorithm in the Diagnostic Management of Suspected Pulmonary Embolism. TH Open. 2019;03(01):e22-e7.

12. Rodger M, Makropoulos D, Turek M, Quevillon J, Raymond F, Rasuli P, et al. Diagnostic value of the electrocardiogram in suspected pulmonary embolism. Am J Cardiol. 2000;86(7):807-9, a10.

13. Stein PD, Dalen JE, McIntyre KM, Sasahara AA, Wenger NK, Willis PW. The electrocardiogram in acute pulmonary embolism. Progress in cardiovascular diseases. 1975;17(4):247-57.

14. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. 2013;62(25 Supplement):D34-D41.

15. Henkens IR, Mouchaers KT, Vonk-Noordegraaf A, Boonstra A, Swenne CA, Maan AC, et al. Improved ECG detection of presence and severity of right ventricular pressure load validated with cardiac magnetic resonance imaging. American Journal of Physiology-Heart and Circulatory Physiology. 2008;294(5):H2150-H7.

16. Draisma HH, Schalij MJ, van der Wall EE, Swenne CA. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006;3(9):1092-9.

17. Kamphuis VP, Haeck ML, Wagner GS, Maan AC, Maynard C, Delgado V, et al. Electrocardiographic detection of right ventricular pressure overload in patients with suspected pulmonary hypertension. Journal of electrocardiology. 2014;47(2):175-82.

18. Meijer FMM, Kies P, Jongbloed MRM, van Wijngaarden SE, Swenne CA, Man S, et al. ECG derived ventricular gradient exceeds echocardiography in the early detection of pulmonary hypertension in scleroderma patients. International Journal of Cardiology. 2018;273:203-6.

19. Draisma H, Swenne C, Van de Vooren H, Maan A, van Huysduynen BH, Van der Wall E, et al., editors. LEADS: an interactive research oriented ECG/VCG analysis system. Computers in Cardiology, 2005; 2005: IEEE.

20. Greve G, Chen R, Barron D, White PA, Redington AN, Penny DJ. Right ventricular distension alters monophasic action potential duration during pulmonary arterial occlusion in anaesthetised lambs: evidence for arrhythmogenic right ventricular mechanoelectrical feedback. Experimental physiology. 2001;86(5):651-7.

21. Couperus L, Vliegen H, Henkens I, Maan A, Treskes R, de Vries J, et al. Electrocardiographic detection of pulmonary hypertension in patients with systemic sclerosis using the ventricular gradient. Journal of electrocardiology. 2016;49(1):60-8.

22. Kossmann CE, Brody DA, Burch GE, Hecht HH, Johnston FD, Kay C, et al. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Circulation. 1967;35(3):583-602.

23. Huisman MV, Klok FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. Journal of thrombosis and haemostasis : JTH. 2013;11(3):412-22.

24. Draper HW, Peffer CJ, STALLMANN FW, Littmann D, PIPBERGER HVJC. The corrected orthogonal electrocardiogram and vectorcardiogram in 510 normal men (Frank lead system). 1964;30(6):853-64.

25. PIPBERGER HV, GOLDMAN MJ, Littmann D, MURPHY GP, Cosma J, SNYDER JRJC. Correlations of the orthogonal electrocardiogram and vectorcardiogram with constitutional variables in 518 normal men. 1967;35(3):536-51.

26. Scherptong RW, Henkens IR, Man SC, Le Cessie S, Vliegen HW, Draisma HH, et al. Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. 2008;41(6):648-55.

27. ter Haar CC, Maan AC, Schalij MJ, Swenne CAJJoe. Directionality and proportionality of the ST and ventricular gradient difference vectors during acute ischemia. 2014;47(4):500-4.

28. ter Haar CC, Maan AC, Warren SG, Ringborn M, Horáček BM, Schalij MJ, et al. Difference vectors to describe dynamics of the ST segment and the ventricular gradient in acute ischemia. 2013;46(4):302-11.

29. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2019.

30. Qaddoura A, Digby GC, Kabali C, Kukla P, Zhan ZQ, Baranchuk AM. The value of electrocardiography in prognosticating clinical deterioration and mortality in acute pulmonary embolism: A systematic review and meta-analysis. Clinical cardiology. 2017;40(10):814-24.

31. Sreeram N, Cheriex EC, Smeets JL, Gorgels AP, Wellens HJ. Value of the 12-lead electrocardiogram at hospital admission in the diagnosis of pulmonary embolism. Am J Cardiol. 1994;73(4):298-303.

32. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315-52.

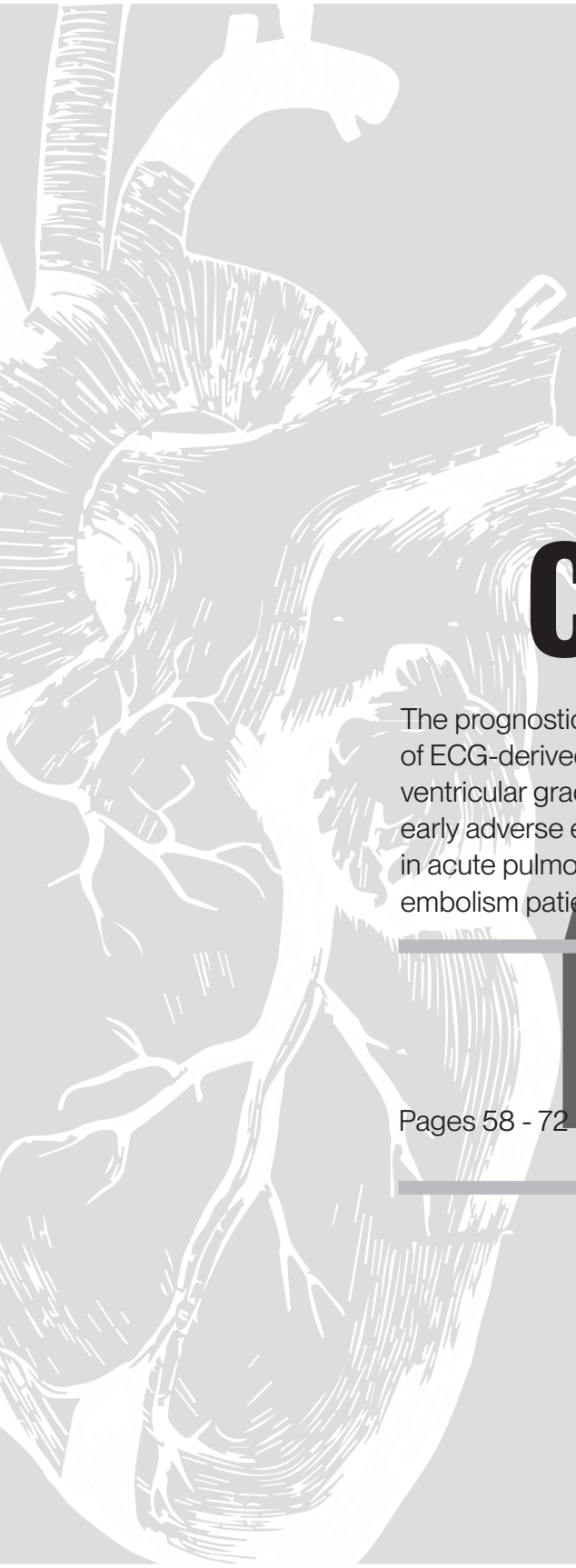
33. Lui CYJJoe. Acute pulmonary embolism as the cause of global T wave inversion and QT prolongation: a case report. 1993;26(1):91-5.

34. Ermıs N, Ermıs H, Sen N, Kepez A, Cuglan BJWkW. QT dispersion in patients with pulmonary embolism. 2010;122(23-24):691-7.

35. Cote B, Jimenez D, Planquette B, Roche A, Marey J, Pastre J, et al. Prognostic value of right ventricular dilatation in patients with low-risk pulmonary embolism. The European respiratory journal. 2017;50(6).

36. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. European heart journal. 2014;35(43):3033-69, 69a-69k.

37. McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol. 1971;28(3):288-94.



CHAPTER 4

The prognostic value of ECG-derived ventricular gradient in early adverse events in acute pulmonary embolism patients

Pages 58 - 72

THE PROGNOSTIC VALUE OF ECG-DERIVED VENTRICULAR GRADIENT IN EARLY ADVERSE EVENTS IN ACUTE PULMONARY EMBOLISM PATIENTS

F.M.M. Meijer, S.V. Hendriks, M.V. Huisman, C.A. Swenne, P. Kiès, M.R.M. Jongbloed, A.D. Egorova, H.W. Vliegen, F.A. Klok

Thrombosis Update 2 (2021): 100033

ABSTRACT

Background

Risk-stratification in pulmonary embolism (PE) includes clinical decision rules, biomarkers and signs of right ventricular (RV) overload. The vector electrocardiogram is a diagnostic tool in which the ECG-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO) can be used to detect patients with increased pulmonary pressure. The primary aim of this study was to assess the association of VG-RVPO and CT-assessed RV/LV diameter ratio as well as the prognostic value of an abnormal VG-RVPO for early adverse events in PE patients.

Methods

In this single-center retrospective study, adult patients with acute PE were identified via the hospital's administrative system. Adverse events were defined as the combined outcome of 30-day overall mortality, recurrent venous thromboembolism, the need for mechanical ventilation, the need for inotropic or vasopressive therapy and/or cardiac resuscitation.

Results

VG-RVPO analysis was available for 164 patients diagnosed with PE between December 2015 and September 2018. Abnormal VG-RVPO was associated with a CTPA-assessed RV/LV diameter ratio >1.0 (OR 2.0; 95%CI 1.0-3.9). The adverse 30-day composite outcome occurred in 16 of 66 patients (24%) with abnormal VG-RVPO compared to 22 of 98 patients (22%) with normal VG-RVPO (OR 1.1, 95%CI 0.53-2.3). The net reclassification

improvement of VG-RVPO on top of RV dilatation for predicting early adverse events was -12%, indicating no additional prognostic value of VG-RVPO on top of RV/LV diameter ratio.

Conclusions
Although we observed an association between RV dilatation, abnormal ECG-derived VG-RVPO was not associated with acute PE associated adverse events.

Introduction
Current treatment guidelines for acute pulmonary embolism (PE) emphasize the importance of proper and simple risk stratification to assess PE severity and guide towards therapeutic decision-making, an improvement of care that has been linked to lower PE-related mortality [1-4]. Current frequently used methods for risk-stratification include clinical decision rules, cardiac biomarkers and radiological findings of right ventricular (RV) overload assessed by echocardiography or computed tomography pulmonary angiography (CTPA).

Electrocardiographic (ECG) parameters may be useful for risk stratification too. The association of specific electrocardiographic changes indicative of RV strain and poor outcome has already been shown in current literature [5]. ECG abnormalities such as T wave inversion in leads V1-V4, a QR pattern in V1, an S1Q3T3 pattern, and incomplete or complete right bundle branch block are associated with increased risk of circulatory shock and mortality in patients with confirmed PE [6].

The vector electrocardiogram (VCG) is an easy to use, cheap and immediately available diagnostic tool in which the ECG-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO) is used to detect patients with increased pulmonary hypertension (PH), a prevalent condition in patients with acute PE [1,7]. The diagnostic value of ECG-derived VG-RVPO has been proven in a heterogeneous group with suspected PH but is limited in the setting of suspected acute PE [7-10]. PH causes pressure overload of the RV with an increase in heart rate and the magnitude and direction of the ventricular de-and repolarization forces change. This is due to increased wall stress and hypertrophy [7-9]. It may, therefore be hypothesized that VG-RVPO is an accurate diagnostic tool for estimating the presence and severity of acute right ventricular pressure overload, and can be used for risk stratification of patients with PE.

We set out to measure VG-RVPO in patients with acute PE to determine the prognostic

value of an abnormal VG-RVPO for occurrence of early adverse events.

Methods

Design

In this retrospective cohort follow-up study, patients diagnosed with acute PE between December 2015 and December 2018 in a Dutch academic medical center (Leiden University Medical Center, Leiden, the Netherlands), were identified via the hospital's administrative system. Patients were eligible for inclusion if they were 18 years or older and had established acute symptomatic or incidental PE involving subsegmental or more proximal pulmonary arteries confirmed by computed tomography pulmonary angiography (CTPA) [11]. ECGs were recorded at first day of admission as part of routine clinical assessment in most of the patients. Patients in whom an ECG could not be retrieved were excluded from the current analysis. Furthermore, as some conditions can influence the electrical activity of the ECG and may give a false-positive or negative outcome, the presence of these conditions led to exclusion: atrial fibrillation, a pacemaker rhythm, prior myocardial infarction, established severe cardiomyopathy and complex congenital heart disease. Finally, non-interpretable ECGs were excluded as well. The need for informed consent was waived by the institutional medical-ethical board review of the Leiden University Medical Center due to the retrospective study design.

Study objectives

The primary aim of this study was to assess the prognostic value of an abnormal VG-RVPO, defined as abnormal with a cut-off value off ≥ -13 mV· ms as derived from previous studies, for early adverse events and clinical deterioration in all patients with acute PE, and specifically for normotensive PE patients.7-9 The secondary aims of this study were 1) to assess the optimal cut-off value of VG-RVPO for predicting early adverse events, 2) to assess the correlation between VG-RVPO values and RV/LV diameter ratio measurements on CTPA and to 3) investigate the added prognostic value of an abnormal VG-RVPO on top of right ventricular dilatation on CTPA for the occurrence of early adverse events in all normotensive PE patients.

ECG measurements

The first ECG's within 24 hours after the clinical presentation were obtained from the patient's medical records and analyzed. To measure all ECG variables in this study, we used the dedicated software program LEADS (online service: www.leadsecg.com) [12]. An independent investigator performed all analyses, blinded to the patient's characteristics and outcome. Vector-cardio graphic ECG variables were extracted by LEADS, after

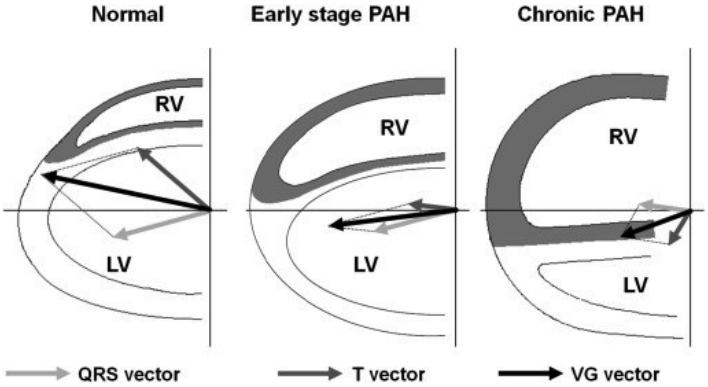
mathematically and automatically synthesizing a vector-cardiogram (VCG) from the ECG. For this study, the ventricular gradient (VG) is the most relevant variable. The VG is defined as the 3D integral of the heart vector over the QT interval. The VG thus indicates the de- and repolarization, i.e. the action potential morphology distribution in the heart [13]. The projection in the 155° azimuth and 27° elevation direction is the most optimal for detecting right ventricular pressure overload because this is the projection directed over the RV. This projection is derived from previous research [7-9]. This optimized projection of VG is referred to as VG-RVPO (ventricular gradient – optimized for right ventricular pressure overload). Normally, the VG-RVPO is negative, with the VG pointing in a leftward direction.14 Increasing right ventricular pressure, the VG turns toward the right, with the VG-RVPO becoming less negative or even positive. In summary, the more positive the value of the VG-RVPO, the higher and more longstanding the right ventricular pressure overload (Figure 1).

Study definitions

The definition of acute PE was an intraluminal filling defect of the subsegmental or more proximal pulmonary arteries confirmed by CTPA [15]. Recurrent VTE was defined as a new intraluminal filling defect on CTPA or confirmation of a new PE at autopsy [16]. The cut-off value for a normal value of the VG-RVPO was set at -13 mV · ms, with < -13 mV ms being considered normal and ≥ -13 mV· ms as abnormal. This cut-off value is based on previous research in which the normal value of the ventricular gradient has been published [8,9,17-19].

Early adverse events were defined as the combined outcome of 30-day overall mortality, recurrent VTE, the need for mechanical ventilation on the intensive care unit (ICU), the need for inotropic or vasopressive treatment and/or cardiac resuscitation. Right ventricular dilatation was defined as an RV/LV diameter ratio greater than 1.0 with ventricular diameters

Figure 1. Change in cardiac vectors from the normal physiologic situation to respectively early stage and chronic PH. Reprinted from with permission 8



PAH, pulmonary arterial hypertension; RV, right ventricle; LV, left ventricle; VG, ventricular gradient

measured in the transverse plane at the widest points between the inner surface of the free wall and the surface of the interventricular septum [20,21].

Statistical analysis

The results are presented as the mean ± standard deviation (SD) for continuous variables with a normal distribution, as the median (interquartile range) for continuous variables with a non-normal distribution, and as numbers (percentage) for categorical variables.

Crude odds ratios (OR) were provided to describe differences with regard to the primary outcomes with corresponding 95% confidence intervals (95%CI). For the secondary outcomes, the area under the curve was estimated with C-statistic and used as a quantitative measure of test performance for the different cut-off values. We calculated net reclassification improvement (NRI) to determine whether the addition of VG-RVPO values to RV/LV ratio measurements improved discrimination. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

Results

Study patients

Between December 2015 and September 2018, 180 patients were diagnosed with acute PE by CTPA in our hospital, of whom 16 were excluded due to non-interpretable ECGs or comorbidity influencing the electrical signal of the ECG. Table 1 summarizes the baseline characteristics of the study patients. Their mean age was 64 years (SD 15), 45% was female and 26% had active malignancy at the time of diagnosis. Renal insufficiency (creatinine clearance < 50 ml/min) was present in 14 patients (10%). Ischemic heart disease was present in 22 patients (13%), and heart failure and COPD in 14 (8.5%) and 19 (12%) patients, respectively. Patients with abnormal VG-RVPO were older than those with a normal VG-RVPO with a mean difference of 6.7 years (95CI% -11 to -2.1). Furthermore, heart failure (OR 6.6; 95% 1.8-25) was more prevalent in those with abnormal VG-RVPO. All patients were treated with anticoagulation therapy.

Table 1. Baseline characteristics of patients with PE selected by VG-RVPO

Demographics	Abnormal VG-RVPO N=66	Normal VG-RVPO N=98	Total population N=164
Age, mean (SD)	67.9 (11.7)	61.2 (15.8)	63.8 (14.7)
Female sex, no (%)	32 (48.5)	42 (42.9)	74 (45.1)
Weight in kg, mean (SD)	85.9 (19.2)	81.6 (16.4)	83.3 (17.6)
Body Mass Index, mean (SD)	30.3 (6.1)	26.2 (4.3)	27.9 (5.5)
Creatinine clearance — no. (%)			
<30 ml/min	1 (1.5)	4 (4.2)	5 (3.0)
30-50 ml/min	5 (7.6)	6 (6.1)	11 (6.7)
50-80 ml/min	33 (50.0)	27 (27.6)	60 (36.6)
>80 ml/min	24 (36.4)	59 (60.2)	83 (50.6)
Missing	3 (4.5)	2 (2.0)	5 (3.0)
VTE risk factors			
Previous venous thromboembolism — no. (%)	17 (25.8)	19 (19.4)	36 (22.0)
COPD — no. (%)	11 (16.7)	8 (8.2)	19 (11.6)
Heart failure — no. (%)	11 (16.7)	3 (3.1%)	14 (8.5)
Ischemic heart disease — no. (%)	11 (16.7)	11 (11.2)	22 (13.4)
Estrogen use — no. (%)			8 (4.9)
Immobilisation — no. (%)	12 (18.2)	32 (32.7)	44 (26.8)
Recent surgery — no. (%)	8 (12.1)	21 (21.4)	29 (17.7)
Active malignancy no. — no. (%)	14 (21.2)	29 (29.6)	43 (26.2)
Recurrent or metastatic cancer — no. (%)			23 (14.0)
VTE presentation			
Signs of RV dilatation, RV / LV ratio > 1.0	39 (59.1)	47 (48.0)	86 (52.4)
Extent of qualifying PE no. (%)			
Subsegmental	4 (6.1)	19 (19.4)	23 (14)
Segmental	25 (37.9)	30 (30.6)	55 (33.5)
Central	31 (47)	45 (46.9)	77 (47.0)

Could not be assessed	3 (4.5)	1 (1.0)	4 (2.4)
Days of admission	11 (14.3)	12.6 (11.1)	11.9 (12.5)
Treatment			
LMWH	20 (30.3)	25 (26.5)	45 (27.4)
LMWH/VKA	20 (30.3)	25 (25.5)	45 (27.4)
DOAC	18 (27.3)	40 (40.8)	58 (35.4)
LMWH/DOAC	8 (12.1)	7 (7.1)	15 (9.1)
Thrombolysis	3 (4.5)	2 (2.0)	5 (3)

PE, pulmonary embolism; VG-RVPO, ECG derived ventricular gradient optimized for right ventricular pressure overload; SD, standard deviation; VTE, venous thromboembolism; COPD, Chronic obstructive pulmonary disease; RV, right ventricle; LV, left ventricle; VKA, vitamin K antagonists; DOAC, direct anticoagulants.

Primary outcome

A total of 18 patients died during the 30-day follow up (11%). One patient was diagnosed with recurrent VTE and ICU admissions were needed in 25 (15%) patients. Of the latter, ten patients were admitted because of the need for inotropic treatment, 14 required mechanical ventilation and seven needed ICU care after cardiac resuscitation. For the

Table 2. Outcomes of study patients stratified according to VG-RVPO

	Abnormal VG-RVPO N=66	Normal VG-RVPO N=98	OR	95% CI
Total 30-day adverse outcome	16	22	1.1	(0.53 – 2.3)
- overall mortality	8	10	1.3	(0.49 – 3.5)
- ICU admission	11	14	1.3	(0.53 – 3.0)
-recurrent VTE	0	1	-	-
-PE-related Mortality	4	5	1.3	(0.34 – 5.1)

VG-RVPO, ECG derived ventricular gradient optimized for right ventricular pressure overload; CI, confidence interval; ICU, intensive care unit; VTE, venous thromboembolism; PE, pulmonary embolism;

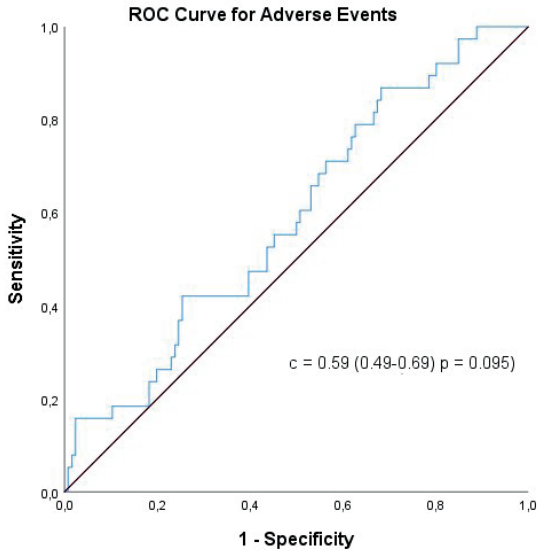
complete cohort, the incidence of the primary outcome was 24% (16 of 66 patients) in those with an abnormal VG-RVPO compared to 22% (22 of 98 patients) with a normal VG-RVPO, for an OR of 1.1 (95%CI 0.53 - 2.3; Table 2). For normotensive PE patients, the incidence of the primary outcome was 15% (7 of 48 patients) for those with an abnormal VG-RVPO compared to 15% (13 of 85 patients) with a normal VG-RVPO, for an OR of 0.95 (95%CI 0.35-2.6).

Secondary outcomes

The overall predictive accuracy of VG-RVPO for early adverse events was moderate with an AUC of 0.59 (0.49-0.69) (Figure 2). The AUC of the predefined threshold of -13 mV · ms showed 42% sensitivity and 60% specificity, resulting in an AUC of 0.51. We were unable to identify a threshold with a relevantly higher AUC.

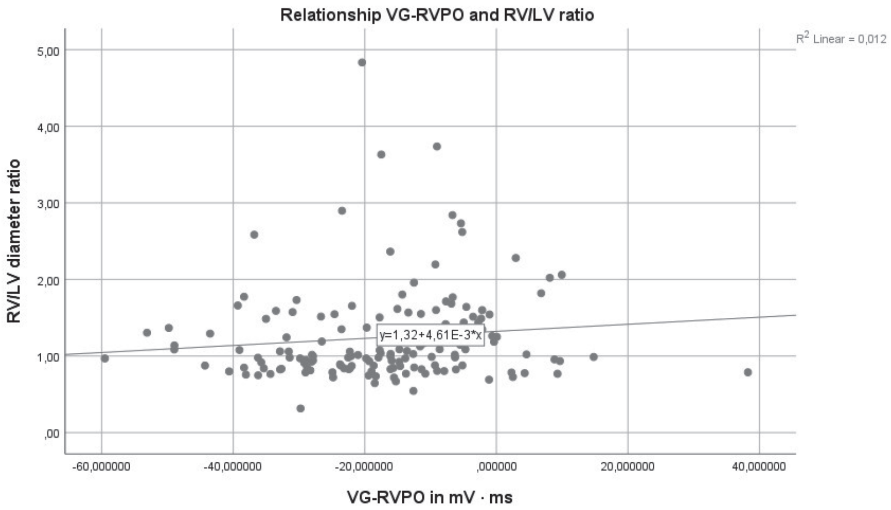
As expected, we found a correlation between VG-RVPO and CTPA-assessed RV/LV diameter ratio. More positive VG-RVPO was associated with higher RV/LV diameter ratio (Pearson correlation value of 0.11, Figure 3) and an RV/LV diameter ratio >1.0 was 2-times more prevalent among patients with an abnormal VG-RVPO than with a VG-RVPO below the predefined threshold (OR 2.0, 95%CI 1.0-3.9).

Figure 2. ROC curve of the VG-RVPO based on occurrence of the 30-day composite end-point for adverse events



VG-RVPO, ECG derived ventricular gradient optimized for right ventricular pressure overload; ROC; receiver operator curve

Figure 3. Correlation between VG-RVPO and RV/LV diameter ratio



VG-RVPO, ECG derived ventricular gradient optimized for right ventricular pressure overload; RV, right ventricular; LV, left ventricular

Table 3. Net reclassification improvement shown in detail for adding VG-RVPO to the RV dilatation on CTPA

Event		RV/LV ratio		Total, split	Total
Non-event		Abnormal	Normal		
VG-RVPO	Abnormal	9	6	15	59
		30	14	44	
	Normal	16	6	22	95
		31	42	73	
Total, split		25	12	37	
		61	56	117	
Total		86	68		154

NRI events = (6-16)/86 = -0.116. NRI non-events = (31-14)/68 = 0.25. Overall NRI = 0.134. NRI, net reclassification improvement; VG-RVPO, ECG derived ventricular gradient optimized for right ventricular pressure overload; RV, right ventricular

The NRI of VG-RVPO on top of RV dilatation on CTPA for predicting early adverse events was -12% (Table 3), indicative of the absence of additional prognostic value of VG-RVPO on top of CTPA assessed signs of RV dilatation. The addition of VG-RVPO would have resulted in 6 patients correctly reclassified at high risk for adverse events, in whom an adverse event occurred. In contrast, 16 patients would have been incorrectly reclassified as low-risk who experienced an adverse event within the 30-day follow-up.

Discussion

Although we confirmed the association between VG-RVPO and RV overload as assessed on CTPA, VG-RVPO was not associated with poor adverse outcomes in patients with acute PE. This was observed in the overall population as well as in normotensive patients, the latter for whom risk stratification is most relevant. VG-RVPO had no additional prognostic value on top of RV/LV diameter ratio measurements, which are easily available and currently one of the pillars of PE risk stratification as recommended by international guidelines [22].

Based on current literature we expected a better incremental prognostic value of the VG-RVPO for two main reasons. Firstly, prior studies in which ECG-signs for ventricular strain (S1Q3T3, right bundle branch block (RBBB), or T wave inversions in V1-V4) were analyzed, a significant correlation was shown between the number of ECGs signs of ventricular strain and pulmonary artery pressure in PE patients [23,24]. The association between in-hospital death or clinical deterioration and the presence of these ECG abnormalities have previously been described. A meta-analysis reported ECG signs, i.e. SQQ3T3, complete RBBB, T-wave inversion ,and right axis deviation, as good predictors for in-hospital mortality. Similar findings were observed for clinical deterioration [25]. Besides, Vanni et al reported at multivariate survival analysis an association between right ventricular strain and clinical deterioration and in-hospital mortality (HR 2.58; 95% CI, 1.05-6.36) [5].

Secondly, the association of RV overload and an increased risk of PE-associated early mortality is widely acknowlegded [26]. Previous research has already shown that there is a correlation between VG-RVPO and pressure overload in patients with pulmonary hypertension .7-9,27 The hypothesis in these studies was that the pressure overload of the RV caused by an increase in RV wall tension results in RV hypertrophy and RV dilatation over time. Indeed, the VG-RVPO in patients with PH was significantly higher than in patients without PH [8,9].

Taking a closer look at the association between VG-RVPO and RV dysfunction, the

difference between the acute and chronic setting may be explained by different pathophysiological mechanisms. In the case of acute PH in patients with PE, the ECG changes as a result of obstruction of the pulmonary artery, pulmonary neurogenic reflexes and myocardial ischemia related to hemodynamic alterations associated with PE [28]. In chronic PH there is a structural and functional adaptation of the RV, causing the direction of the vector changes to change (Figure 1) [7,27,29]. This may explain the poor predictive value of VG-RVPO and the outcome of patients with acute PE.

Although we could not observe an incremental prognostic value of an abnormal VG-RVPO for PE patients in the acute setting, VG-RVPO may still be useful for the follow-up of patients with acute PE. The VG-RVPO may, for example, be useful to identify patients with chronic thromboembolic pulmonary hypertension (CTEPH), which occurs in ~3% of patients with PE [30]. CTEPH is still an underdiagnosed disease with a long diagnostic delay. Early diagnosis is of vital importance since diagnostic delay has been associated with a more advanced disease stage at the moment of diagnosis as well as with higher overall mortality [31-33]. The current diagnostic delay of CTEPH is a year or even more, which is reflecting the inefficiency of the current diagnostic tools and the lack of clear guideline recommendations regarding the optimal follow-up of patients with acute PE [34-38]. In this specific patient group, serial measurements of the VG-RVPO may be used to detect early changes in ventricular pressure overload, which may facilitate early detection like previously described in patients with systemic sclerosis [9].

Strong points of this study are the novelty of our data: this is the first study assessing the prognostic value of an abnormal VG-RVPO for early adverse events and clinical deterioration in patients with acute PE. Furthermore, the ECG analysis was done by an independent investigator and all endpoints were adjudicated by independent experts. Some limitations should be taken into account as well. Selection bias is likely present because of the retrospective study design. Also, in some patients ECGs were or of insufficient quality. Lastly, the resulting relative small sample size has led to limited statistical power for the performed analyses.

In conclusion, although we observed an association between RV dilatation and an abnormal ECG-derived VG-RVPO, we could not confirm a higher odds for either an adverse 30-day composite outcome or 30-day overall mortality for those with abnormal VG-RVPO. Also, we could not establish an incremental prognostic value of abnormal VG-RVPO either as a stand-alone test or in addition to CTPA assessed RV dilation for the risk stratification of PE patients.

References

1. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. Nature reviews Disease primers 2018;4:18028.

2. Barco S, Mahmoudpour SH, Valerio L, et al. Trends in mortality related to pulmonary embolism in the European Region, 2000-15: analysis of vital registration data from the WHO Mortality Database. The Lancet Respiratory medicine 2020;8:277-87.

3. Konstantinides SV, Meyer G. The 2019 ESC Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism. Eur Heart J 2019;40:3453-5.

4. Barco S, Valerio L, Ageno W, et al. Age-sex specific pulmonary embolism-related mortality in the USA and Canada, 2000-18: an analysis of the WHO Mortality Database and of the CDC Multiple Cause of Death database. The Lancet Respiratory medicine 2020.

5. Vanni S, Polidori G, Vergara R, et al. Prognostic value of ECG among patients with acute pulmonary embolism and normal blood pressure. 2009;122:257-64.

6. Shopp JD, Stewart LK, Emmett TW, Kline JA. Findings From 12-lead Electrocardiography That Predict Circulatory Shock From Pulmonary Embolism: Systematic Review and Meta-analysis. Acad Emerg Med 2015;22:1127-37.

7. Kamphuis VP, Haeck ML, Wagner GS, et al. Electrocardiographic detection of right ventricular pressure overload in patients with suspected pulmonary hypertension. Journal of electrocardiology 2014;47:175-82.

8. Couperus L, Vliegen H, Henkens I, et al. Electrocardiographic detection of pulmonary hypertension in patients with systemic sclerosis using the ventricular gradient. Journal of electrocardiology 2016;49:60-8.

9. Meijer FMM, Kies P, Jongbloed MRM, et al. ECG derived ventricular gradient exceeds echocardiography in the early detection of pulmonary hypertension in scleroderma patients. International Journal of Cardiology 2018;273:203-6.

10. Meijer FMM, Hendriks SV, Huisman MV, et al. Lack of diagnostic utility of the ECG-derived ventricular gradient in patients with suspected acute pulmonary embolism. Journal of electrocardiology 2020;61:141-6.

11. Huisman MV, Klok FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. Journal of thrombosis and haemostasis : JTH 2013;11:412-22.

12. Draisma H, Swenne C, Van de Vooren H, et al. LEADS: an interactive research oriented ECG/VCG analysis system. Computers in Cardiology, 2005; 2005: IEEE. p. 515-8.

13. Draisma HH, Schalij MJ, van der Wall EE, Swenne CA. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm 2006;3:1092-9.

14. Kossmann CE, Brody DA, Burch GE, et al. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Circulation 1967;35:583-602.

15. Huisman MV, Klok FA. How I diagnose acute pulmonary embolism. Blood 2013;121:4443-8.

16. Barco S, Konstantinides S, Huisman MV, Klok FA. Diagnosis of recurrent venous thromboembolism. Thrombosis research 2018;163:229-35.

17. Draper HW, Peffer CJ, STALLMANN FW, Littmann D, PIPBERGER HVJC. The corrected orthogonal electrocardiogram and vectorcardiogram in 510 normal men (Frank lead system). 1964;30:853-64.

18. PIPBERGER HV, GOLDMAN MJ, Littmann D, MURPHY GP, Cosma J, SNYDER JRJC. Correlations of the orthogonal electrocardiogram and vectorcardiogram with constitutional variables in 518 normal men. 1967;35:536-51.

19. Scherptong RW, Henkens IR, Man SC, et al. Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. 2008;41:648-55.

20. van der Meer RW, Pattynama PM, van Strijen MJ, et al. Right ventricular dysfunction and pulmonary obstruction index at helical CT: prediction of clinical outcome during 3-month follow-up in patients with acute pulmonary embolism. Radiology 2005;235:798-803.

21. Ende-Verhaar YM, Kroft LJM, Mos ICM, Huisman MV, Klok FA. Accuracy and reproducibility of CT right-to-left ventricular diameter measurement in patients with acute pulmonary embolism. PloS one 2017;12:e0188862.

22. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS) The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2020;41:543-603.

23. Daniel KR, Courtney DM, Kline JA. Assessment of Cardiac Stress From Massive Pulmonary Embolism With 12-Lead ECG. Chest 2001;120:474-81.

24. Yoshinaga T, Ikeda S, Shikuwa M, Miyahara Y, Kohno SJCj. Relationship between ECG findings and pulmonary artery pressure in patients with acute massive pulmonary thromboembolism. 2003;67:229-32.

25. Qaddoura A, Digby GC, Kabali C, Kukla P, Zhan Z-Q, Baranchuk AM. The value of electrocardiography in prognosticating clinical deterioration and mortality in acute pulmonary embolism: A systematic review and meta-analysis. 2017;40:814-24.

26. Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. Eur Heart J 2019;40:902-10.

27. Henkens IR, Mouchaers KT, Vonk-Noordegraaf A, et al. Improved ECG detection of presence and severity of right ventricular pressure load validated with cardiac magnetic resonance imaging. American Journal of Physiology-Heart and Circulatory Physiology 2008;294:H2150-H7.

28. Alpert JS, Godtfredsen J, Ockene IS, Anas J, Dalen JEJC. Pulmonary hypertension secondary to minor pulmonary embolism. 1978;73:795-7.

29. Henkens IR, Mouchaers KT, Vliegen HW, et al. Early changes in rat hearts with developing pulmonary arterial hypertension can be detected with three-dimensional electrocardiography. American Journal of Physiology-Heart and Circulatory Physiology 2007;293:H1300-H7.

30. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. The

European respiratory journal 2017;49.

31. Delcroix M, Kerr K, Fedullo P. Chronic Thromboembolic Pulmonary Hypertension. Epidemiology and Risk Factors. Annals of the American Thoracic Society 2016;13 Suppl 3:S201-6.

32. Klok FA, Barco S, Konstantinides SV, et al. Determinants of diagnostic delay in chronic thromboembolic pulmonary hypertension: results from the European CTEPH Registry. The European respiratory journal 2018;52.

33. Boon G, Bogaard HJ, Klok FA. Essential aspects of the follow-up after acute pulmonary embolism: An illustrated review. Research and practice in thrombosis and haemostasis 2020;4:958-68.

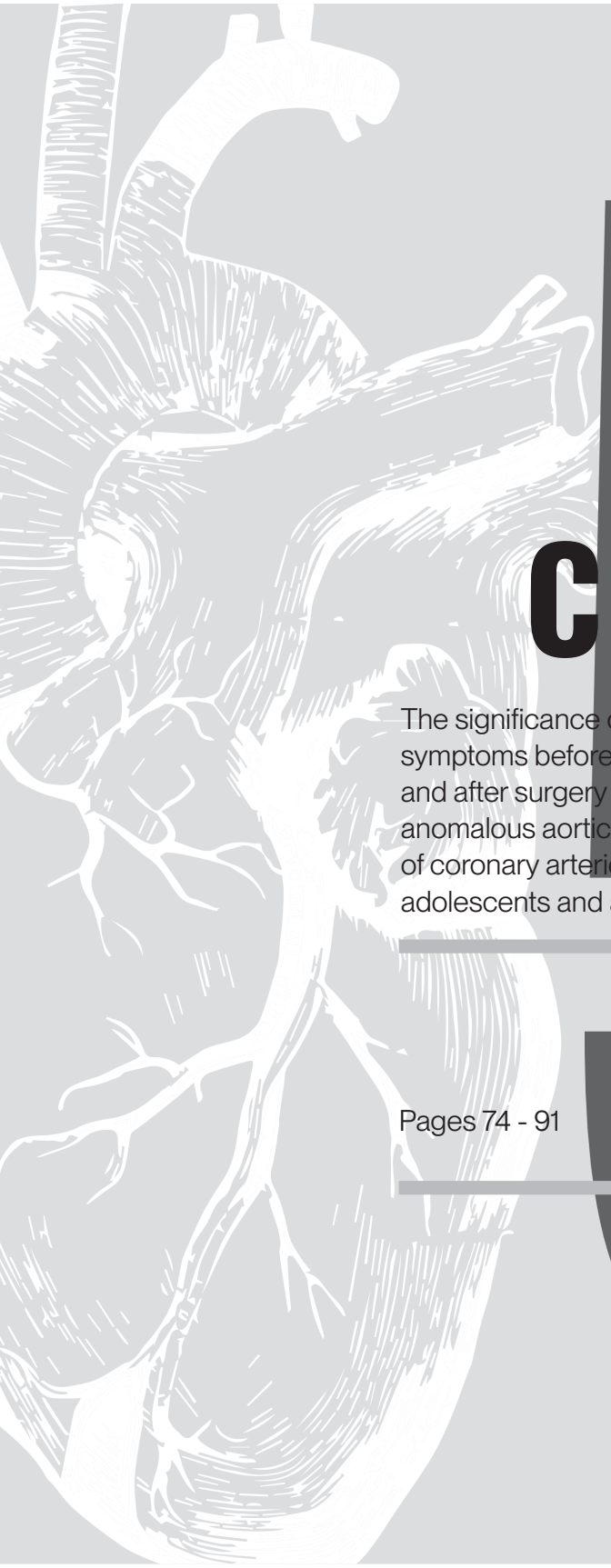
34. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011;124:1973-81.

35. Delcroix M, Lang I, Pepke-Zaba J, et al. Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension: Results From an International Prospective Registry. Circulation 2016;133:859-71.

36. Ende-Verhaar YM, van den Hout WB, Bogaard HJ, et al. Healthcare utilization in chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Journal of thrombosis and haemostasis : JTH 2018;16:2168-74.

37. Barco S, Klok FA, Konstantinides SV, et al. Sex- specific differences in chronic thromboembolic pulmonary hypertension. Results from the European CTEPH registry. 2019.

38. Delcroix D TA, Gopalan D, Sitbon O, Klok FA, Lang I, Jenkins D, Kim NH, Humbert M, Jais X, Vonk Noordegraaf A, Pepke-Zaba J, Brénot P, Dorfmuller P, Fadel E, Ghofrani HA, Hoeper MM, Jansa P, Madani M, Matsubara H, Ogo T, Grünig E, D'Armini A, Galie N, Meyer B, Corkery P, Meszaros G, Mayer E, Simonneau G. ERS Statement on Chronic Thromboembolic Pulmonary Hypertension. Eur Respir J 2020.



CHAPTER 5

The significance of symptoms before and after surgery for anomalous aortic origin of coronary arteries in adolescents and adults

Pages 74 - 91

THE SIGNIFICANCE OF SYMPTOMS BEFORE AND AFTER SURGERY FOR ANOMALOUS AORTIC ORIGIN OF CORONARY ARTERIES IN ADOLESCENTS AND ADULTS

F.M.M. Meijer, A.D. Egorova, M.R.M. Jongbloed, C. Koppel, G. Habib, M.G. Hazekamp H.W. Vliegen, P. Kiès

Interactive CardioVascular and Thoracic Surgery. 2021; 32: 122-129

ABSTRACT

Objectives

The aim of this study is to describe the significance of symptoms preoperatively and at medium-term follow up in adolescent and adult patients who underwent surgery of AAOCA.

Methods

Consecutive patients who underwent surgery for AAOCA in our tertiary referral center between 2001 to 2018 were included. Clinical characteristics and symptoms were evaluated and medium-term outcomes were recorded. Symptoms were classified according to the '2019 ESC guidelines on chronic coronary syndromes'.

Results

A total of 53 (55% male) patients with mean age of 44 at time of surgery underwent surgical repair of AAOCA. Data on symptoms and events more than 3 months after surgery were available in 34 patients with a median follow up of 3 years (IQR 1.0 – 5.3). Pre-operatively, only 35% patients had typical anginal complaints. After surgical correction of AAOCA, 59% of the patients were free of symptoms, compared to 6% pre-operatively ($p < 0.001$). A total of 3 (9%) patients needed a re- operation/re-intervention related to the operated AAOCA. All 3 patients presented post-operatively with novel typical anginal complaints.

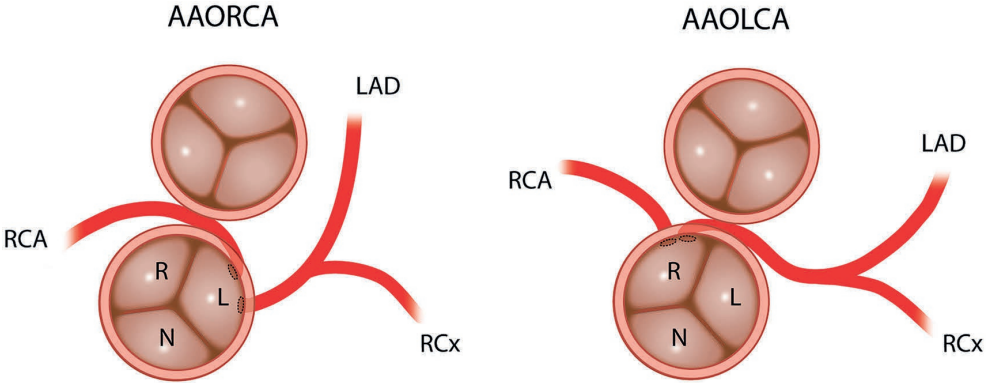
Conclusion

Adolescent and adult patients with AAOCA present with varying symptoms. Only 35% have typical anginal complaints. Surgical correction of AAOCA reduces the symptoms in the vast majority of patients. One should be aware of potential lesions of the operated coronary artery in patients presenting with typical anginal complaints post-operatively.

Introduction

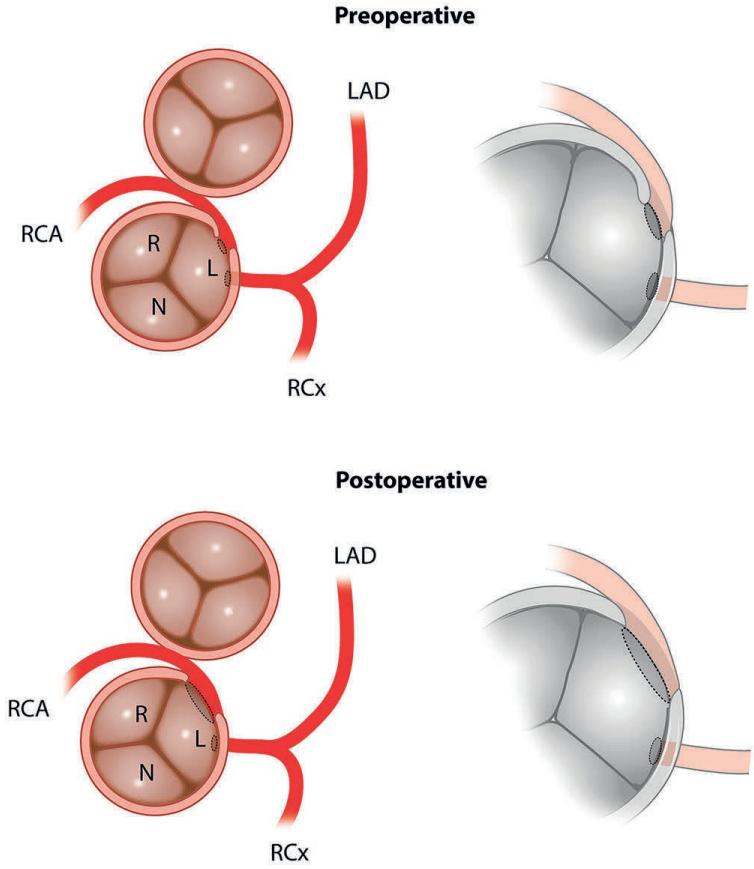
Anomalous aortic origin of the coronary arteries (AAOCA) is a rare congenital condition with a reported incidence between 0.26 and 1.3%, [1-3]. Anomalous coronary arteries which arise from the opposite sinus of Valsalva or contralateral coronary artery are a potential cause of sudden cardiac death, especially in athletes and active young adults (Figure 1) [11]. Presenting symptoms differ largely amongst patients [2,4,52]. To date there is no consensus on indications for surgery versus conservative treatment, especially in middle aged and older patients. Due to lack of long-term follow-up of patients after surgical treatment, indications for surgical treatment are ambiguous, especially in asymptomatic patients [6-9]. The main objective of surgery is to reduce the risk of sudden cardiac death (SCD) and alleviate ischemia. The decision to operate a patient is based on the ostial anatomy and course of the anomalous coronary artery and demonstrated ischemia. The role of symptoms in decision making with regards to the surgical intervention and post-operative outcomes is ambiguous. Several surgical techniques for correcting AAOCA have been used, most commonly unroofing of the intramural segment (Figure 2), coronary reimplantation and

Figure 1. Schematic representation of AAORCA and AAOLCA anatomy with an interarterial and intramural course of the anomalous artery (imaging view).



AAORCA, anomalous aortic origin of a right coronary; AAOLCA, anomalous aortic origin of a left coronary; RCA, right coronary artery; LAD, left anterior descending artery; RCx, ramus circumflex artery; R, right coronary cusp; L, left coronary cusp; N, non coronary cusp

Figure 2. Schematic representation of AAORCA anatomy prior to and after surgical correction (imaging view)



AAORCA, anomalous aortic origin of a right coronary; RCA, right coronary artery; LAD, left anterior descending artery; RCx, ramus circumflex artery; R, right coronary cusp; L, left coronary cusp; N, non coronary cusp

coronary artery bypass grafting (CABG) [10, 11]. A few studies have reported persistent symptoms, restenosis of the operated anomaly after surgery, ischemia and even cases of SCD [9, 12-15].

The aim of this study is to describe the significance of symptoms preoperatively and at medium-term follow up in adolescent/ adult patients who underwent surgery of AAOCA.

Material and methods

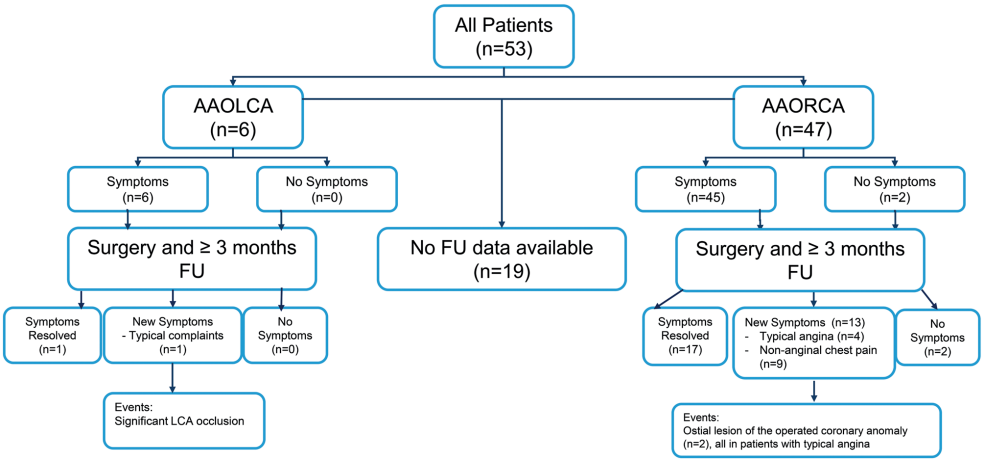
Study population and data collection

The Leiden University Medical Center (LUMC) serves as a national referral center for

patients with congenital heart disease. Consecutive patients who underwent surgical correction of an anomalous aortic origin of a left coronary artery (AAOLCA) or anomalous right coronary artery (AAORCA) arising from the opposite sinus of Valsalva at our center between 2001 and 2018 were included in this study (Figure 3). Patients with concomitant congenital heart defects (e.g. transposition of the great arteries, tetralogy of Fallot, and certain forms of pulmonary atresia), and patients unable or unwilling to communicate with the research team were excluded from analysis. Patient data were collected from the electronic medical file system (EPD-Vision®) and included: patient demographic data, symptoms, sex, indications for surgery, anatomy of the anomalous coronary artery, surgical techniques, imaging modalities, functional tests, clinical course and outpatient visit reports. Major adverse cardiac events included sustained ventricular tachycardia (VT) or fibrillation (VF), re-operation or percutaneous coronary intervention (PCI) on the operated coronary artery, and/or (cardiac) death. The study focused on medium-term outcomes. Therefore in hospital events in post-operative setting (< 1 month) and patients with less than 3 months follow-up were excluded.

All patients were asked about recurrence of chest pain related symptoms and reinterventions. All chest pain (related) complaints were classified according to the '2019 ESC guidelines on chronic coronary syndromes ' [16]: Chest pain is classified as "typical angina", "atypical angina" and "non-anginal chest pain". Typical angina is defined as 1. "constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm", 2. "precipitated by physical exertion" and 3. "relieved by rest or nitrates within 5 minutes". Atypical angina meets 2 of these criteria and non-anginal chest pain satisfies one or none of the above-mentioned characteristics. Patients were also categorized into the "typical" group if there were other complaints that were strongly associated with ischemia. All chest

Figure 3. Overview of the 34 patients with follow-up



pain related symptoms were categorized independently into above mentioned groups by 2 experienced cardiologists (HWV and PKI) who were blinded for the results.

Statistical analysis

Analyses were performed with SPSS Statistics (version 23, IBM Corp, Armonk, New York, USA). Descriptive statistics were used for data analysis and were expressed as mean ± standard deviation (SD) and median (IQR; interquartile range). Binary data were expressed in numbers with percentages. All reported p values were two-sided, and values of $p < 0.050$ were considered significant.

Results

Baseline patient characteristics at initial presentation

Baseline patient characteristics are described in Table 1. This study consisted of 53 patients who underwent surgery for correction of AAOCA; 47 (89%) patients had an AAORCA and 6 (11%) patients an AAOLCA. All patients had an intramural course of the anomalous coronary artery. The mean age at surgery was 44 ± 15 years (range 11-68) and 55% were male. Four patients were younger than 16 years old. Fifty-one of 53 patients (96%) had symptoms of some sort at initial presentation. The most common reason for cardiac analysis in these patients was suspicion of ischemia (42 patients, 79%). Three (6%) patients presented with an aborted sudden cardiac death (1 patient with AAOLCA and 2 patients with AAORCA, Table 2). The first patient (patient 2, AAORCA) was 17 years old and playing sports at the time of the cardiac event. No symptoms or cardiac events preceded the cardiac arrest based on ventricular fibrillation. There were no risk factors. The second patient with an AAORCA was 25 years old. This patient was resuscitated due to ventricular fibrillation during exercise, before this event the patient had some non-specific thoracic complaints during exercise and he was a smoker. In 5 (9%) patients AAOCA was an incidental finding and in 3 (6%) patients were identified through familial screening for coronary anomalies. Although no hard evidence exists regarding familial screening in coronary artery anomalies, in these patients screening was performed by the referring center driven by patient desire.

Preoperative testing

Patients were referred to our center with different imaging modalities and functional tests, performed in the referring hospital. Of the 53 patients who were accepted for surgery by the heart-team, 50 (94%) patients underwent computed tomographic angiography (CTA) (Figure 3), 35 (66%) coronary angiography (CAG) and 8 (15%) cardiac magnetic resonance imaging (MRI). Functional ischemia testing was performed in 74% of the patients (Table 1).

In 36 patients (68%) exercise ECG testing was performed, of which 22% had an ischemic response. Ten (19%) patients underwent a nuclear stress test, of which 40% were positive for ischemia.

Initial surgical repair

Surgical techniques used included: unroofing (72%), coronary reimplantation (8%), CABG (2%), patch augmentation (10%), or a combination of the above (8%). None of the anomalous LCA patients underwent patch augmentantion of ostium and main stem (Table 1). Concomitant procedures during the surgical repair were performed in 15 cases and consisted predominantly of aortic valve resuspension in order to prevent aortic regurgitation due to manipulation after unroofing or because of pre-existing aortic regurgitation.

Clinical follow-up

One patient (1/53, 1.9%) died one week after LCA ostioplasty due to severe heparin induced thrombocytopenia (HIT) causing disseminated intravascular coagulation (DIC). The central death administration was consulted, and except for the aforementioned patient, every patient (52/53, 98.1%) was still alive at follow-up (median 5 ± 16 years (IQR 2-18)).

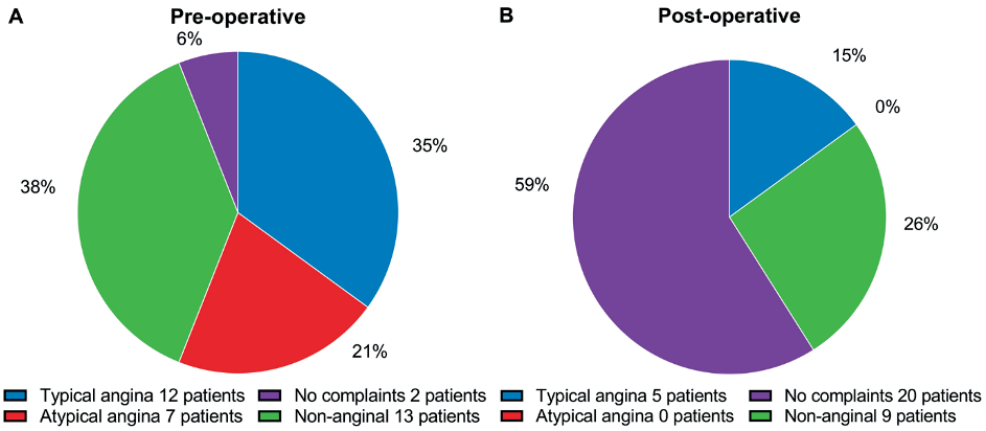
Full follow up data of more than 3 months was available in 34 out of 53 (64%) patients. In 19 (36%) patients full follow-up data could not be obtained due to migration, significant language barrier or inability to contact the patient. In these 34 patients median follow-up of 3.0 years (IQR 1.0 – 5.3, Figure 1) was attained.

The pre- and post-operative symptoms in the 34 patients with more than 3 months follow-up are shown in Figure 4. Pre-operatively, 35% (12/34) of patients presented with typical angina, 21% (7/34) with atypical angina and 38% (13/34) had non-anginal chest pain. Only 6% of the patients (2/34) were asymptomatic before surgery. After surgical correction, 59% (20/34) of the patients reported to be free of symptoms, this is a significant reduction in the total burden ($p<0001$). In 15% (5/34) of the patients, a post-operative catheterisation was performed due to typical complaints after surgery (Table 2). In three of these patients (9%, 3/34), lesions of the operated AAOCA were diagnosed, detailed in Table 2. Patient 6 presented with typical complaints 5 years after surgery, on CAG there was an occlusion of the LAD, thus not associated to the unroofed RCA. Patient 7 (reimplantation of AAOLCA) had a significant left main stenosis for which a successful PCI was performed. Patient 19, also presented with typical complaints, however on catheterisation no stenosis was seen and no additional treatment was performed. Patient 21 (unroofing of AAORCA) had a flattened ostium of the RCA for which a PCI was performed. Patient 30 (unroofing of AAORCA) presented with a near-collapse and angiography revealed ostial stenosis of the RCA for which a CABG was performed (right internal mammary artery graft on the RCA,

clip proximal RCA).

Table 3 is an overview of the remaining 27 patients and their clinical and anatomical characteristics, surgical course and follow-up. All patients with atypical angina at presentation were free of symptoms after surgery. Two patients were asymptomatic prior to surgery and remained asymptomatic postoperatively and during follow-up. In these patients, AAOCA was diagnosed through familial screening and was judged to be a malignant variant and therefore, these patients underwent surgical correction.

Figure 4. Preoperative and postoperative symptoms of 34 patients with follow-up classified according to the "2019 ESC Guidelines on chronic coronary syndromes".



Discussion and conclusion

In this study we report on the medium term outcomes (median of 3 years IQR 1.0 – 5.3) of 34 patients who underwent surgical correction for AAOCA. Our main findings are the following:

1. Of patients who were referred to our center with AAOCA, 94% initially present with symptoms: 35% have typical complaints, 21% atypical complaints, 38% non-anginal complaints, and 6% have no complaints at all.
2. After surgical correction of AAOCA, 59% of the patients are free of symptoms. Compared to 6% pre-operatively ($p < 0.001$).
3. Patients who had significant lesions of the operated coronary artery during medium term follow up (3/34, 9%), all presented with novel typical anginal complaints in the outpatient clinic.

The clinical presentation of adults with an AAOCA varies. In our study 35% of patients presented with typical angina which is comparable to previous reports [4,13,17]. Consequently,

the indication for intervention is based on other clinical factors [18, 19]. Guidelines of the American College of Cardiology, American Heart Association and Thoracic Surgery suggest that surgical intervention may be warranted in younger patients with evidence of ischemia [18]. Palmieri et al reported good clinical outcomes after conservative treatment strategy (exercise restriction) in 23 young athletes [19].

To our knowledge, we are the first group to report specifically on an adolescent and adult group, with mean age of 44 years at time of surgery. Particularly in older patients with AAORCA without signs of ischemia, indication for intervention is currently not clearly defined. In previous studies the risk of SCD appears highest in young patients and particularly in interarterial AAOLCA, therefore the indication for surgical correction in this group is not up for debate [5, 20]. The current guidelines recommend revascularization for interarterial AAOLCA, regardless of ischemia of symptoms [21]. In patients with AAORCA without signs of ischemia the indication for intervention relies on numerous factors to guide management. Clinical presentation, anatomical and functional characteristics of the AAOCA as well as patient specific factors all have to be taken into account [18, 21].

Perioperative mortality in our study was 1.9% (1/53), which is in line with previously reported post-operative mortality rates of AAOCA correction in children and young adults [9, 22-24]. According to literature, in the majority of the patients AAOCA is an incidental finding, probably due to a vast increase of the use of CT and MRI imaging in our current clinical practice. In our study only 9% of the patients were diagnosed with AAOCA as an incidental finding, reflecting the subselection of patients who were operated. In current clinical practice, therefore, numerous anatomical, (patho)physiological factors and the individual operative risk are considered when evaluating an AAOCA patient. Our results show a low discriminative value of the type of complaints as over 60% of all AAOCA patients did not have typical complaints at initial evaluation.

After more than 3 months following the surgical correction of AAOCA, 59% of the patients were free of symptoms. This was a significant improvement compared to the preoperative situation and was unrelated to the type of pre-operative complaints. Interestingly, out of the 5 patients having typical complaints at follow-up, 3 (60%) needed re-intervention due to a significant lesion of the operated artery. This is in line with previous literature [15, 25]. In our series 9% (3/34) of the operated patients needed re-intervention due to a significant lesion in the operated artery. The rate of re-intervention is relatively high in relation to literature which varies between 1.7 and 3.3% [9, 13, 14]. This may be a reflection of the older age of the study population compared to most series reporting on pediatric patients [7, 26].

Mainwaring et al. report on a significantly younger group with 115 AAOCA patients with a follow up of 6 years, the median age at surgery was 16 years [13]. In this study two patients had recurrent symptoms of chest pain and underwent reoperation (one had revision of the initial repair and one had repair of a myocardial bridge) [13]. Nees et al. 14 reported on 2 patients with AAOLCA that needed reoperation due to restenosis of the anomalous coronary artery, 2 months and 6 years after surgery, respectively. One patient, aged 68 had recurrent chest pain, showed an abnormal electrocardiogram and was treated with a bypass graft because of significant stenosis of the operated artery. The other patient, aged 10, survived an aborted SCD 6 years post-operatively and CT and interoperative examination showed ostial narrowing due to fibrous tissue around the left coronary orifice [14]. In the study of Padalino et al. 3 patients needed re-intervention of the operated artery [9]. These cases, together with our data indicate that restenosis of the corrected anomalous artery is a complication that can be observed during medium and long term follow-up of adult patients. It therefore seems justified to perform lifetime follow-up in patients after surgical correction of AAOCA.

Limitations

Despite our role as a national referral center, the sample size is small, reflecting the rarity of the condition. The nature of the data is largely descriptive, and symptoms may be subjective, particularly when evaluated retrospectively. However, the complaints were judged by 2 independent cardiologist who were blinded for the results. Given our role as a referral center, patients are typically sent back to the referring cardiologist for life-long follow up at the local hospital. This contributed to the high rate of loss to follow up.

Conclusions

Our data shows the varying symptoms at presentation in adolescent and adult patients with AAOCA. Only 35% have typical anginal complaints. Surgical correction of AAOCA reduces the symptoms in the vast majority of patients. One should be aware of potential lesions of the operated coronary artery in patients presenting with typical anginal complaints post-operatively.

Acknowledgements

The authors would like to thank Ronald Slagter (Department of Anatomy & Embryology, Leiden University Medical Center, the Netherlands) for his assistance with Figures 1 and 2.

References

1. Gatzoulis MA WG, Daubeney PEF. . Part X: Coronary anomalies of the coronary arteries. . Diagnosis and management of adult congenital heart disease 3rd edition. . Philadelphia: PA: Elsevier, 2018. ; 2018. p. P.588.

2. Yamanaka O, Hobbs RE. Coronary artery anomalies in 126,595 patients undergoing coronary arteriography. Catheterization and cardiovascular diagnosis. 1990;21(1):28-40.

3. Labombarda F, Coutance G, Pellissier A, Mery-Alexandre C, Roule V, Maragnes P, et al. Major congenital coronary artery anomalies in a paediatric and adult population: a prospective echocardiographic study. European heart journal cardiovascular Imaging. 2014;15(7):761-8.

4. Basso C, Maron BJ, Corrado D, Thiene G. Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes. Journal of the American College of Cardiology. 2000;35(6):1493-501.

5. Taylor AJ, Rogan KM, Virmani R. Sudden cardiac death associated with isolated congenital coronary artery anomalies. J Am Coll Cardiol. 1992;20(3):640-7.

6. Brothers JA, Frommelt MA, Jaquiss RDB, Myerburg RJ, Fraser CD, Jr., Tweddell JS. Expert consensus guidelines: Anomalous aortic origin of a coronary artery. J Thorac Cardiovasc Surg. 2017;153(6):1440-57.

7. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation. 2008;118(23):e714-833.

8. King N-M, Tian DD, Munkholm-Larsen S, Buttar SN, Chow V, Yan T. The Aberrant Coronary Artery–The Management Approach. Heart, Lung and Circulation. 2017.

9. Padalino MA, Franchetti N, Sarris GE, Hazekamp M, Carrel T, Frigiola A, et al. Anomalous aortic origin of coronary arteries: Early results on clinical management from an international multicenter study. International journal of cardiology. 2019;291:189-93.

10. Poynter JA, Williams WG, McIntyre S, Brothers JA, Jacobs ML, Overman D, et al. Anomalous Aortic Origin of a Coronary Artery A Report From the Congenital Heart Surgeons Society Registry. World Journal for Pediatric and Congenital Heart Surgery. 2014;5(1):22-30.

11. Mainwaring RD, Reddy VM, Reinhartz O, Petrossian E, Punn R, Hanley FL. Surgical repair of anomalous aortic origin of a coronary artery. European Journal of Cardio-Thoracic Surgery. 2014;46(1):20-6.

12. Wittlieb-Weber CA, Paridon SM, Gaynor JW, Spray TL, Weber DR, Brothers JA. Medium-term outcome after anomalous aortic origin of a coronary artery repair in a pediatric cohort. J Thorac Cardiovasc Surg. 2014;147(5):1580-6.

13. Mainwaring RD, Murphy DJ, Rogers IS, Chan FP, Petrossian E, Palmon M, et al. Surgical repair of 115 patients with anomalous aortic origin of a coronary artery from a single institution. World Journal for Pediatric and Congenital Heart Surgery. 2016;7(3):353-9.

14. Nees SN, Flyer JN, Chelliah A, Dayton JD, Touchette L, Kalfa D, et al. Patients with anomalous aortic origin of the coronary artery remain at risk after surgical repair. J Thorac Cardiovasc Surg. 2018;155(6):2554-64

e3.

15. Brothers JA, McBride MG, Seliem MA, Marino BS, Tomlinson RS, Pampaloni MH, et al. Evaluation of myocardial ischemia after surgical repair of anomalous aortic origin of a coronary artery in a series of pediatric patients. Journal of the American College of Cardiology. 2007;50(21):2078-82.

16. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. 2019.

17. Angelini P, Velasco JA, Flamm S. Coronary anomalies incidence, pathophysiology, and clinical relevance. Circulation. 2002;105(20):2449-54.

18. Brothers JA, Frommelt MA, Jaquiss RD, Myerburg RJ, Fraser CD, Tweddell JSJTJot, et al. Expert consensus guidelines: anomalous aortic origin of a coronary artery. 2017;153(6):1440-57.

19. Palmieri V, Gervasi S, Bianco M, Cogliani R, Poscolieri B, Cuccaro F, et al. Anomalous origin of coronary arteries from the "wrong" sinus in athletes: diagnosis and management strategies. 2018;252:13-20.

20. Cheitlin MD, De Castro CM, MCALLISTER HA. Sudden death as a complication of anomalous left coronary origin from the anterior sinus of Valsalva: a not-so-minor congenital anomaly. Circulation. 1974;50(4):780-7.

21. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al. ACC/AHA 2008 Guidelines for the Management of Adults With Congenital Heart Disease. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease) Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. 2008;52(23):e143-e263.

22. Nguyen A, Haas F, Evens J, Breur J. Sudden cardiac death after repair of anomalous origin of left coronary artery from right sinus of Valsalva with an interarterial course. Netherlands Heart Journal. 2012;20(11):463-71.

23. Davies JE, Burkhart HM, Dearani JA, Suri RM, Phillips SD, Warnes CA, et al. Surgical management of anomalous aortic origin of a coronary artery. The Annals of thoracic surgery. 2009;88(3):844-8.

24. Brothers J, Gaynor JW, Paridon S, Lorber R, Jacobs M. Anomalous aortic origin of a coronary artery with an interarterial course: understanding current management strategies in children and young adults. Pediatric cardiology. 2009;30(7):911-21.

25. Sachdeva S, Frommelt MA, Mitchell ME, Tweddell JS, Frommelt PCJTJot, surgery c. Surgical unroofing of intramural anomalous aortic origin of a coronary artery in pediatric patients: Single-center perspective. 2018;155(4):1760-8.

26. Mery CM, De Leon LE, Molossi S, Sexson-Tejtel SK, Agrawal H, Krishnamurthy R, et al. Outcomes of surgical intervention for anomalous aortic origin of a coronary artery: A large contemporary prospective cohort study. J Thorac Cardiovasc Surg. 2018;155(1):305-19.e4.

Table 1. Patient characteristics

Patient characteristics	All patients (n=53)
Male, n (%)	29 (55)
Age at surgery, years, mean ± SD	44 (15)
Diabetes mellitus n (%)	3 (6)
Hypertension n (%)	10 (19)
Previous ischemic coronary disease n (%)	0
Hypercholesterolemia n (%) TIA/CVA n (%)	13 (25)
AAOLCA n (%)	6 (11)
AAORCA n (%)	47 (89)
Symptoms present, n (%)	51 (96)
Primary presentation, n (%)	
Suspicion of ischemia	42 (79)
Aborted sudden cardiac death	3 (6)
Familial screening	3 (6)
Incidental finding	5 (9)
Diagnostic imaging techniques, n (%)	
CTA	50 (94)
CAG	35 (66)
MRI	8 (15)
Diagnostic functional test, n (%)	-
Exercise ECG	36 (68)
Positive	8 (22)
Nuclear stress test	10 (19)
Positive	4 (40)
Adenosine stress perfusion CT	4 (8)
Positive	1 (25)

Dobutamine stress MRI	2 (4)
Positive	0
PET-CT	2 (4)
Positive	0
No test	14 (26)
Surgical technique, n (%)	
Unroofing	38 (72)
Reimplantation	4 (8)
Unroofing + reimplantation	3 (6)
Unroofing + CABG	1 (2)
Ostioplasty	5 (10)
Unroofing + ostioplasty	1 (2)
CABG	1 (2)
Concomitant procedure, n (%)	15 (28)
Aortic valve repair	6
Tricuspid valve repair	1
Mitral- and aortic valve repair	1
Epicardial lead placement	1
Excision of cardiac lipoma	1
Pulmonary vein isololation, left atrial resection, aortic valve repair	1
CABG Ao-D-LAD	1

CTA, computed tomographic angiography; CAG, coronary angiography; MRI, magnetic resonance imaging; PET-CT, position emission tomography computed tomography; CABG, coronary artery bypass grafting; AAOLCA, anomalous left coronary artery; AAORCA, anomalous right coronary artery; CABG, coronary artery bypass grafting; Ao, aorta, D, diagonal branch; LAD, left anterior descending artery

Table 2. Consecutive patients with > 3 months follow-up after surgical correction for anomalous aortic origin of a coronary artery with interarterial course and post-operative complaints driven catheterization (n=5)

Pt	Lesion	Age (years)	Clinical presentation	Ischemia detection	Surgical repair	Pre-operative symptoms	Post-operative symptoms	Δt surgery and events (months)	Post-operative events/complications + treatment
6	AAORCA	47	suspected ischemia	positive	unroofing	non-anginal	typical	60	PCI proximal LAD
7	AAOLCA	58	suspected ischemia	positive	reimplantation	typical	typical	1	significant main stem stenosis, PCI main stem
19	AAORCA	49	suspected ischemia	positive	unroofing	typical	typical	15	no stenosis on CAG
21	AAORCA	64	suspected ischemia	positive	unroofing	typical	typical	13	flattening ostium RCA, PCI proximal RCA
30	AAORCA	44	suspected ischemia	negative	unroofing	atypical	typical (near-collapse)	10	stenosis ostium RCA, RIMA-RCA, clip on proximal RCA

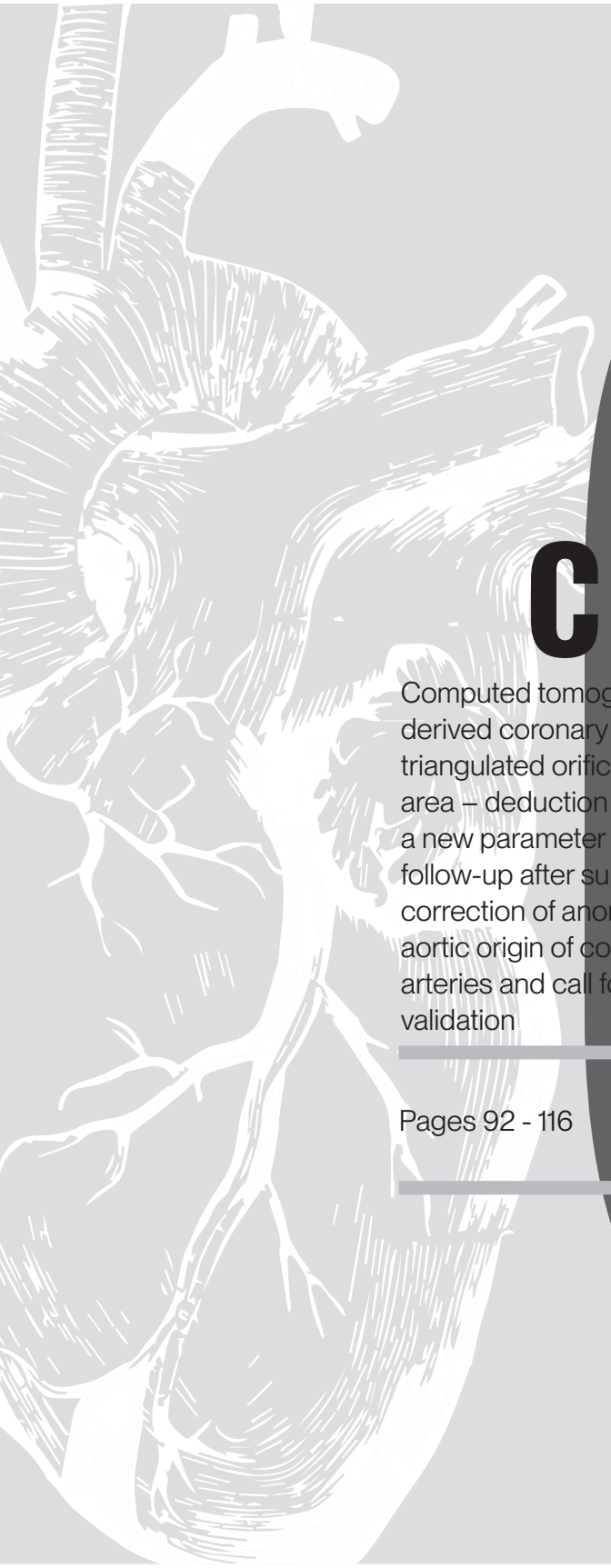
Table 3. Consecutive patients with > 3 months follow-up after surgical correction for anomalous aortic origin of a coronary artery with interarterial course and no post-operative events (n=29).

Pt	Lesion	Age	Clinical pre-sentation	Ischemiade-tection	Surgical repair	Pre-operative symptoms	Post-oper-ative symp-toms
1	AAORCA	25	screening	negative	unroofing and reimplantation	typical	no complaints
2	AAORCA	17	aborted SCD	not conclusive	reimplantation	typical	no complaints
3	AAORCA	53	suspected ischemia	negative	reimplantation	atypical	no complaints
4	AAORCA	46	suspected ischemia	negative	unroofing and reimplantation	typical	no complaints
5	AAORCA	34	screening	positive	reimplantation	no complaints	no complaints
8	AAORCA	66	suspected ischemia	negative	unroofing and CABG non anomalous vessel	atypical	non-anginal: chest discom-fort
9	AAORCA	66	suspected ischemia	negative	CABG of anomalous vessel	typical	no complaints
10	AAORCA	25	suspected ischemia	negative	unroofing	non-anginal	no complaints
11	AAORCA	45	suspected ischemia	positive	unroofing	atypical	no complaints

Pt	Lesion	Age	Clinical pre-sentation	Ischemiade-tection	Surgical repair	Pre-operative symptoms	Post-oper-ative symp-toms
12	AAORCA	56	suspected ischemia	negative	unroofing	atypical	non-anginal: tiredness/ loss of condition
13	AAORCA	20	suspected ischemia	positive	unroofing	atypical	no complaints
14	AAORCA	50	suspected ischemia	positive	unroofing	non-anginal	no complaints
15	AAORCA	46	suspected ischemia	negative	unroofing	typical	non-anginal: tiredness/ loss of condition
16	AAORCA	13	suspected ischemia	negative	unroofing	atypical	non-anginal: tiredness/ loss of condition
17	AAOLCA	15	aborted SCD	negative	ostiumplasty	typical	no complaints
18	AAORCA	29	screening	positive	unroofing	non-anginal	non-anginal: palpitations
20	AAORCA	51	screening	positive	unroofing	atypical	non-anginal: sharp chest pain
22	AAORCA	53	suspected ischemia	positive	unroofing	non-anginal	non-anginal: tiredness/ loss of condition

23	AAORCA	48	suspected ischemia	positive	unroofing	non-anginal	non-anginal: sharp chest pain
24	AAORCA	59	suspected ischemia	positive	unroofing	non-anginal	non-anginal: tiredness/ loss of condition
25	AAORCA	67	suspected ischemia	positive	unroofing	non-anginal	no complaints
26	AAORCA	42	suspected ischemia	positive	unroofing	non-anginal	no complaints
27	AAORCA	15	screening	positive	unroofing	no complaints	no complaints
28	AAORCA	63	suspected ischemia	positive	unroofing	non-anginal	no complaints
29	AAORCA	11	suspected ischemia	negative	unroofing	non-anginal	no complaints
31	AAORCA	66	suspected ischemia	positive	unroofing	non-anginal	no complaints
32	AAORCA	52	screening	negative	unroofing	typical	no complaints
33	AAORCA	43	suspected ischemia	negative	unroofing	non-anginal	no complaints
34	AAORCA	47	suspected ischemia	not conclusive	unroofing	atypical	no complaints

Pt: consecutive patient number; Ischemic detection: outcome of ischemic detection pre-operatively; AAORCA: anomalous right coronary artery; AAOLCA: anomalous left coronary artery; FU: follow up; Δt time between surgery and event in months; aSCD: aborted sudden cardiac death; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; RDA: right descending artery; RIMA: right internal mammary artery; VF: ventricular fibrillation



CHAPTER 6

Computed tomography derived coronary triangulated orifice area – deduction of a new parameter for follow-up after surgical correction of anomalous aortic origin of coronary arteries and call for validation

COMPUTED TOMOGRAPHY DERIVED CORONARY TRIANGULATED ORIFICE AREA – DEDUCTION OF A NEW PARAMETER FOR FOLLOW-UP AFTER SURGICAL CORRECTION OF ANOMALOUS AORTIC ORIGIN OF CORONARY ARTERIES AND CALL FOR VALIDATION

F.M.M. Meijer, P. Kiès, D.B.H. Verheijen, M.R.M. Jongbloed, M.G. Hazekamp, H.J. Lamb, H.W. Vliegen, A.D. Egorova

Frontiers in Cardiovascular Medicine 8 (2021): 668503

ABSTRACT

Objectives

Anomalous aortic origin of a coronary artery (AAOCA) from the opposite sinus of Valsalva is a rare congenital abnormality. Computed tomography angiography (CTA) is primarily used as a diagnostic tool to evaluate the anatomy and identify potentially malignant AAOCA variants. Limited data is available on the role of CTA during post-operative follow-up. We aimed to develop an objective CTA derived parameter for diagnostic evaluation and follow-up after surgical correction of AAOCA and correlate the anatomical features to the postoperative outcome.

Methods

All consecutive patients who underwent surgical repair of AAOCA from 2001 to 2018 and had pre and post-operative CTA imaging available were included. A retrospective analysis of the pre- and postoperative CTA and the outcomes was performed. The origin and course of the anomalous coronary artery and the ostial dimensions were evaluated and correlated with restenosis of operated coronary artery. To allow an accurate evaluation of the effective orifice area at diagnosis and after surgical repair we deduce and propose a new parameter - the coronary triangulated orifice area (CTOA).

Results

Out of the 54 patients who underwent surgical treatment for AAOCA, 11 fulfilled the inclusion criteria. The median follow-up was 19 months [IQR 3;42]. The mean age at surgery was 41 ± 16 years, with 6 patients (55%) being male. Postoperatively, the angle between the proximal coronary artery and the aortic wall increased from 20 ± 5° to 28 ± 9° ($p<0.01$) and ostial diameter in the transversal plane increased from 4.1 ± 2.5mm to 6.2 ± 2.7mm ($p<0.01$). The median CTOA increased significantly from 1.6 mm^2 [IQR 0.9;4.9] to 5.5 mm^2 [IQR 3;11.8] ($p<0.005$). During follow-up, in 3 patients a restenosis of the operated coronary artery was suspected. In these patients, the CTOA only showed a limited postoperative increase of ≤ 1.4 mm^2.

Conclusions

CTA can play an important role in the evaluation of the pre- and postoperative anatomy in AAOCA patients. CTOA may be of use in conjunction with the acute angle take-off and ostial diameter order to comprehensively evaluate the operated ostium after unroofing or patch angioplasty.

Introduction

Anomalous aortic origin of coronary arteries (AAOCA) from the opposite sinus of Valsalva is a rare congenital abnormality affecting 0.03-0.1% of the population and involving an abnormal origin and course of a coronary artery [1, 2]. Depending on anatomical and clinical characteristics, some AAOCA variants are associated with an increased risk of ischemia and sudden cardiac death in children and active young adults and are designated malignant [3, 4]. Surgical repair of malignant AAOCA is reported to be safe and effective [4-6]. However, data on long term follow-up is currently lacking and there are remaining concerns on identifying the patients at risk of suboptimal surgical outcomes and long-term complications.

In adults, coronary anatomy can be accurately evaluated using computed tomography angiography (CTA) [7, 8] and CTA is the imaging modality of choice to assess the AAOCA origin and course, degree of luminal narrowing, its relationship to surrounding structures and concomitant obstructive coronary artery disease[9]. The various pathologic aspects of malignant AAOCA all contribute to a significantly reduced functional ostial area of the anomalous coronary artery causing ischemia and potentially lethal arrhythmias. Limited data is available on the role of CTA during follow-up and the expert consensus on AAOCA does not reflect on the role of CTA in the postoperative setting [10]. A number of studies refer to the status of the neo-ostium after surgery[11-15]. However, to our knowledge, no objective

non-invasive method for measuring and quantifying the functional ostium has been established, and the spectrum of application of CTA in the postoperative setting is yet to be fully explored [11, 13, 14, 16]. Given the prominent role of surgery in the adequate management of this often young patient group in need of life long surveillance, it is of interest to know how the (neo-) ostial parameters are effected by the surgical interventions and to correlate this with the clinical outcomes [6].

In this study we compared the pre- and postoperative CTA features of a series of patients who underwent surgical correction of malignant AAOCA and deduce a new CTA derived parameter, the coronary triangulated orifice area (CTOA). The origin and course of the anomalous coronary artery and the ostial dimensions were evaluated and correlated with restenosis of operated coronary artery during follow-up.

Materials and Methods

All consecutive patients (n=54) who underwent surgical repair of AAOCA from the opposite sinus of Valsalva at the Leiden University Medical Center between 2001 to 2018 were reviewed. In that era, postoperative CTA was not a part of routine clinical follow-up and was performed at discretion of the cardiologist. Adolescent and adult patients who had adequate pre- and postoperative CTA imaging available were approached for informed consent and included in further analysis. Patients unable or unwilling to communicate with the research team were excluded. Cases where CTA imaging was of insufficient quality were excluded.

Patient data were collected from the electronic medical file system (EPD-Vision®, Leiden) and included: gender, age, comorbidities (a.o. diabetes, hypertension, previous ischemic coronary artery disease), type of AAOCA (originating from left or right sinus of Valsalva), dominancy of the coronary system, presence of symptoms at diagnosis and at follow-up, diagnostic imaging techniques (CTA, coronary angiography or magnetic resonance imaging (MRI)), the surgical technique used (unroofing or ostioplasty), concomitant procedures, adverse cardiac events at follow-up (re-operation or percutaneous coronary intervention (PCI) on the operated coronary artery). The study focused on medium-term outcomes. Therefore in hospital events in the post-operative setting (< 1 month) were excluded.

Patients were scanned using a 64-row CT scanner (Aquillion64, Toshiba Medical Systems, Otawara, Japan; General Electrics LightSpeed VCT, Milwaukee, WI, USA) or with a 320-row CT scanner (Aquilion ONE, Toshiba Medical Systems) using an ECG-triggered protocol. Before scanning patients' heart rate and blood pressure were monitored. In the absence

of contraindications, patients with a heart rate exceeding 65 b.p.m. received 50-100 mg oral metoprolol, or 5–10 mg metoprolol intravenously. For optimal heart phase selection, retrospective ECG gating was used. CTA images were reviewed with PACS® software and were reconstructed in multiphase data sets. Datasets were reconstructed from the retrospectively gated raw data with an effective slice thickness of 0.5-0.625 mm using standardized window/ level software CTA settings for vascular structures. Coronary artery anatomy was evaluated using the reconstruction dataset with the least motion artefacts, ranging from the end-systolic phase and mid-to end diastolic phase, depending on the heart rate of the patient.

All scans were evaluated by the primary investigator (FMMM), sub-investigator (DBHV) and an experienced radiologist (HJL). Multiplanar reconstructions in the oblique view at

Figure 1. Take-off angles pre-operatively (panel A) and postoperatively (panel B) in obtained in multiplanar reconstructions in the oblique view at the level of the AAOCA ostium, in the same patient. The angle increased from 11.7˚ to 28.7˚.

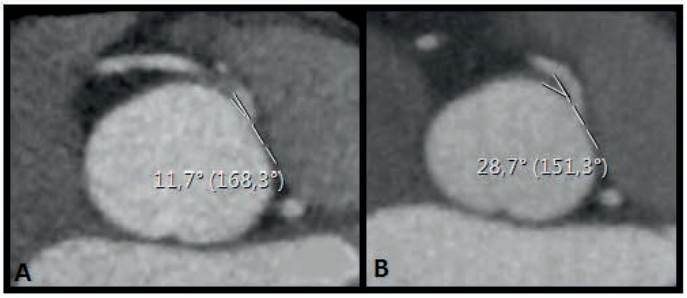
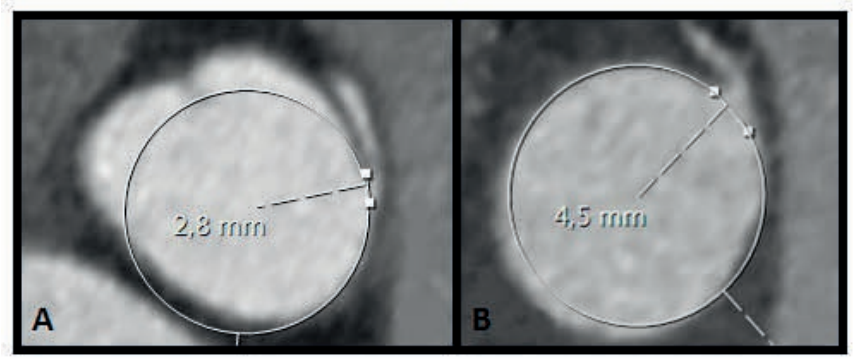
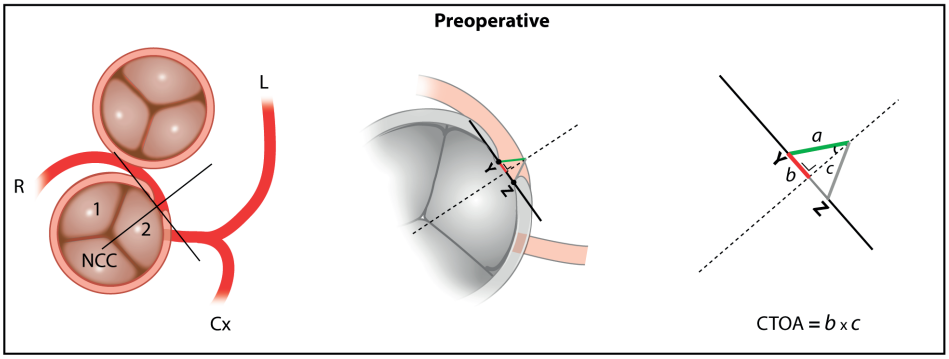


Figure 2. Ostial diameter in the transverse plane pre-operatively (panel A) and postoperatively (panel B) obtained in multiplanar reconstructions in the oblique view at the level of the AAOCA ostium, in the same patient. The ostial diameter increased from 2.8 mm to 4.5 mm.



the level of the AAOCA ostium using the smallest available slice thickness were obtained and assessed for (1) the presence of an acute angle take-off (Figure 1), defined as the angle between the proximal coronary artery and the tangent line to the aortic wall and (2) the ostial diameter of the AAOCA (Figure 2)[17, 18].Since the ostial diameter is a linear parameter and does not take into account the intraluminal depth of the (operated) coronary ostium, it might not fully reflect the functional ostial area of the coronary artery or the benefit attained

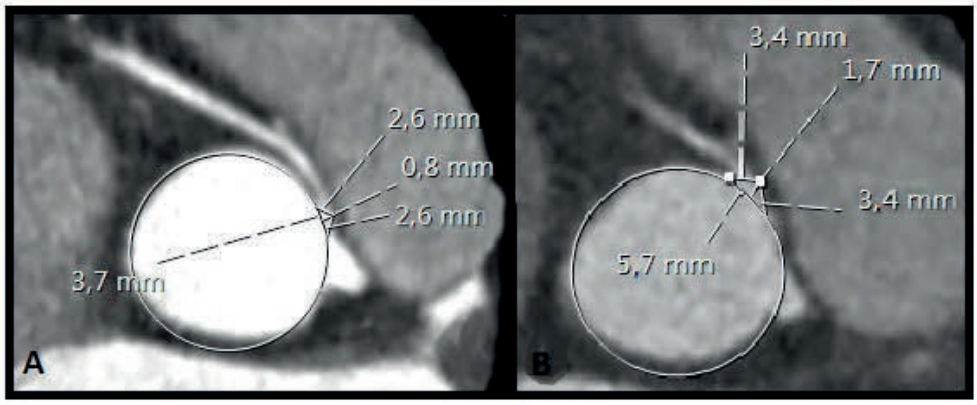
Figure 3 . Schematic representation of the of the coronary triangulated orifice area (CTOA). CTOA = 2 × (½× b × c) = b × c; b = ½ ostial diameter; c = the depth of the triangle measured on CTA. The effective coronary ostial area as measured by the CTOA increases after the surgical correction of the coronary anomaly.
R, right coronary artery; L, left coronary artery; Cx, circumflex coronary artery; NCC, non-coronary cusp; The area of the triangle is formed by 2 equilateral triangles. Y, representing the acute angle the outer edge of the orifice point; Z, representing the end of the ostium of the coronary anomaly; b , the base of the triangle; c, the depth of the triangle.



after surgical correction. This can, in particularly, be the case in patients after surgical patch angioplasty. We therefore deduced the concept of a coronary triangulated ostial area (CTOA) and the methodology of its quantification, which although a 2-dimensional technique, does take into consideration the ostial depth (Figure 3).A step by step guide on how to obtain the necessary reconstructions and measure the CTOA can be found in the online supplement (Supplementary data). In short, a double oblique multiplanar reformation (MPR) reconstruction perpendicular to the aortic valve annulus and parallel to

the ascending aorta should be obtained. Next, the investigator scrolls through the double oblique MPR of the aortic root until the center of the orifice of the AAOCA is encountered. A circle is then projected in the orifice of the AAOCA to define where the vessel wall of the AAOCA takes off from the aorta. Next, a tangent line is drawn from the inner edge of the orifice point "Y" to the opposing end of the ostium "Z". A perpendicular line is placed in the middle of the tangent line which extends to the end of the proximal part of the vessel. Two equilateral triangles are then formed. The area of these 2 triangles combined is the CTOA. The formula that is used to calculate the area of the ostial triangle is: 2 x (½ x b x c), simplified as b x c. In this formula "b" is the length of the base of the triangle (equal to ½ of the ostial diameter obtained in multiplanar reconstructions in the oblique view at the level of the AAOCA ostium) and "c" the depth of the triangle measured on CTA (Figure 3 and 4). To assess the interobserver agreement of CTOA, measurements were repeated by DBHV, blinded to the measurements of FMMM.

Figure 4. Coronary triangulated orifice area (CTOA) pre- and postoperatively in the same patient (panels A and B, respectively). The ostial diameter increased from 3.7 mm to 5.7 mm. The CTOA increased from 1.5 mm² to 4.9 mm².



Statistical Analysis

All statistical analyses were performed using IBM SPSS statistics package V.23 (Armonk, New York, USA). Normally distributed continuous data are displayed as mean ± standard deviation (SD) and non-normally distributed continuous data are displayed as median ± interquartile range [IQR1; IQR3]. Proportions are displayed as numbers (percentages, %). For the comparison of values pre- and postoperatively, paired samples t-tests or Wilcoxon rank-sum tests were used as appropriate. Interobserver agreement was visually assessed by calculation of the mean difference between observed values and constructing the limits of agreement (±1.96 SD of the difference, thus including 95% of measurements) according

to Bland and Altman 19. In addition interobserver agreement was statistically assessed with calculation of intraclass correlation coefficients (ICC). All reported p values were two-sided, and a value of $p < 0.050$ was considered statistically significant.

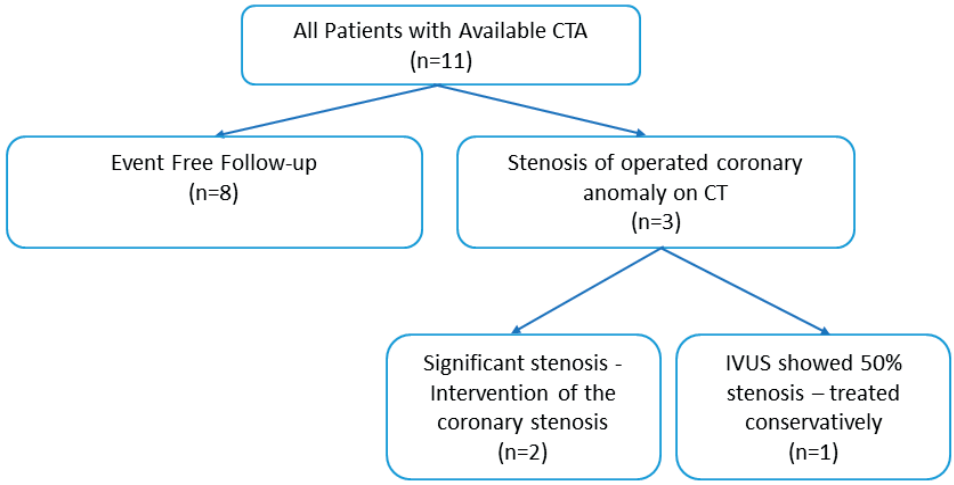
Ethics statement

All tests and procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 2013 Helsinki declaration or comparable ethical standards. Appropriate local scientific board approval was obtained for this retrospective medical record study. All patients provided consent for coded registration, analysis and publication of their data.

Results

Of the 54 consecutive patients, 11 were included for further analysis (Figure 5). Patient characteristics are shown in Table 1. The mean age at surgery was 41 ± 16 years, with 6 patients (55%) being male. Pre-operatively, one patient had an anomalous left coronary artery LCA (patient 5), all other patients had an anomalous RCA. All patients had an interarterial course with the vessel take-off at or above the pulmonic valve commissure, with the artery traversing between the aorta and the right ventricular outflow tract. Nine patients (82%) had a right coronary dominant system. The majority of the patients underwent coronary artery unroofing (82%). Two patients (18%, patient 5 and 11) underwent

Figure 5. Schematic overview of the study cohort and the outcomes.



CTA, computed tomography angiography; IVUS, intravascular ultrasound.

Table 1. Baseline characteristics of the patient cohort described in this study.

Patient characteristics	All patients (n=11)
Male, n (%)	6 (55)
Age at surgery, years, mean (SD)	41 (16)
Diabetes mellitus n (%)	1 (9)
Hypertension n (%)	2 (18)
Previous ischemic coronary artery disease n (%)	0
Hypercholesterolemia n (%)	3 (27)
AAOLCA n (%)	1 (9)
AAORCA n (%)	10 (91)
Right dominant system n (%)	9 (82)
Symptoms present, n (%)	10 (91)
Primary presentation, n (%)	
Suspicion of ischemia	8 (73)
Aborted sudden cardiac death	2 (18)
Incidental finding	1 (9)
Diagnostic imaging techniques, n (%)	-
CTA	11 (100)
CAG	8 (73)
MRI	2 (18)
Interval to follow-up CTA, median months [IQR1; IQR3]	6 [1;27]
Indication for follow-up CTA, n (%)	
Follow-up	4 (36)
Symptoms	
non-anginal complaints	6 (43)

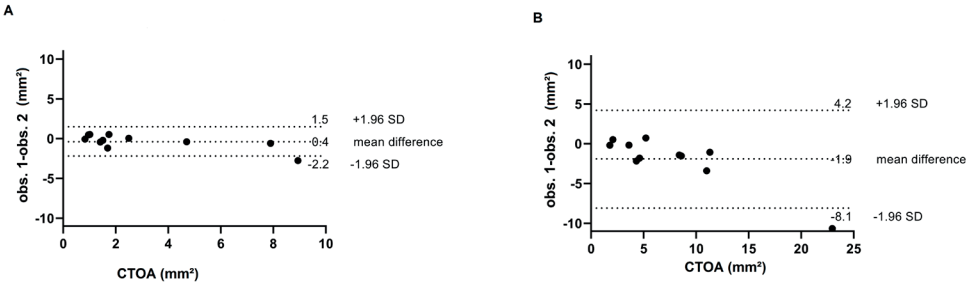
typical complaints	1 (9)
Surgical technique, n (%)	
Unroofing	9 (82)
Ostioplasty	2 (18)
Concomitant procedure, n (%)	
Pulmonary artery patch augmentation	1 (9)

AAOLCA, anomalous aortic origin of the left coronary artery; AAORCA, anomalous aortic origin of the right coronary artery; CAG, coronary angiography; CTA, computed tomographic angiography; IQR, interquartile range; MRI, magnetic resonance imaging; SD, standard deviation.

an enlargement of the ostium with a saphenous vein patch.

The median interval from operation to CTA was 6 months [IQR1;27]. Figure 5 shows a schematic representation of the CTA findings and consequences and Table 2 shows the patient details. The interobserver variability of the CTOA was evaluated. The intraclass correlation coefficient (ICC) for CTOA is good (ICC = 0.947 , p < 0.050 for the preoperative

Figure 6. Bland-Altman plots in (A) the pre-operative and (B) post-operative setting.



The mean value of the CTOA is plotted on the x-axis and the difference between the two observers on the y-axis. The mean differences of all observations are close to zero, indicating no important bias between the two observers.

measurements and ICC 0.874, p < 0.050 for the postoperative measurements). The measurements of both observers are visualized in Bland–Altman plots (Figure 6). This visually confirms that the limits of agreement (dotted lines) of CTOA are acceptable.A restenosis of the operated coronary artery was suspected in 3/11 patients (27%) based on the CTA (patient 3, 7 and 11). This was further evaluated with coronary artery angiography

(CAG) and intravascular ultrasound (IVUS) in all cases. Patient 3 experienced non-anginal complaints and CTA performed 43 months post-operatively suggested an ostial stenosis of the RCA. During CAG a 50% ostial lesion of the RCA was visualized and considered hemodynamically non-significant. The patient was treated conservatively and symptoms resolved. Patient 7 had typical anginal complaints and underwent a CTA that suggested a significant ostial stenosis of the RCA. This was confirmed at CAG with concomitant IVUS evaluation (persistent ostial narrowing after unroofing, visual stenosis of up to 80%, minimum lumen area of proximal RCA 3.3mm2) and the patient underwent a PCI with stent implantation. Patient 11 also underwent a CTA 2 months after surgery due to non-anginal

Table 2. Individual patient characteristics at surgery and follow-up.

Patient	Age at surgery (years)	AAOCA	Surgical technique	Interval to follow-up CTA (months)	Indication for follow-up CTA
1	20-25	RCA	unroofing	6	unknown
2	30-35	RCA	unroofing	<1	post-operative evaluation
3	56-60	RCA	unroofing	43	non-anginal complaints
4	45-50	RCA	unroofing	2	non-anginal complaints
5	10-15	LCA	patch angioplasty	<1	post-operative evaluation
6	25-30	RCA	unroofing	42	non-anginal complaints
7	60-65	RCA	unroofing	13	typical complaints
8	45-50	RCA	unroofing	27	non-anginal complaints
9	55-60	RCA	unroofing	25	non-anginal complaints
10	45-50	RCA	unroofing	1	non-anginal complaints
11	25-30	RCA	patch angioplasty	2	non-anginal complaints

AAOCA, anomalous aortic origin of coronary artery; CTA, computed tomography angiography; LCA, left coronary artery; RCA, right coronary artery.

complaints that revealed an ostial lesion of the RCA. A CAG with IVUS assessment was performed and this revealed an ostial stenosis of (60-70%) and a 70% stenosis distally of the venous patch with minimum lumen area of 3.3 and 3.5 mm2, respectively. This was treated with PCI with implantation of 2 stents (with overlap).A retrospective analysis of the pre- and postoperative CTA characteristics was performed, Table 3. The angle between the proximal coronary artery and the aortic wall significantly increased from 20 ± 5° to 28 ± 9° (p< 0.01) postoperatively. The ostial diameter, significantly increased from 4.1 ± 2.5 mm to 6.2 ± 2.7 mm postoperatively (p<0.01).

Table 3. Pre- and postoperative CTA characteristics

CTA Parameters	Preoperative (n = 11)	Postoperative (n = 11)	p-value
Acute angle take-off (°) mean ± SD	20 ± 5	28 ± 9	<0.001
Ostial diameter (mm) mean ± SD	4.1 ± 2.5	6.2 ± 2.7	<0.001
Coronary triangulated orifice area (mm^2) median [IQR1; IQR3]	1.6 [0.9;4.9]	5.5 [3.7;11.8]	<0.005
No significant stenosis (n=8) [IQR1;IQR3]	2.0 [1.5-7.4]	9.2 [5.4;12.5]	<0.005
≥ 50% stenosis (n=3) [IQR1;IQR2]	0.9 [0.75;0.85]	1.9 [1.81;1.88]	0.011

CTA, computed tomography angiography; IQR interquartile range; SD, standard deviation.

The median CTOA increased significantly from 1.6 mm^2 [IQR 0.9;4.9] to 5.5 mm^2 [IQR 3;11.8] (p<0.005). In every patient there was a consistent increase in CTOA compared to preoperative imaging (Table 3). Interestingly, the 3 patients suspected of a restenosis, based on the follow-up CTA all had an only marginal CTOA increase of ≤ 1.4 mm^2 (Supplementary Table 1).

Discussion

Computed tomography angiography (CTA) is an important tool for evaluation of the pre-

and postoperative anatomy in AAOCA patients. Previously described high-risk findings in coronary artery anomalies include an acute angle take-off of the coronary artery relative to the aorta, an initial aortic intramural course, a 'slit like' coronary artery ostium and coursing of the artery between the aorta and the pulmonary trunk. In this study, we compare several objective CTA parameters before and after surgical correction of AAOCA. To allow an accurate evaluation of the effective orifice area we deduce a new parameter - the coronary triangulated orifice area (CTOA). We evaluate the CTOA and correlate the anatomical features to the postoperative outcome in our patient cohort. The main findings of this study are that after surgical correction, the angle between the proximal coronary artery and the aortic wall and the ostial diameter both increase significantly. The CTOA also shows a significant increase postoperatively. Of interest, in patients with a restenosis of the operated coronary artery, the CTOA only showed a very limited postoperative increase.

CTA is currently one of the preferred techniques to evaluate AAOCA. Guidelines provide a Class I recommendation for either CT or magnetic resonance imaging coronary angiography to be used as the initial evaluation method for coronary anomalies as these techniques have the ability to characterize multiple anatomical features of AAOCA [20]. The AHA/ACC 2018 or the ESC 2020 guidelines, however, do not give guidance on how to use CTA in the postoperative setting of AAOCA [21].

In the literature an acute angle is defined as the angle between the proximal coronary artery and the aortic wall of less than 45° [22, 23]. It is measured as the angle between the plane formed by the ostium center to a point 5 mm along the vessel centerline, and a plane tangent to the aorta in multiplanar axial reconstruction at the level of the AAOCA ostium using the smallest available slice thickness (allowing for highest spatial resolution) [22, 24]. In 2 autopsy studies an acute angle was frequently encountered in patients with AAOCA who presented with sudden cardiac death [25, 26]. In our patient cohort we observed a significant increases in the angle postoperatively from 20 ± 5° to 28 ± 9° ($p<0.01$). According to the current definition, however, the acute angle persisted in all of our patients. This suggests that the finding of an acute angle alone is not reflective of surgical success in a substantial number of patients and cannot as such be predictive of the clinical outcome.

Another parameter used to assess surgical success is shortening of the intramural segment of the AAOCA. Prior research illustrates that there is a high correlation in the use of CTA to identify an intramural course and direct anatomical findings during surgery, and that there is an association with the length of the intramural segment and prognosis of the patients [15, 23, 27]. Histologically, an intramural coronary is defined as an coronary artery

partly sharing the media of the aortic wall with no adventitia interposed [10, 28]. However, this parameter is very hard to accurately delineate on CTA due to the spatial resolution of this technique. For this reason we did not measure the intramural segment in our study. Instead, we opted for measuring the ostial diameter on CTA and calculating the CTOA. This is a geometric derivative of the ostial diameter and ostial luminal depth. In our patient group surgery led to consistent improvement of CTOA from 1.6 mm² [IQR 0.9;4.9] to 5.5 mm² [IQR 3;11.8] ($p<0.005$), respectively. This parameter may be used to objectify the functional increase in the orifice surface area after surgery. This is particularly applicable in patch augmentation techniques and unroofing in which the ostium is widened. In our study 2 patients underwent PCI of the ostial segment of the operated coronary artery during follow-up. Although the mechanism is not entirely elucidated, ostial restenosis may be caused by fibrous scar tissue formation post-operatively [29]. Of interest, in the patients who required PCI during follow-up, the CTOA only showed a very limited postoperative increase of < 1.4 mm² to an absolute CTOA of < 4mm² (Supplementary Table 1). It would be important to evaluate whether there is an absolute minimal ostial area required for preservation of coronary patency in the postoperative setting and whether a (limited) increase in CTOA has any prognostic value.

The majority of patients with high risk features of an AAOCA undergo unroofing, this was also the case with 9 out of 11 patients in the current series. With unroofing the (inside) aortic wall part of the intramural course is removed, creating an expanded ostium. The aim of this treatment is to discard the slit like orifice, acute angle, as well as the intramural course. An alternative method is enlargement of the ostium using a patch. This was performed in 2 patients in our study. Since the ostial diameter is a linear parameter and does not take into account the depth of the (operated) coronary ostium which is widened with unroofing and osteoplasty, it might not fully reflect the surgical benefit, the CTOA does take this depth into account. Our recent work showed that adolescents and adults with AAOCA can present with a wide range of complaints, only 35% of them being classified as 'typical' according to the current criteria. Although surgical correction leads to a reduction of symptoms in the vast majority of patients, novel anginal complaints after surgery should prompt further evaluation for potential lesions of the operated coronary artery and suboptimal surgical outcomes [30]. CTA can play an important role in the initial objective assessment of the post-operative ostium (and systematic comparison of the post-operative result to the preoperative anatomy). One should, however, realize that this is only measured during a fixed phase of the heart cycle, not allowing for the thorough evaluation of the dynamic component of AAOCA. However, the full spectrum of application of CTA in the postoperative setting is yet to be explored and no objective non-invasive method for

measuring and quantifying the ostial area has been established. The current study is one step further to determine the optimal way to non-invasively quantify the coronary orifice area after surgery and correlate this with clinical outcomes and should be technically and clinically validated in the setting of the larger prospective cohort [31].

Limitations and future perspectives

Despite the role of the Leiden University Medical Center as a national referral center for patients with AAOCA, the patient cohort size is small, reflecting the rarity of the condition and the lack of (historical) structural CTA follow-up. Due to the retrospective nature of this study it is subject to inherent bias, including selection bias based on the clinical and anatomical characteristics of patients that were referred for surgery and therefore underwent more extensive preoperative testing and those with postoperative symptoms requiring further analysis and follow-up.

It is important to note that measurement of the CTOA requires strict adherence to a predefined protocol to ensure its reproducibility (particularly when looking to compare the pre- and postoperative anatomy), which may challenge its robust clinical implementation. Also, the accuracy of the CTOA may in practice be limited by the spatial resolution of the CTA. In theory, the highest in-plane spatial resolution achievable approaches 0.4 mm. In practice, coronary artery motion produces both spatial and temporal blurring, resulting in an effective spatial resolution closer to 0.5 mm [32]. The current results, however, do provide us with potentially useful conceptual tools to evaluate surgical outcomes in patients with AAOCA and call for further prospective validation in a larger patient group. The potential of artificial intelligence in automated measurements of CTOA remains to be explored.

One should be aware of the inherent limitations of CTA, predominantly useful when evaluating 'high risk' anatomical features, but lacking the ability to adequately asses the physiological consequences of an AAOCA. In the setting of AAOCA associated ischemia, future research should also take into account the functional (dynamic) consequences of these anatomical features and correlate CTA findings with functional evaluation at rest and during (physical) stress using a.o. intravascular ultrasound and fractional flow reserve assessment [33]. Adrenalin and dobutamine infusions can be used to mimic physical exercise stress (increasing heart rate and stroke volume) according to the previously published protocols [33,34]. Multicenter studies with standardized preoperative and follow-up protocols are essential in this. To this aid a national protocol for evaluation and management of AAOCA patients has recently been initiated as part of the MuSCAT study [31].

References

1. Angelini P, Velasco JA, Flamm S. Coronary anomalies incidence, pathophysiology, and clinical relevance. Circulation. 2002;105(20):2449-54.

2. Yamanaka O, Hobbs RE. Coronary artery anomalies in 126,595 patients undergoing coronary arteriography. Catheterization and cardiovascular diagnosis. 1990;21(1):28-40.

3. Palmieri V, Gervasi S, Bianco M, Cogliani R, Poscolieri B, Cuccaro F, et al. Anomalous origin of coronary arteries from the "wrong" sinus in athletes: Diagnosis and management strategies. International journal of cardiology. 2018;252:13-20.

4. Basso C, Maron BJ, Corrado D, Thiene G. Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes. Journal of the American College of Cardiology. 2000;35(6):1493-501.

5. Frommelt PC, Sheridan DC, Berger S, Frommelt MA, Tweddell JS. Ten-year experience with surgical unroofing of anomalous aortic origin of a coronary artery from the opposite sinus with an interarterial course. The Journal of thoracic and cardiovascular surgery. 2011;142(5):1046-51.

6. Padalino MA, Franchetti N, Hazekamp M, Sojak V, Carrel T, Frigiola A, et al. Surgery for anomalous aortic origin of coronary arteries: a multicentre study from the European Congenital Heart Surgeons Association. European journal of cardio-thoracic surgery. 2019;56(4):696-703.

7. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, et al. Assessment of coronary artery disease by cardiac computed tomography a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation. 2006;114(16):1761-91.

8. van Ooijen PM, Dorgelo J, Zijlstra F, Oudkerk M. Detection, visualization and evaluation of anomalous coronary anatomy on 16-slice multidetector-row CT. European radiology. 2004;14(12):2163-71.

9. Dodd JD, Ferencik M, Liberthson RR, Cury RC, Hoffmann U, Brady TJ, et al. Congenital anomalies of coronary artery origin in adults: 64-MDCT appearance. American Journal of Roentgenology. 2007;188(2):W138-W46.

10. Brothers JA, Frommelt MA, Jaquiss RD, Myerburg RJ, Fraser CD, Tweddell JS. Expert consensus guidelines: anomalous aortic origin of a coronary artery. The Journal of thoracic and cardiovascular surgery. 2017;153(6):1440-57.

11. Cho S-H, Joo H-C, Yoo K-J, Youn Y-N. Anomalous origin of right coronary artery from left coronary sinus: surgical management and clinical result. The Thoracic and cardiovascular surgeon. 2015;63(05):360-6.

12. Kooij M, Vliegen HW, de Graaf MA, Hazekamp MG. Surgical treatment of aberrant aortic origin of coronary arteries. European Journal of Cardio-Thoracic Surgery. 2015:ezu549.

13. Fabozzo A, DiOrio M, Newburger JW, Powell AJ, Liu H, Fynn-Thompson F, et al., editors. Anomalous Aortic Origin of Coronary Arteries: A Single-Center Experience. Seminars in Thoracic and Cardiovascular Surgery; 2016: Elsevier.

14. Sharma V, Burkhart HM, Dearani JA, Suri RM, Daly RC, Park SJ, et al. Surgical unroofing of anomalous

aortic origin of a coronary artery: a single-center experience. The Annals of thoracic surgery. 2014;98(3):941-5.

15. Kaushal S, Backer CL, Popescu AR, Walker BL, Russell HM, Koenig PR, et al. Intramural coronary length correlates with symptoms in patients with anomalous aortic origin of the coronary artery. The Annals of thoracic surgery. 2011;92(3):986-92.

16. Kooij M, Vliegen HW, de Graaf MA, Hazekamp MG. Surgical treatment of aberrant aortic origin of coronary arteries. Eur J Cardiothorac Surg. 2015;48(5):724-30; discussion 30-1.

17. Shriki JE, Shinbane JS, Rashid MA, Hindoyan A, Withey JG, DeFrance A, et al. Identifying, Characterizing, and Classifying Congenital Anomalies of the Coronary Arteries. RadioGraphics. 2012;32(2):453-68.

18. Miller JA, Anavekar NS, El Yaman MM, Burkhart HM, Miller AJ, Julsrud PR. Computed tomographic angiography identification of intramural segments in anomalous coronary arteries with interarterial course. The international journal of cardiovascular imaging. 2012;28(6):1525-32.

19. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. Journal of the Royal Statistical Society: Series D (The Statistician). 1983;32(3):307-17.

20. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2019;73(12):e81-e192.

21. Baumgartner H, De Backer J. The ESC Clinical Practice Guidelines for the Management of Adult Congenital Heart Disease 2020. Eur Heart J. 2020;41(43):4153-4.

22. Nasis A, Machado C, Cameron JD, Troupis JM, Meredith IT, Seneviratne SK. Anatomic characteristics and outcome of adults with coronary arteries arising from an anomalous location detected with coronary computed tomography angiography. The international journal of cardiovascular imaging. 2015;31(1):181-91.

23. Cheezum MK, Ghoshhajra B, Bittencourt MS, Hulten EA, Bhatt A, Mousavi N, et al. Anomalous origin of the coronary artery arising from the opposite sinus: prevalence and outcomes in patients undergoing coronary CTA. European Heart Journal-Cardiovascular Imaging. 2016;18(2):224-35.

24. Zhang L-J, Wu S-Y, Huang W, Zhou C-S, Lu G-M. Anomalous origin of the right coronary artery originating from the left coronary sinus of valsalva with an interarterial course: diagnosis and dynamic evaluation using dual-source computed tomography. Journal of computer assisted tomography. 2009;33(3):348-53.

25. Taylor AJ, Rogan KM, Virmani R. Sudden cardiac death associated with isolated congenital coronary artery anomalies. Journal of the American College of Cardiology. 1992;20(3):640-7.

26. Lipsett J, Cohle S, Berry P, Russell G, Byard R. Anomalous coronary arteries: a multicenter pediatric autopsy study. Pediatric pathology. 1994;14(2):287-300.

27. Ashrafpoor G, Danchin N, Houyel L, Ramadan R, Belli E, Paul J-F. Anatomical criteria of malignancy by computed tomography angiography in patients with anomalous coronary arteries with an interarterial course. European radiology. 2015;25(3):760-6.

28. Gittenberger-de AG, Sauer U, Quaegebeur JJTJot, surgery c. Aortic intramural coronary artery in three hearts with transposition of the great arteries. 1986;91(4):566-71.

29. Nees SN, Flyer JN, Chelliah A, Dayton JD, Touchette L, Kalfa D, et al. Patients with anomalous aortic origin of the coronary artery remain at risk after surgical repair. J Thorac Cardiovasc Surg. 2018;155(6):2554-64 e3.

30. Meijer FMM, Egorova AD, Jongbloed MRM, Koppel C, Habib G, Hazekamp MG, et al. The significance of symptoms before and after surgery for anomalous aortic origin of coronary arteries in adolescents and adults. Interactive Cardiovascular and Thoracic Surgery. 2021;32(1):122-9.

31. Koppel C, Driesen B, de Winter R, van den Bosch A, van Kimmenade R, Wagenaar L, et al. The first multicentre study on coronary anomalies in the Netherlands: MuSCAT. Netherlands Heart Journal. 2021:1-7.

32. Angelini P, Flamm SD. Newer concepts for imaging anomalous aortic origin of the coronary arteries in adults. Catheterization and Cardiovascular Interventions. 2007;69(7):942-54.

33. Bigler MR, Ashraf MA, Seiler C, Praz F, Ueki Y, Windecker S, et al. Hemodynamic relevance of anomalous coronary arteries originating from the opposite sinus of Valsalva-in search of the evidence. Frontiers in cardiovascular medicine. 2020;7:424.

34. Driesen BW, Warmerdam EG, Sieswerda GJT, Schoof PH, Meijboom FJ, Haas F, et al. Anomalous coronary artery originating from the opposite sinus of Valsalva (ACAOS), fractional flow reserve- and intravascular ultrasound- guided management in adult patients. Catheterization and Cardiovascular Interventions. 2018;92(1):68-75.

Supplementary Table 1. CTA characteristics per individual patient

Patient	Ostial diameter pre-operatively (mm)	Ostial diameter post-operatively (mm)	Ostial dept pre-operatively	Ostial dept-post-operatively	Delta ostial diameter (mm)	CTOA pre-operatively (mm2)	CTOA post-operatively (mm2)	Delta CTOA (mm2)	Post-operative CTA findings	CAG and IVUS
1	3.3	6.5	1.5	2.8	3.2	2.5	9.1	6.6	n.a.d.	n/a
2	2.7	5.4	1.2	2.0	2.7	1.6	5.4	3.8	n.a.d.	n/a
3	1.9	2.9	0.9	1.3	1.0	0.9	1.9	1.0	Significant ostial stenosis RCA	Ostium RCA stenosis 50%treated conservatively
4	2.5	6.9	1.3	1.6	4.4	1.6	5.5	3.9	n.a.d.	n/a
5	8.6	11.1	2.4	5.1	2.5	10.3	28.3	18	n.a.d.	n/a
6	4.9	7.7	2.0	3.3	2.8	4.9	12.7	7.8	n.a.d.	n/a
7	3.0	3.3	0.5	1.1	0.3	0.8	1.8	1.0	Significant ostial stenosis RCA	Ostium flattened + treated by PCI + stent
8	9.1	10.3	1.8	2.3	1.2	8.2	11.9	3.7	n.a.d.	n/a
9	1.8	4.8	0.8	3.9	3.0	0.8	9.4	8.6	n.a.d.	n/a
10	3.7	5.7	0.8	1.7	2.0	1.5	4.9	3.4	n.a.d.	n/a
11	3.8	3.9	1.2	1.9	0.1	2.3	3.7	1.4	Significant ostial stenosis RCA	Stenosis proximal and distal to the Patch + treated by PCI + stent

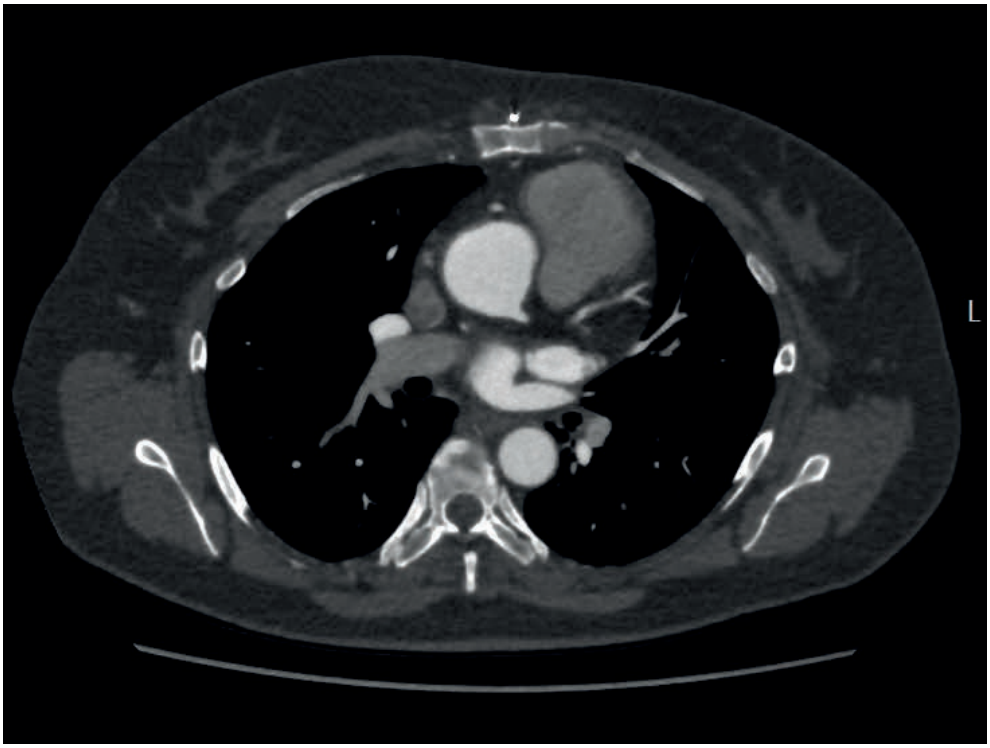
CTOA, coronary triangulated orificel area; n.a.d, no abnormalities detected; n/a, not applicable; CTA, computed tomography angiography; RCA, right coronary artery; CAG, coronary angiography; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention

Supplementary document

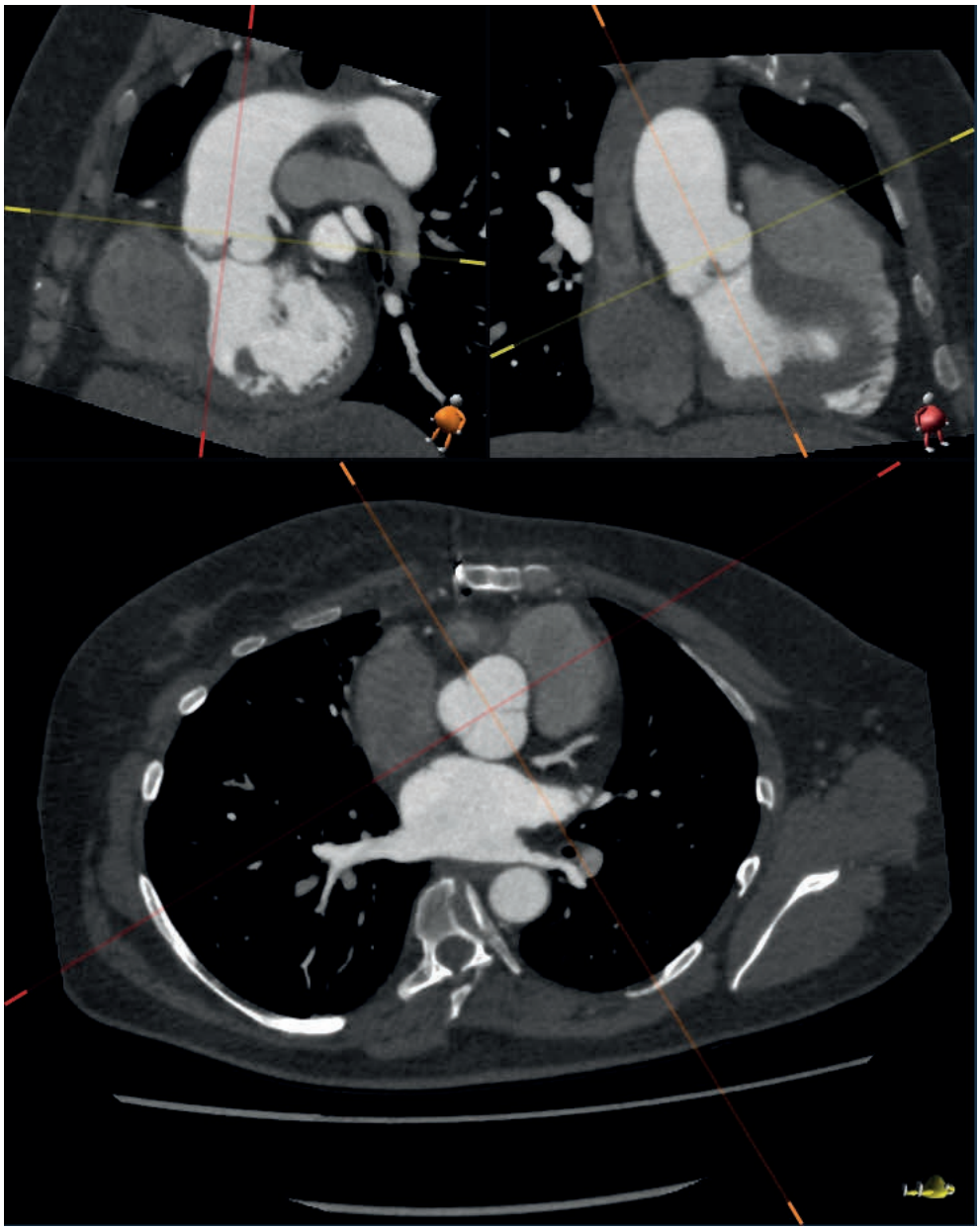
Step by Step Guide to measure CTOA

1. Start in the standard axial plane at the level of the aortic valve annulus (supplementary Figure 1).
2. Perform a double oblique multiplanar reformation (MPR) perpendicular to the aortic valve annulus and parallel to the ascending aorta (supplementary Figure 2).
3. Scroll through the MPR (double oblique, short axis) of the aortic root until the center of the orifice of the AAOCA appears in the plane you are viewing (supplementary Figure 3).
4. Project a circle in the orifice of the AAOCA to define where the vessel wall of the AAOCA takes off from the aorta (supplementary Figure 4).
5. To measure the CTOA, draw a tangent line from the inner edge of the orifice point "Y" to the opposing end of the ostium "Z" (supplementary Figure 5).
6. A perpendicular line is placed in the middle of the tangent line which extends to the end of the proximal part of the vessel. Two equilateral triangles are then formed.
7. The area of these 2 triangles combined is the CTOA. The formula that is used to calculate the area of the ostial triangle is: 2 x (½ x b x c), simplified as b x c, where "b" is the length of the base of the triangle and "c" the depth of the triangle.

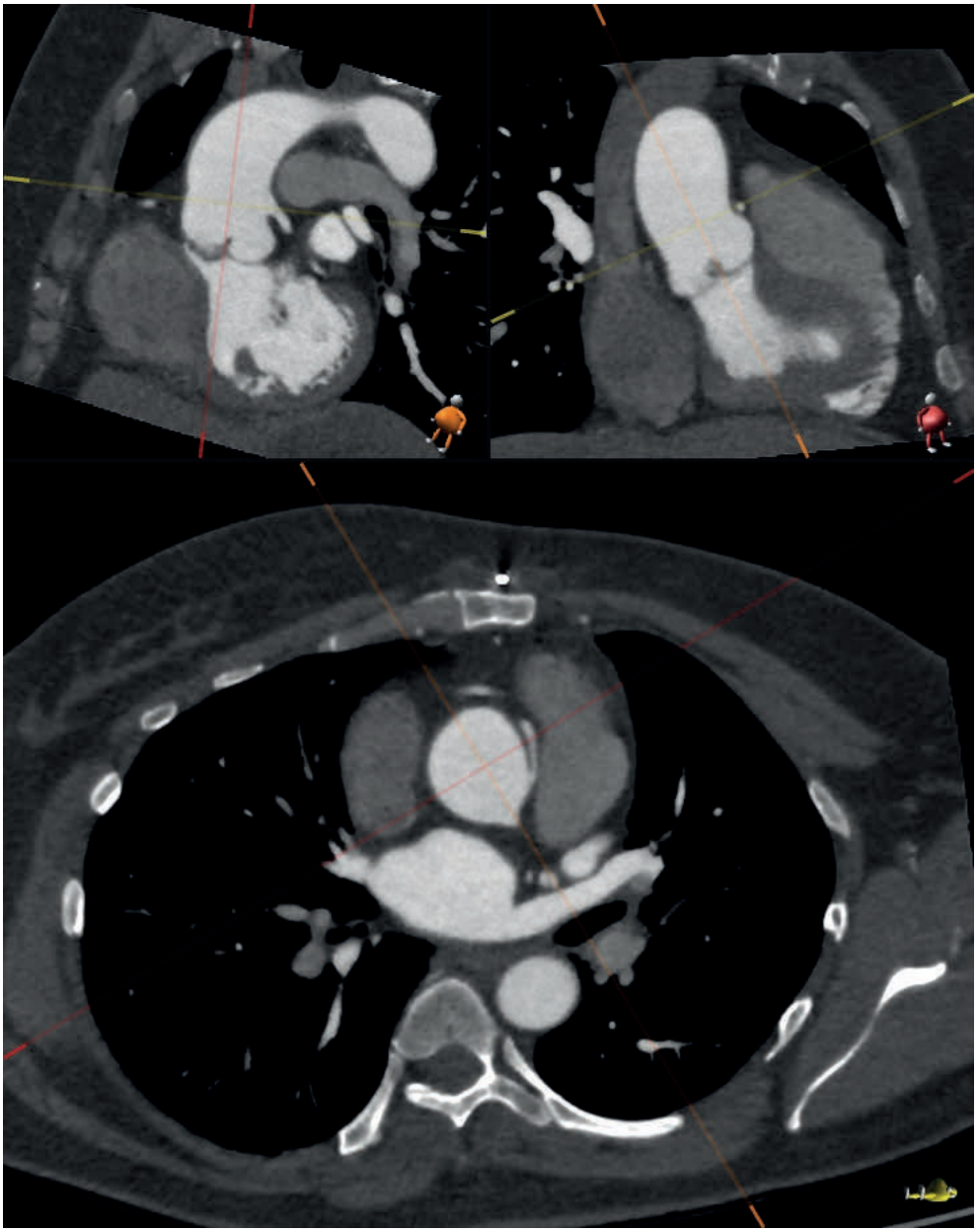
Supplementary Figure 1. Step 1



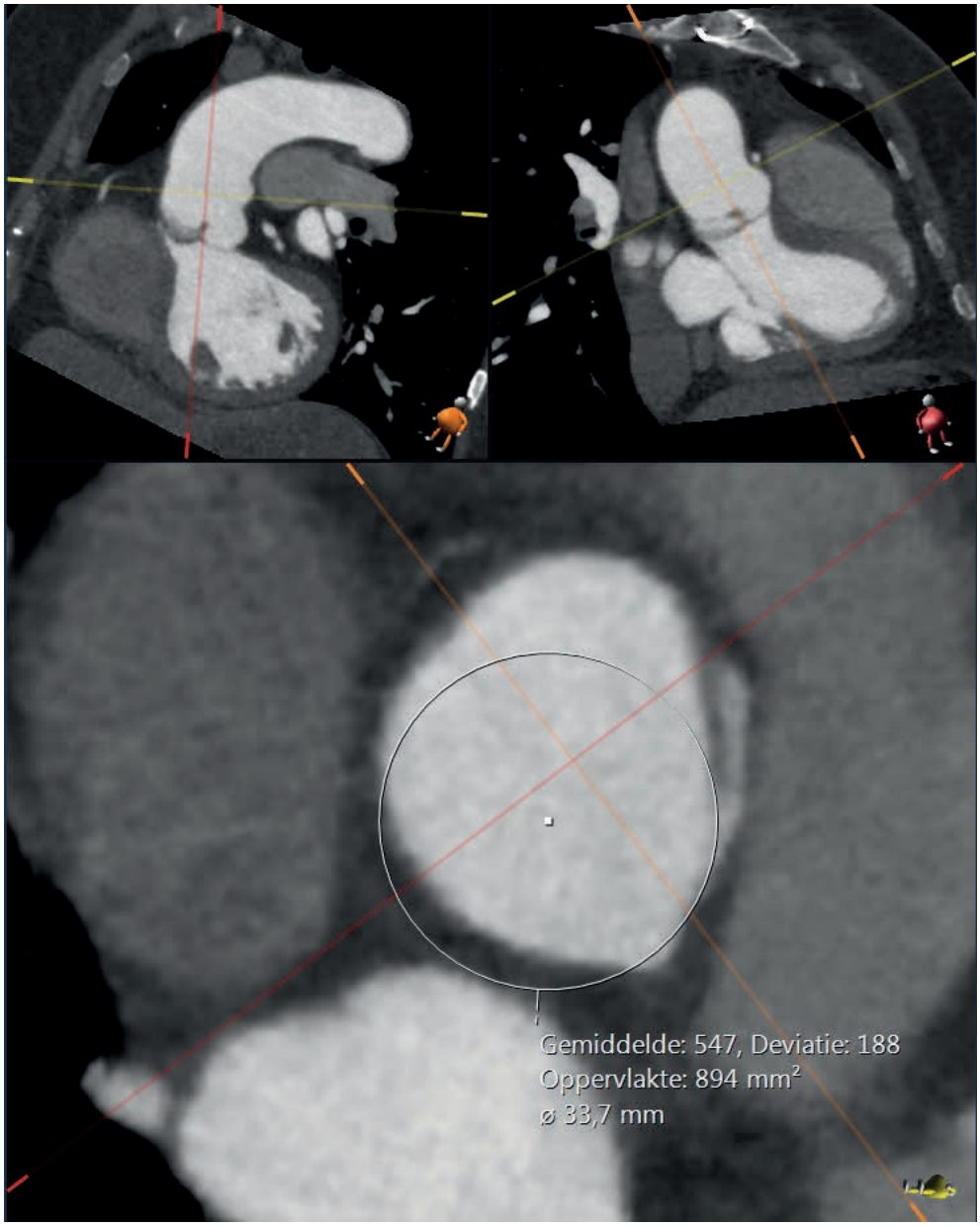
Supplementary Figure 2. Step 2



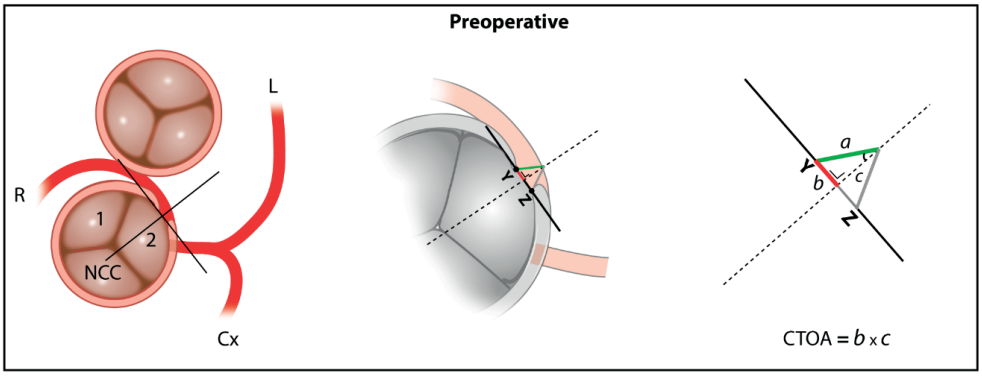
Supplementary Figure 3. Step 3

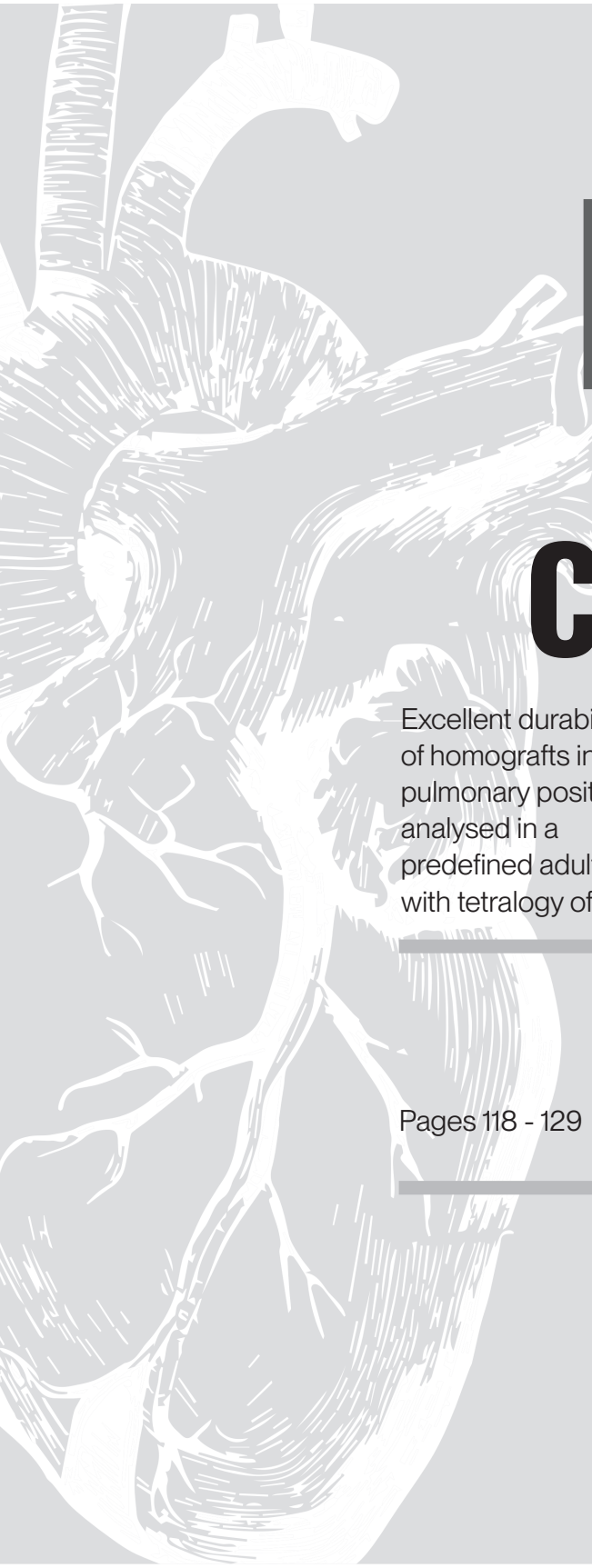


Supplementary Figure 4. Step 4



Supplementary Figure 5. Step 5-7





CHAPTER 7

Excellent durability of homografts in pulmonary position analysed in a predefined adult group with tetralogy of Fallot

EXCELLENT DURABILITY OF HOMOGRAFTS IN PULMONARY POSITION ANALYSED IN A PREDEFINED ADULT GROUP WITH TETRALOGY OF FALLOT

F.M.M. Meijer, P. Kiès, M.R.M. Jongbloed, M.G. Hazekamp, D.R. Koolbergen, N.A. Blom, A. de Roos, M.J. Schalij, H.W. Vliegen

Interactive CardioVascular and Thoracic Surgery. 2019; 28: 279-283

ABSTRACT

Objectives

In a repaired tetralogy of Fallot, surgical pulmonary valve replacement (PVR) is in certain cases required. Our institution reported earlier about 26 patients who received a pulmonary homograft via PVR. To date, we have data from more than 17 years of follow-up. The aim of this retrospective study was to evaluate the late haemodynamic and clinical outcomes in this predefined patient group.

Methods

Between 1993 and 2001, 26 patients underwent PVR for pulmonary regurgitation (58% men; 30.4±8.9 years). The rates of mortality and of complications (re-PVR, ablation and cardioverter defibrillator implants) were analysed. Other main study outcomes were haemodynamic parameters determined from cardiovascular magnetic resonance imaging: pulmonary regurgitation; right ventricular (RV) end diastolic volume; RV ejection fraction; left ventricular end diastolic volume; left ventricular ejection fraction; New York Heart Association functional class at the latest follow-up visit; and echocardiographic parameters of the right ventricle.

Results

The median follow-up time was 17±1.1 years. Overall freedom from complications was 61.5% (95% confidence interval: 47.5-78.6%). One patient died 18 months after surgery of unknown causes. Two patients needed replacement of the homograft at 24 and 39 months

after PVR. The indication in both patients was recurrence of severe homograft regurgitation with important RV dilatation. Six patients received an implantable cardioverter defibrillator at a median age of 41 years (interquartile range, 36-47); 12 patients experienced supra- and/or ventricular arrhythmias and 6 of these needed ablation. There was no significant deterioration of haemodynamic function or functional class.

Conclusions

The patients who underwent PVR exhibited long-term follow-up stabilization of RV function and impressive functional durability of the graft. After a follow-up of 17 years, 23 out of 26 patients (89%) were alive without redo PVR. Event-free survival was good (61.5%).

Introduction

Tetralogy of Fallot (TOF) is the most common type of cyanotic congenital heart disease [2]. Advanced surgical techniques have drastically increased the survival rate of this patient group and have led to an increasing prevalence of adult survivors of TOF repair. These adult patients are prone to develop severe pulmonary regurgitation, which may lead to volume overload, right ventricular dilatation, heart failure, arrhythmias and/or death [3-6]. Eventually, most of these patients require pulmonary valve replacement (PVR). Initially there was great concern about the durability of a pulmonary homograft. Today, there is a large group of patients with a repaired TOF who underwent PVR, and more clinical data are available. In 2002, Vliegen et al. reported 26 patients who received a pulmonary homograft via a PVR: To date, we have data from more than 17 years of follow-up [7]. The aim of this retrospective study was to evaluate clinical outcomes and late hemodynamics in this predefined patient group.

Patients and Methods

Between 1993 and 2001, 26 patients underwent PVR with a cryopreserved pulmonary homograft for pulmonary regurgitation (PR) (58% men; 30.4±8.9 years). Homografts were inserted in the orthotopic pulmonary position with 1 proximal and 1 distal end-to-end running suture after longitudinally opening the proximal pulmonary artery and slightly extending this incision if necessary across the former pulmonary annulus. Calcified outflow tract patch material was resected as much as possible. The medical records of all patients were reviewed. Cardiovascular magnetic resonance (CMR) imaging was executed as previously described [7] and was performed in 19 patients at least 9.5 years after PVR with a median of 130 months (interquartile range [IQR], 86-196).

Primary study outcomes were mortality rate, redo PVR, ablation and use of an implantable

cardioverter defibrillator (ICD). Moreover, hemodynamic parameters determined with cardiovascular magnetic resonance imaging at the latest follow-up visit were analysed: pulmonary regurgitation (PR) fraction; right ventricular end-diastolic volume; RV ejection fraction; left ventricular end diastolic volume; and left ventricular ejection fraction. The volume parameters were indexed for body surface area. Echocardiographic parameters were also evaluated: maximum gradient over the pulmonary valve, presence of pulmonary regurgitation (PR) and presence of tricuspid regurgitation. PR was defined as mild when the PR fraction was below 20%, moderate when the PR fraction was between 20% and 40% and severe when the fraction was > 40%.

Statistical analyses

Results are expressed as mean ± standard deviation, number with frequencies and percentages or median with IQR. Comparisons between postoperative and late follow-up data were performed with the paired Student t-tests. Values of $p < 0.05$ were considered to be statistically significant. Event-free survival was analysed using the Kaplan-Meier method with 95% confidence intervals.

Results

Table 1 lists the personal and surgical characteristics of those patients who had pulmonary valve replacement. The median follow-up time was 17±1.1 years. In Table 2, the preoperative, early postoperative and late follow-up parameters are shown. The latest cardiac MRI was performed at a median of 130 (IQR 86 -196) months after PVR. Not every patient operated on received a follow-up MRI due to ICD implantation. Haemodynamic RV- and LV function remained stable over time; the same applies to RV volume. Only the PR fraction had mildly but significantly increased ($p = 0.028$) from 3.7% to 8% (both in the range of mild PR). Echocardiograms confirmed the excellent durability of the graft; 89% had none to mild pulmonary regurgitation at the latest follow-up. Moreover, there was no deterioration of NYHA functional class. There were no symptoms of endocarditis documented. Overall event-free survival (no death, ablation, ICD insertion or redo surgery) was 61.5% (95% confidence interval: 47.5-78.6%) after 18 years (Fig. 1). One patient died unexpectedly 18 months after surgery; no autopsy was performed. This patient had a good validity of 98% on an exercise test 9 months prior to death; no other details are known. Two patients needed redo surgery of the homograft at 24 and 39 months after PVR. The indication for redo surgery in the first patient was the recurrence of severe pulmonary homograft regurgitation in combination with serious right ventricular dilatation. This patient received a surgical Contegra conduit and reconstruction of the right ventricular outflow tract. The other patient received a percutaneous Edward Sapiens prosthesis due to recurrence

of severe pulmonary homograft regurgitation. Twelve patients experienced arrhythmias (supraventricular or ventricular), and 6 of them needed 1 or more ablations. Six patients received an ICD at a median age of 41 (interquartile range, 36-47) (Table 3); freedom from ICD implantation was 77% at 12 years (Fig. 1). In all cases, the indication for an ICD was secondary prevention of ventricular tachycardias.

Table 1: Demographic and Surgical Characteristics

Number of patients	26
Male, n (%)	15 (58)
Age at initial correction, years (years) (n,%)	5 ± 4.2
Initial surgical correction/type of RVOT reconstruction at initial correction	
Total correction (n,%)	12 (46.2)
Myectomy/valvulotomy (n,%)	5 (19)
Right ventricle patch (n,%)	1 (3.8)
Transannular patch (n,%)	10 (38.5)
Unknown (n,%)	10 (38.5)
Previous shunt procedure	
Waterston (n,%)	3 (11.5)
Blalock-Taussig (n,%)	8 (30.8)
Potts anastomosis (n,%)	1 (3.8)
Hancock conduit (n,%)	1 (3.8)
Unknown (n,%)	1 (3.8)
Surgical PVR (n,%)	
Age at PVR, years (mean, SD)	30.4 ± 8.9
Concomitant procedures	
Resection infundibulum (n,%)	1 (3.8)
Tricuspid valve repair (n,%)	4 (11.5)
Closure VSD (n,%)	4 (15.4)
Closure of atrial septal defect & tricuspid valve repair (n,%)	1 (3.8)
Xenopericardial reconstruction (n,%)	3 (11.5)
No additional procedure (n,%)	14 (53.8)

Data are expressed as number of patients (%), mean with SD, median with IQR and mean with minimum and maximum. ICD: implantable cardioverter defibrillator; IQR: interquartile range; PVR: pulmonary valve replacement; SD: standard deviation.

Table 2. Preoperative, early postoperative and late follow-up parameters

	Before PVR	Early after PVR	Late Follow up	Δ Post - late follow-up	p-value Post – late follow-up
CMR	n = 25	n = 25	n = 19		
Time, CMR from PVR (months)	-4.5(-7 – -3)	10 (8 – 16)	130 (86 – 196)		
PR fraction (%)*	46 ± 11	3.7 ± 6.8	8 ± 9	4 ± 10	0.028
RV EDV (mL)*	302 ± 60	207 ± 69	212 ± 67	-6 ± 30	0.46
RV EDV-I (mL/m²)	163 ± 33	115 ± 40	111 ± 35	-9 ± 17	0.09
RV ESV (mL)*	177 ± 53	120 ± 65	115 ± 59	-14 ± 34	0.3
RV ESV-I (mL/m²)	97 ± 36	67 ± 41	60 ± 32	-11 ± 20	0.06
RV EF (%)*	43 ± 11	44 ± 11	46 ± 10	2 ± 7	0.47
LV EDV (mL)*	145 ± 40	152 ± 34	156 ± 44	5 ± 34	0.53
LV EDV-I (mL/m²)	80 ± 23	83 ± 15	85 ± 17	-1 ± 19	0.8
LV ESV (mL)*	64 ± 32	68 ± 19	76 ± 26	6 ± 19	0.41
LV ESV-I (mL/m²)	36 ± 18	37± 9	41 ± 12	1 ± 10	0.9
LV EF (%)*	55 ± 14	56 ± 8	55 ± 7	-1 ± 8	0.94
NYHA					
NYHA class	3.0 ± 0.2	1.3 ± 0.5	1.1 ± 0.3		
Echo	n = 25		n = 25		
Time, echo from PVR (months)	-10 (-11.5 – -3.5)		187 (183–207)		
PV max. gradient (mmHg)	27 ± 26		19 ± 13		
PR present (%)					
Severe (grade 4)	66		0		
Moderate-severe (grade 3)	31		0		
Moderate (grade 2)	0		8		
Mild (grade 1)	0		89		
TR present (%)					
Moderate/severe	85		20		

None/mild	15		80		
Residual lesions	0		0		

Data were described as median with interquartile range and mean with standard deviation. Δ post – Late follow-up, change between early after PVR and late follow-up; P-value, significance level between early and late follow-up. *Was not measured in all patients. PVR: pulmonary valve replacement;CMR: cardiovascular magnetic resonance; PR: pulmonary regurgitation; RV: right ventricle; EDV: end diastolic volume; I: indexed for body surface area; ESV: end-systolic volume; EF: ejection fraction; LV: left ventricle; NYHA: New York Heart Association; PR: pulmonary regurgitation; TR: tricuspid regurgitation.

Table 3. Clinical events after pulmonary valve replacement

Total follow-up (years)	17 (1.1)
Deaths (%)	1 (3.8)
Arrhythmias (%)	12 (46.2)
Ablation performed (%)	6 (23.1)
ICDs	6 (23.1)
Age at ICD insertion (years) (IQR)	41 (36: 47)
Time from PVR to ICD insertion (years) (IQR)	7.1 (4:11)
ICD shocks	2 (7.7)
Redo PVR (%)	2 (8)
Time from PVR to redo PVR (months) (min, max)	32 (24 to 39)

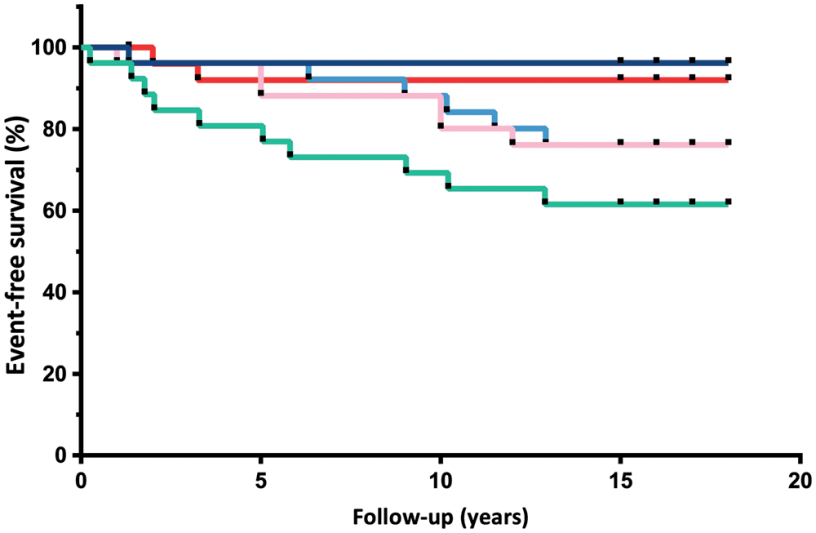
Data are expressed as number of patients (%), mean with SD, median with IQR and mean with minimum and maximum. ICD: implantable cardioverter defibrillator; IQR: interquartile range; PVR: pulmonary valve replacement; SD: standard deviation

Discussion

In this update of a previous study,[7] we evaluated the long-term hemodynamic and clinical outcomes of previously corrected patients with TOF. The present study demonstrates a stabilization of RV function and impressive durability of the pulmonary homograft. Furthermore, there was good event-free survival.

PVR has been advocated to reduce RV volume overload, thereby improving RV performance and decreasing the risk of sudden death and ventricular failure. One patient who needed redo PVR had relatively early severe homograft regurgitation in combination with serious right ventricular dilatation. There is a vicious circle between PR, RV dilatation and tricuspid regurgitation that results in deterioration of RV function and the rapid development of symptoms [8, 9]. One of the mechanisms underlying PR of the homograft is this dilatation of

Figure 1. Event-free survival after pulmonary valve replacement. Patient who died was excluded from the analysis.



Number at risk

Death	26	25	25	25
Redo PVR	26	23	23	23
Ablation performed	26	23	21	19
ICD implantation	26	24	22	19
Combined endpoints	26	20	16	11

the RV. It has been suggested that including resection of a right ventricular outflow tract aneurysm during pulmonary valve surgery will result in improved RV mechanics [10]. In this patient, no additional RV resection was done during the initial PVR operation. In retrospect, it might have been better to include right ventricular outflow tract reconstruction at the time of the PVR. In later patients, this procedure became the routine in our centre. In contrast, Geva et al.[11] performed a randomized controlled trial and concluded that there was no benefit from RV remodeling. However, the postoperative evaluation was done 6 months after surgery, which could be too early to detect changes.

Timing of the pulmonary valve replacement

We recognize that the indications for PVR are a matter of debate, especially in patients

who are asymptomatic. RV deterioration can be irreversible if PVR is performed too late [4, 12]. A recent study from our group stated that preoperative RV end-systolic volume (ESV) is superior to RV end diastolic volume and RV ejection fraction in predicting mid-to-late RV normalization. In the same study, half of the patients operated on with preoperative RV ESV > 95 ml/m² had a suboptimal mid-to-late outcome, whereas in patients operated on when preoperative RV ESV was 80-95 ml/m², a suboptimal mid-to-late outcome was unlikely. The present study demonstrates reverse remodeling to some extent, especially in the early stages after the PVR. In the longer term, there is stabilization of the remodeling. This result underlines the fact that intensive monitoring of this patient group is necessary to detect sudden deterioration and prevent the "point of no return".

Durability of the homograft

In our group, there was excellent durability of the homograft with an 88% freedom from redo PVR or death after a mean of 17 years (Fig. 1). In addition, none of the patients met the criteria of echocardiographically measured moderate to severe pulmonary regurgitation at the latest follow-up visit. In the literature, long-term (>10 years) analysis is lacking [13]. The 10-year freedom from redo PVR in other reports ranges from 69% to 85% [13-16]. An explanation for the varying numbers in previous studies could be that the other groups comprise a mix of adults and children. Children are susceptible to earlier reoperation due to increased somatic growth and accelerated valve degeneration.

Event-Free Survival

Event-free survival (no deaths, ablation, ICDs or redo PVR in the overall group) was 61.5% after 18 years. Although long-term results for PVR are good, this finding is not surprising because a substantial number of patients still have adverse events during the follow-up period. Almost half of the patients (46.2%) developed arrhythmias. Gengsakul et al.[17] and Harrild et al.[18] found no significant improvement in the frequency of arrhythmias after PVR whereas Lee et al.[19] and Thierrien et al.[20] reported a reduction, in combination with antiarrhythmic surgery during PVR. The latter is done more frequently nowadays.

Limitations

The current study is retrospective; the results are influenced by this study design, in terms of missing data, and there was no structured follow-up protocol. Therefore the magnetic resonance images (MRI), echocardiograms and clinical parameters are not measured on exactly the same time points. In terms of selection bias, the patients who had available MRI data may have had a better overall outcome because they did not receive an ICD. The small sample size is another limitation of our study. However, the study comprises a group

that was defined 17 years ago and has been followed for 17 years.

Conclusion

In 2002, Vliegen et al.[7] described a remarkable early postoperative hemodynamic improvement after PVR in patients with TOF who had a total correction. This follow-up study of the predefined group showed at 17.1 years of follow-up stabilization of RV function and impressive functional durability of the graft. Event-free survival was good (61.5%).

Acknowledgments

We thank all participating patients.

References

1. Full Issue PDF. Journal of the American College of Cardiology. 2018;71:A1-A2675.

2. Hoffman JI and Kaplan S. The incidence of congenital heart disease. Journal of the American college of cardiology. 2002;39:1890-1900.

3. Knauth Meadows A, Ordovas K, Higgins CB and Reddy GP. Magnetic resonance imaging in the adult with congenital heart disease. Seminars in roentgenology. 2008;43:246-258.

4. Therrien J, Siu SC, McLaughlin PR, Liu PP, Williams WG and Webb GD. Pulmonary valve replacement in adults late after repair of tetralogy of Fallot: are we operating too late? Journal of the American College of Cardiology. 2000;36:1670-1675.

5. Wald RM, Lyseggen E, Oechslin EN, Webb GD and Silversides CK. Variability in surgical referral patterns for pulmonary valve replacement in adults with repaired tetralogy of Fallot. Congenital heart disease. 2009;4:231-238.

6. Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W and Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. Journal of the American College of Cardiology. 1997;30:1374-1383.

7. Vliegen HW, van Straten A, de Roos A, Roest AA, Schoof PH, Zwinderman AH, Ottenkamp J, van der Wall EE and Hazekamp MG. Magnetic resonance imaging to assess the hemodynamic effects of pulmonary valve replacement in adults late after repair of tetralogy of Fallot. Circulation. 2002;106:1703-1707.

8. Shaher RM, Foster E, Farina M, Spooner E, Sheikh F and Alley R. Right heart reconstruction following repair of tetralogy of Fallot. The Annals of thoracic surgery. 1983;35:421-426.

9. Misbach GA, Turley K and Ebert PA. Pulmonary valve replacement for regurgitation after repair of tetralogy of Fallot. The Annals of thoracic surgery. 1983;36:684-691.

10. del Nido PJ. Surgical Management of Right Ventricular Dysfunction Late After Repair of Tetralogy of Fallot: Right Ventricular Remodeling Surgery. Seminars in Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual. 2006;9:29-34.

11. Geva T, Gauvreau K, Powell AJ, Cecchin F, Rhodes J, Geva J and del Nido P. Randomized trial of pulmonary valve replacement with and without right ventricular remodeling surgery. Circulation. 2010;122:S201-S208.

12. Oosterhof T, van Straten A, Vliegen HW, Meijboom FJ, van Dijk AP, Spijkerboer AM, Bouma BJ, Zwinderman AH, Hazekamp MG and de Roos A. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation. 2007;116:545-551.

13. Cavalcanti PEF, Sá MPBO, Santos CA, Esmeraldo IM, de Escobar RR, de Menezes AM, de Azevedo OM, de Vasconcelos Silva FP, de Albuquerque Lins RF and de Carvalho Lima R. Pulmonary valve replacement after operative repair of tetralogy of Fallot: meta-analysis and meta-regression of 3,118 patients from 48 studies. Journal of the American College of Cardiology. 2013;62:2227-2243.

14. Boethig D, Goerler H, Westhoff-Bleck M, Ono M, Daiber A, Haverich A and Breymann T. Evaluation

of 188 consecutive homografts implanted in pulmonary position after 20 years. European Journal of Cardio-Thoracic Surgery. 2007;32:133-142.

15. Christenson JT, Sierra J, Colina Manzano NE, Jolou J, Beghetti M and Kalangos A. Homografts and Xenografts for Right Ventricular Outflow Tract Reconstruction: Long-Term Results. The Annals of Thoracic Surgery. 2010;90:1287-1293.

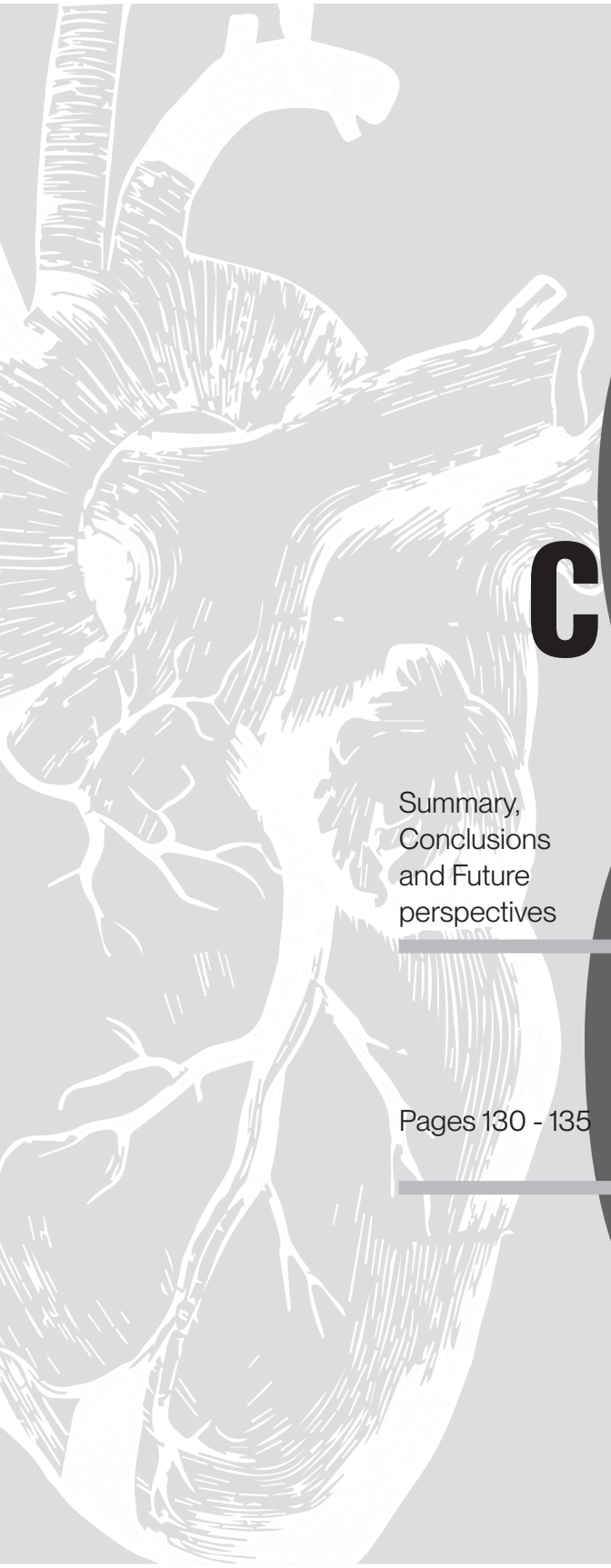
16. Brown JW, Ruzmetov M, Rodefeld MD, Eltayeb O, Yurdakok O and Turrentine MW. Contegra Versus Pulmonary Homografts for Right Ventricular Outflow Tract Reconstruction: A Ten-Year Single-Institution Comparison. World Journal for Pediatric and Congenital Heart Surgery. 2011;2:541-549.

17. Gengsakul A, Harris L, Bradley TJ, Webb GD, Williams WG, Siu SC, Merchant N and McCrindle BW. The impact of pulmonary valve replacement after tetralogy of Fallot repair: a matched comparison. European Journal of Cardio-Thoracic Surgery. 2007;32:462-468.

18. Harrild DM, Berul CI, Cecchin F, Geva T, Gauvreau K, Pigula F and Walsh EP. Pulmonary valve replacement in tetralogy of Fallot. Circulation. 2009;119:445-451.

19. Lee C, Kim YM, Lee C-H, Kwak JG, Park CS, Song JY, Shim W-S, Choi EY, Lee SY and Baek JS. Outcomes of Pulmonary Valve Replacement in 170 Patients With Chronic Pulmonary Regurgitation After Relief of Right Ventricular Outflow Tract Obstruction: Implications for Optimal Timing of Pulmonary Valve Replacement. Journal of the American College of Cardiology. 2012;60:1005-1014.

20. Therrien J, Siu S, Harris L, Dore A, Niwa K, Janousek J, Williams W, Webb G and Gatzoulis M. Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of Fallot. Circulation. 2001;103:2489-2494.



CHAPTER 8

Summary, Conclusions and Future perspectives

Pages 130 - 135

Summary, Conclusions and Future Perspectives

The goal of this thesis is to gain a better understanding of the diagnosis and follow-up of patients with systemic sclerosis (SSc), pulmonary embolisms (PE), Tetralogy of Fallot (TOF), and anomalous coronary arteries, with the goal of preventing disease progression and complications and thus improving prognosis. Chapter 1 gives background information on the pathophysiology of pulmonary hypertension (PH) and highlights the distinction between PH and pulmonary arterial hypertension (PAH). A wide variety of clinical conditions can cause PH. Based on their pathogenic, pathophysiological, and therapeutic characteristics, five groups are defined. PAH (group 1) is a well-known complication of, amongst others, congenital heart disease (CHD) and SSc. Likewise, patients with pulmonary embolisms get PH (group 4). As a consequence, in these patients, the right ventricle (RV) adjusts itself to these elevated pulmonary pressures, and eventually this may lead to RV failure. Unfortunately, despite the development of treatment methods, PH remains a progressive disease with high morbidity and mortality. Therefore, screening and follow-up in patients with PH is crucial. Early detection results in early treatment and a deceleration of disease progression. The ECG derived ventricular gradient (VG), when projected in the optimal direction for detection of RV pressure overload (VG-RVPO), has introduced new possibilities in evaluating PH.

The necessity of follow-up in congenital cardiac disease, patients with anomalous aortic origin of a coronary artery from the opposite sinus (AAOCA), and patients with Tetralogy of Fallot cannot be overstated. Coronary anomalies are uncommon and patient presentation varies widely. Management depends, among others, on the clinical presentation and anatomy. Limited follow-up data is available for patients with AAOCA and there are still numerous knowledge gaps concerning the evaluation and management of these patients. In patients with Tetralogy of Fallot, deterioration of the pulmonary valve may occur due to previous surgery. These patients require one or more pulmonary valve replacements during their lifetime. Durability research remains a topic for these new valves.

Part 1 of this thesis examines the use of the VG-RVPO in patients with (suspected) PAH. The goal of the study presented in Chapter 2 was to evaluate the VG-RVPO as a screening and monitoring tool for early PAH in SSc patients. Because the LUMC uses a specialized care path to evaluate patients with SSc, serial electrocardiograms (ECGs) and transthoracic echocardiograms (TTEs) of these patients were available. TTE, on the other hand, is a time-consuming and relatively expensive screening tool. The ECGs and TTEs of patients with PAH (as determined by right heart catheterization) (RHC) were studied retrospectively. The changes in pulmonary arterial pressure measured with TTE and VG-RVPO over time

in PAH patients versus non-PAH patients were investigated. The results show that the VG-RVPO was significantly higher in PAH patients than in non-PAH patients. Furthermore, in patients with PH, the VG-RVPO increased over time compared to patients without PAH. Furthermore, when compared to the TTE, the VG was more sensitive to detecting disease progression in earlier stages of the disease. As a result of this study, serial measurements of the VG-RVPO, which are easily applicable and inexpensive, can be used as a follow-up instrument to detect early changes in right ventricular pressure over time. The role of the VG-RVPO in improving the efficiency of the YEARS algorithm was investigated in Chapter 3. The YEARS algorithm is a validated tool for ruling out PE in a large number of patients, thereby eliminating the need for computed tomography pulmonary angiography (CTPA). Approximately half of the patients needed to be referred for CTPA. In patients with PE, PH can occur, resulting in RV pressure overload. The VG-RVPO has already been shown to detect PH in various patient groups. We hypothesized that VG-RVPO could improve the YEARS algorithm's efficiency even further.

We measured VG-RVPO in patients with suspected PE who were managed using the YEARS algorithm and evaluated the diagnostic value of VG-RVPO for PE as well as the added diagnostic value of VG-RVPO to the YEARS algorithm. 479 ECGs were examined. However, neither as a stand-alone diagnostic test nor when combined with the YEARS algorithm, the VG-RVPO had any diagnostic value for suspected acute PE. This can be explained by the VG-low RVPO's sensitivity, as not all PEs cause RV pressure overload. In chapter four, we investigated the accuracy of VG-RVPO in estimating the presence and severity of acute right ventricular pressure overload, as well as the prognostic value of an abnormal VG-RVPO in PE patients. This was accomplished by comparing CTPA assessed RV/LV ratios and VG-RVPO to the occurrence of early adverse events. In patients with PE, PH causes RV pressure overload, which results in RV dilation. Because this alters the RV/LV ratio, this measurement can be used to detect PE and is currently used for risk stratification. The VG-RVPO has been shown to be effective in a heterogeneous group of patients with suspected PH, but it is limited in the setting of suspected acute PE. There was an association between VG-RVPO and RV overload as measured by CTPA, but this was not associated with poor adverse outcomes in patients with acute PE. Furthermore, the VG-RVPO provided no additional prognostic value over RV/LV diameter ratio measurements, which are widely available and are currently one of the pillars of PE risk stratification as recommended by international guidelines. VG-RVPO may still help find people with chronic thromboembolic pulmonary hypertension (CTEPH) when people with acute PE (CTEPH) are being checked up on.

Part 2 of this thesis discusses the importance of follow-up and monitoring in AAOCA and Tetralogy of Fallot patients. In Chapter 5, the medium-term outcome of AAOCA patients is described and linked to pre-and postoperative symptoms. There is currently no agreement on the indications for surgery versus conservative treatment, particularly in middle-aged and older patients. Clinical and anatomical features influence the decision to operate. The role of symptoms is debatable. According to the data, patients present with a variety of symptoms, with only 35% having typical complaints. Overall, surgical correction of AAOCA significantly reduces symptoms. Furthermore, life-long follow-up after surgical correction appears justified, as adult patients' follow-up may reveal restenosis of the corrected anomalous artery. The coronary triangulated orifice area (CTOA) measured on computed tomography angiography (CTA) was introduced in Chapter 6. CTA is primarily used as a diagnostic tool, but there is little data on its role during post-operative follow-up. The CTOA on pre-and post-operative CTAs of patients with AAOCA was compared and related to anatomy and post-operative outcome. Following surgery, the median CTOA increased significantly from 1.6 mm2 to 5.5 mm2. A restenosis of the operating coronary artery was suspected in three patients during follow-up. The CTOA only showed a mean 1.4 mm2 postoperative increase in these patients. These results suggest that CTA can be used to look at the anatomy of AAOCA patients before and after surgery.

In Chapter 7, the medium-term outcomes of AAOCA patients are described and linked to pre-and postoperative symptoms.
Tetralogy of Fallot repair frequently results in late pulmonary regurgitation, and these patients may need pulmonary valve replacement (PVR). PVR is performed using pulmonary homografts and bioprostheses. Initially, there was great concern about the pulmonary homograft's durability. Vliegen et al. reported on 26 patients who received pulmonary homografts in 2002, and the current study re-evaluates the late clinical outcome and hemodynamics in this predefined patient group. The findings show that after 17.1 years of follow-up, there was a stabilization of RV function and an impressive durability of the homograft, as well as a high event-free survival (61.5 percent).

Future Perspectives
Although major achievements have been made in diagnosing and assessing pulmonary hypertension, PH remains a progressive and fatal disease with multifactorial etiology. Early identification of patients with the highest risk of developing PH is of vital importance as early treatment delays the progression of the disease and improves symptoms and survival. This thesis describes how vector analysis of the standard 12-lead ECG can improve risk stratification. The ECG derived vectorcardiogram, in contrast to the normal

ECG, mostly relies on quantitative measurements instead of human judgement of the ECG. Future research in serial vector-cardiogram measurements as a screening tool in patients suspected of PH is necessary to gain more insight into the prognostic relevance of early signs of RV pressure overload. Computer programs for the interpretation of electrocardiograms are now widely used. However, there is limited data on the performance of these classical algorithms that computer programs use, which precludes their use as a standalone diagnostic tool. It would also be beneficial if standard equipment was enhanced with vectorcardiographic analysis. This would bridge the gap between existing data and expanded clinical research. The research in this thesis also demonstrates that VGRVPO is well suited for individual trend analysis. The vector ECG can be integrated into patient follow-up care pathways. Because almost every patient already has a standard ECG, if the software is available, it can be done with little extra effort or cost. Recent studies have demonstrated the potential of using machine learning in serial electrocardiography. This opens a series of perspectives for future research and clinical application.

Currently, knowledge gaps in the evaluation and management of AAOCA are still present. Cardiologists are frequently undecided about how to advise their patients due to a lack of guidelines regarding cardiac imaging, activity restriction, and treatment in people of all ages with AAOCA. Because the evidence in the current literature is rather weak, recommendations and their variations are broad and still being debated. Indications for surgical correction remain controversial in some cases, and noninvasive imaging techniques such as CTA, which were mentioned in this thesis, may become even more important in the future. The precise description of anatomic high-risk features and tests for detecting myocardial ischemia is critical in the assessment and treatment of individuals with AAOCA. Future research should aim to clarify the pathophysiological determinants that link each type of coronary anomaly to myocardial ischemia, as well as how to assess the true impact on an individual's risk of life-threatening events. Unfortunately, the relative rarity of such conditions, their clinical and phenotypic variability, and ethical concerns may make large prospective studies in this context difficult to design. (Inter)national collaborations and multicenter registries may be able to help alleviate some of the current uncertainties. We are happy to say that our center has recently started a clinical care path, and we hope that more information will be gathered for future research.

Since patients with ToF are aging, they may require one or more PVRs in their lifetime. In order to obtain more information on hemodynamic changes and related to the timing of placing the new valve, future research protocols should continue to include serial follow-up measurements in all TOF patients. These serial measurements would be most easily

obtained if standardized protocols were implemented in all tertiary referral centers in the Netherlands. All TOF patients should have a comprehensive series of exams performed at standardized intervals after birth. This could lead to a better understanding of the adverse RV remodeling process, as well as better predictors of early RV failure and better treatment options. The long-term outcome of surgical PVR with homografts must be determined. Additionally, transcatheter valves are now available and approved for use in circumferential RVOTs. It is possible and becoming more common to use these valves for RVOTs that don't have a conduit. This would be an interesting topic for future research.

CHAPTER 9

Nederlandse samenvatting en Discussie

Pages 138- 141

Samenvatting, conclusies en toekomstperspectieven

Het doel van dit proefschrift is een beter begrip te krijgen van de diagnose en follow-up van patiënten met systemische sclerose (SSc), longembolieën (PE), Tetralogie van Fallot (TOF) en aberrante coronairen, met als doel ziekteprogressie en complicaties te voorkomen en zo de prognose te verbeteren. **Hoofdstuk 1** geeft achtergrondinformatie over de pathofysiologie van pulmonale hypertensie (PH) en belicht het onderscheid tussen PH en pulmonale arteriële hypertensie (PAH). Een grote verscheidenheid aan aandoeningen kan PH veroorzaken. Op basis van hun pathogene, pathofysiologische en therapeutische kenmerken worden vijf groepen gedefinieerd. PAH (groep 1) is een bekende complicatie van onder meer congenitale hartziekten (CHD) en SSc. Ook patiënten met longembolieën krijgen PH (groep 4). Bij deze patiënten past de rechterventrikel (RV) zich aan deze verhoogde pulmonale druk aan, wat uiteindelijk kan leiden tot RV-falen. Helaas blijft PH, ondanks de ontwikkeling van behandelingsmethoden, een progressieve ziekte met een hoge morbiditeit en mortaliteit. Daarom zijn screening en follow-up bij patiënten met PH van cruciaal belang. Vroegtijdige opsporing leidt tot vroegtijdige behandeling en een vertraging van de ziekteprogressie. De van het ECG afgeleide ventriculaire gradiënt (VG), indien geprojecteerd in de optimale richting voor de detectie van RV-drukoverbelasting (VG-RVPO), heeft nieuwe mogelijkheden geïntroduceerd voor de evaluatie van PH.

De noodzaak van follow-up bij congenitale hartziekten, aberrante coronairen en patiënten met Tetralogie van Fallot kan niet genoeg worden benadrukt. Coronaire anomalieën zijn ongewoon en de presentatie van de patiënten loopt sterk uiteen. De behandeling hangt onder meer af van de klinische presentatie en de anatomie. Voor patiënten met AAOCA (anomalous aortic origin of a coronary artery from the opposite sinus)zijn beperkte follow-upgegevens beschikbaar en er zijn nog talrijke leemten in de kennis over de evaluatie en behandeling van deze patiënten. Bij patiënten met Tetralogie van Fallot kan verslechtering van de pulmonale klep optreden als gevolg van eerdere operaties. Bij deze patiënten moeten tijdens hun leven een of meerdere malen de pulmonaal klep vervangen worden. Onderzoek naar de duurzaamheid van deze kleppen blijft een onderwerp van interesse.

Deel 1 van dit proefschrift onderzoekt het gebruik van de VG-RVPO bij patiënten met (vermoedelijke) PAH. Het doel van het in **hoofdstuk 2** gepresenteerde onderzoek was het evalueren van de VG-RVPO als screenings- en controle-instrument voor vroege PAH bij SSc-patiënten. Omdat het LUMC een gespecialiseerd zorgpad gebruikt om patiënten met SSc te evalueren, waren seriële elektrocardiogrammen (ECG's) en transthoracale echocardiogrammen (TTE's) van deze patiënten beschikbaar. TTE wordt ook gebruikt om de pulmonaal drukken te vervolgen, echter is dit een tijdrovend en relatief duur

screeningsinstrument. De ECG's en TTE's van patiënten met PAH (zoals vastgesteld door rechtshartkatheterisatie) (RHC) werden retrospectief bestudeerd. De veranderingen in pulmonale arteriële druk gemeten met TTE en VG-RVPO in de tijd bij PAH-patiënten versus niet-PAH-patiënten werden onderzocht. De resultaten laten zien dat de VG-RVPO significant hoger was bij PAH-patiënten dan bij niet-PAH-patiënten. Bovendien nam bij patiënten met PH de VG-RVPO in de tijd toe in vergelijking met patiënten zonder PAH. In vergelijking met de TTE was de VG bovendien gevoeliger voor het opsporen van ziekteprogressie in vroegere stadia van de ziekte. Het resultaat van dit onderzoek is dat seriële metingen van de VG-RVPO, die gemakkelijk toepasbaar en goedkoop zijn, kunnen worden gebruikt als follow-up instrument om vroege veranderingen in de rechter ventrikel druk in de tijd te detecteren.

De rol van de VG-RVPO bij het verbeteren van de efficiëntie van het YEARS-algoritme is onderzocht in **hoofdstuk 3**. Het YEARS-algoritme is een gevalideerd instrument voor het uitsluiten van PE bij een groot aantal patiënten, waardoor computertomografie van de longen (CTPA) niet meer nodig is. Maar ondanks dit algoritme wordt nog steeds de helft van de patiënten doorverwezen voor CTPA. Bij patiënten met PE kan PH optreden, wat resulteert in RV-drukoverbelasting. Van de VG-RVPO is reeds aangetoond dat hij PH kan opsporen in verschillende patiëntengroepen. Wij veronderstelden dat VG-RVPO de efficiëntie van het YEARS-algoritme nog zou kunnen verbeteren. Wij hebben hiervoor de VG-RVPO gemeten bij patiënten met verdenking op PE en die werden behandeld volgens het YEARS-algoritme. Hierbij hebben we de diagnostische waarde van VG-RVPO voor PE geëvalueerd, evenals de toegevoegde diagnostische waarde van VG-RVPO aan het YEARS-algoritme. Er werden 479 ECG's onderzocht. De VG-RVPO had echter noch als zelfstandige diagnostische test noch in combinatie met het YEARS-algoritme enige diagnostische waarde voor vermoedelijke acute PE. Dit kan worden verklaard door de gevoeligheid van de VG-RVPO, aangezien niet alle PE's RV-drukoverbelasting veroorzaken.

In **hoofdstuk 4** onderzochten wij de nauwkeurigheid van de VG-RVPO bij het schatten van de aanwezigheid en de ernst van acute rechter ventrikel drukoverbelasting, alsmede de prognostische waarde van een afwijkende VG-RVPO bij PE-patiënten. Dit werd bereikt door CTPA beoordeelde RV/LV ratio's en VG-RVPO te vergelijken met het optreden van vroege ongewenste voorvallen. Bij patiënten met PE veroorzaakt PH overbelasting van de RV, hetgeen resulteert in RV dilatatie. Omdat dit de RV/LV-ratio verandert, kan deze meting worden gebruikt om PE op te sporen en wordt zij momenteel gebruikt voor risicostratificatie. De VG-RVPO is effectief gebleken in een heterogene groep patiënten

met vermoedelijke PH, maar is beperkt in de setting van vermoedelijke acute PE. Er was een verband tussen VG-RVPO en RV-overload zoals gemeten met CTPA, maar dit was niet geassocieerd met slechte uitkomsten bij patiënten met acute PE. Bovendien leverde de VG-RVPO geen extra prognostische waarde op ten opzichte van RV/LV diameter ratio metingen, die ruim beschikbaar zijn en momenteel een van de pijlers zijn van PE risico stratificatie zoals aanbevolen door internationale richtlijnen. VG-RVPO kan waarschijnlijk helpen bij het vinden van mensen met chronische trombo-embolische pulmonale hypertensie (CTEPH).

Deel 2 van dit proefschrift bespreekt het belang van follow-up en monitoring bij AAOCA- en Tetralogie van Fallot-patiënten. In **hoofdstuk 5** wordt de uitkomst op middellange termijn van AAOCA-patiënten beschreven en gekoppeld aan pre- en postoperatieve symptomen. Er bestaat momenteel geen overeenstemming over de indicaties voor chirurgie versus conservatieve behandeling, met name bij patiënten van middelbare leeftijd en ouder. Klinische en anatomische kenmerken beïnvloeden de beslissing om te opereren. De rol van symptomen is discutabel. Volgens de gegevens presenteren patiënten zich met uiteenlopende symptomen, waarbij slechts 35% typische klachten heeft. In het algemeen vermindert chirurgische correctie van AAOCA de symptomen aanzienlijk. Bovendien lijkt levenslange follow-up na chirurgische correctie gerechtvaardigd, aangezien bij follow-up van volwassen patiënten restenose van de gecorrigeerde anomale slagader aan het licht kan komen. De coronary triangulated orifice area (CTOA) gemeten op computertomografie (CTA) werd geïntroduceerd in **hoofdstuk 6**. CTA wordt voornamelijk gebruikt als diagnostisch instrument, maar er zijn weinig gegevens over de rol ervan tijdens de postoperatieve follow-up. De CTOA op pre- en postoperatieve CTA's van patiënten met AAOCA werd vergeleken en gerelateerd aan anatomie en postoperatief resultaat. Na de operatie nam de mediane CTOA significant toe van 1,6 mm2 tot 5,5 mm2. Bij drie patiënten werd tijdens de follow-up een restenose van de geopereerde kransslagader vermoed. De CTOA vertoonde bij deze patiënten slechts een gemiddelde toename van 1,4 mm2 postoperatief. Deze resultaten suggereren dat CTA kan worden gebruikt om de anatomie van AAOCA-patiënten voor en na de operatie te bekijken.

In **hoofdstuk 7** worden de middellangetermijnresultaten van AAOCA-patiënten beschreven en gekoppeld aan pre- en postoperatieve symptomen.

Chirurgie bij patiënten met een tetralogie van Fallot leidt vaak tot late pulmonale regurgitatie, en deze patiënten kunnen een pulmonale klepvervanging (PVR) nodig hebben. PVR wordt uitgevoerd met pulmonale homografts en bioprothesen. Aanvankelijk

was er grote bezorgdheid over de duurzaamheid van de pulmonale homograft. Vliegen et al. rapporteerden over 26 patiënten die in 2002 een pulmonale homograft kregen, en in de huidige studie worden de late klinische uitkomst en de hemodynamiek in deze vooraf gedefinieerde patiëntengroep opnieuw geëvalueerd. De bevindingen tonen aan dat er na 17,1 jaar follow-up sprake was van een stabilisatie van de RV-functie en een indrukwekkende duurzaamheid van het homograft, alsmede een hoge event-free overleving (61,5%).

Toekomstperspectieven

Hoewel er grote vooruitgang is geboekt bij de diagnose en behandeling van pulmonale hypertensie, blijft PH een progressieve en dodelijke ziekte met een multifactoriële etiologie. Vroegtijdige identificatie van patiënten met het hoogste risico op het ontwikkelen van PH is van vitaal belang omdat vroegtijdige behandeling de progressie van de ziekte vertraagt en de symptomen en de overleving verbetert. Dit proefschrift beschrijft hoe vectoranalyse van het standaard 12-afleidingen ECG de risicostratificatie kan verbeteren. Het van het ECG afgeleide vectorcardiogram berust, in tegenstelling tot het normale ECG, grotendeels op kwantitatieve metingen in plaats van menselijke beoordeling van het ECG. Toekomstig onderzoek naar seriële vectorcardiogrammetingen als screeningsinstrument bij patiënten die verdacht worden van PH is noodzakelijk om meer inzicht te krijgen in de prognostische relevantie van vroege tekenen van RV-drukoverbelasting. Computerprogramma's voor de interpretatie van elektrocardiogrammen worden nu op grote schaal gebruikt. Er zijn echter beperkte gegevens over de prestaties van deze klassieke algoritmen die de computerprogramma's gebruiken, hetgeen hun gebruik als zelfstandig diagnostisch instrument vooralsnog uitsluit. Het zou ook nuttig zijn als standaardapparatuur werd uitgebreid met vectorcardiografische analyse. Dit zou een brug slaan tussen bestaande gegevens en uitgebreid klinisch onderzoek. Het onderzoek in dit proefschrift toont ook aan dat VGRVPO zeer geschikt is voor individuele trendanalyse. Het vector-ECG kan worden geïntegreerd in zorgtrajecten voor patiënten. Omdat bijna elke patiënt al een standaard ECG heeft, kan dit, als de software beschikbaar is, met weinig extra inspanning of kosten worden gedaan. Recente studies hebben het potentieel aangetoond van het gebruik van machinaal leren bij seriële elektrocardiografie. Dit opent een reeks perspectieven voor toekomstig onderzoek en klinische toepassing.

Momenteel zijn er nog hiaten in de kennis over de evaluatie en het beheer van AAOCA. Cardiologen weten vaak niet hoe zij hun patiënten moeten adviseren door een gebrek aan richtlijnen met betrekking tot cardiale beeldvorming, activiteitsbeperking en behandeling bij mensen van alle leeftijden met AAOCA. Omdat het bewijs in de huidige literatuur nogal zwak is, zijn de aanbevelingen en hun variaties breed en staan nog steeds ter discussie.

Indicaties voor chirurgische correctie blijven in sommige gevallen controversieel, en niet-invasieve beeldvormingstechnieken zoals CTA, die in dit proefschrift werden genoemd, kunnen in de toekomst nog belangrijker worden. De nauwkeurige beschrijving van anatomische risicokenmerken en tests voor het opsporen van myocardiale ischemie is van cruciaal belang voor de beoordeling en behandeling van personen met AAOCA. Toekomstig onderzoek moet gericht zijn op het verduidelijken van de pathofysiologische determinanten die elk type coronaire anomalie koppelen aan myocardischemie, en op het beoordelen van de werkelijke impact op het risico van levensbedreigende gebeurtenissen. Helaas kunnen de relatieve zeldzaamheid van dergelijke aandoeningen, hun klinische en fenotypische variabiliteit en ethische bezwaren het opzetten van grote prospectieve studies in deze context bemoeilijken. (Inter)nationale samenwerkingsverbanden en multicenter-registers kunnen wellicht helpen om enkele van de huidige onzekerheden te verlichten. Gelukkig is ons centrum onlangs begonnen met een klinisch zorgpad, en wij hopen dat er meer informatie zal worden verzameld voor toekomstig onderzoek.

Aangezien patiënten met ToF ouder worden, kunnen zij in hun leven een of meer PVR's nodig hebben. Om meer informatie te verkrijgen over hemodynamische veranderingen en met betrekking tot het tijdstip van plaatsing van de nieuwe klep, zouden toekomstige onderzoeksprotocollen seriële follow-up metingen bij alle TOF-patiënten moeten blijven doen. Deze seriële metingen zouden het gemakkelijkst te verkrijgen zijn als in alle tertiaire referentiecentra in Nederland gestandaardiseerde protocollen zouden worden toegepast. Alle TOF-patiënten zouden na de geboorte een uitgebreide serie onderzoeken moeten ondergaan met gestandaardiseerde tussenpozen. Dit zou kunnen leiden tot een beter begrip van het ongunstige RV remodeleringsproces, alsmede tot betere voorspellers van vroeg RV falen en betere behandelingsopties. Het resultaat op lange termijn van chirurgische PVR met homografts moet worden bepaald. Bovendien zijn er nu transkatheter kleppen beschikbaar en goedgekeurd voor gebruik in circumferentiële RVOT's. Het is mogelijk en wordt steeds gebruikelijker om deze kleppen te gebruiken voor RVOT's die geen conduit hebben. Dit zou een interessant onderwerp zijn voor toekomstig onderzoek.

APPENDICES

Dankwoord

Graag wil ik iedereen danken met wie ik heb mogen samenwerken en die de afgelopen jaren aan mijn proefschrift hebben bijgedragen.

Allereerst gaat mijn dank uit naar Hubert, Philippine, Monique en Anastasia, "de Congenitals". Hubert jij bent degene die mij bij jullie heeft binnengehaald en vanaf het begin heb ik veel gehad aan je kritische blik en lange onderzoekservaring. Ik heb je door de jaren heen goed leren kennen en je gastvrijheid en goede smaak in wijn is hartverwarmend. Philippine, je bent een keiharde werker en ondanks dat, heb je regelmatig tot laat tijd vrij gemaakt om de volgende stap in het protmotie traject te kunnen maken. De brainstorm sessies die uiteindelijk ook vaak eindigden in een goed gesprek mis ik af en toe! Monique, dank voor je altijd kritische blik, je oog voor detail is bewonderingswaardig. Anastasia, de nieuwe frisse wind in ons clubje, wat was en ben ik blij met jou als toevoeging. Je snelle feedback en aanmoediging heeft ervoor gezorgd om ook in de laatste fase scherp te blijven en door te gaan.

Dank aan alle onderzoekers in "de Tuin", zonder jullie steun, gezelligheid en afleiding waren de 3 jaar LUMC absoluut niet hetzelfde geweest.

Alle leden van de pulmonale hypertensie werkgroep bedank ik voor de leuke en interessante patiënt-besprekingen. Ik heb hier veel van geleerd.

Uiteraard ook veel dank aan de secretaris van mijn leescommissie, Menno Huisman

Dank aan mijn 2 fantastische paranimfen, Maaike en Sake.

Mijn vriendinnen, voor de steun, afleiding en pep-talks

Liselotte heel veel dank voor het ontwerpen van dit boekje, trots op jou!

Pappa, Mamma, Liselotte en Max, dank voor jullie vertrouwen en positiviteit, ook in tijden als het even niet zo goed ging. Door jullie ben ik nu waar ik nu ben!

Lieve Niek, jij ben degene die achter mij stond. Door jou liefde, kritische blik, motivatie en dat jij mij juist op bepaalde momenten de ruimte en rust gaf is dit proefschrift er.

Curriculum Vitae

Fleur Mathilde Margaux Meijer werd geboren op 1 oktober 1988 te Amsterdam. In 2008 behaalde zij haar VWO diploma aan het Alberdink Thijm College te Hilversum. Zij studeerde eerst 1 jaar European Public Health aan de Universiteit Maastricht waarna zij werd ingeloot voor de studie geneeskunde aan dezelfde Universiteit. Tijdens deze studie heeft zij zich als student vertegenwoordiger ingezet en heeft zij zitting genomen in het directie overleg en faculteitsraad. Als onderdeel van de studie geneeskunde heeft zij 2 coschappen in het buitenland gedaan. In het Kasturba Medical Center in India en in het Steve Biko Hospital in Zuid Afrika. Haar semi-arts stage liep zij in 2007 bij de Cardiologie in het Orbis Medisch Centrum in Sittard. Het laatste half jaar van haar master examen deed zij wetenschappelijk onderzoek op de afdeling Cardiologie in het AMC in Amsterdam. In december 2015 startte zij als ANIOS op de afdeling Cardiologie in het Leids Universitair Medisch Centrum. Aansluitend heeft zij promotieonderzoek verricht op de afdeling Cardiologie van Juli 2016 tot April 2019, waarvan de resultaten zijn beschreven in dit proefschrift. Hierna is zij als ANIOS Cardiologie gestart in het Onze Lieve Vrouwen Gasthuis in Amsterdam. Op 1 December 2019 is zij hier aangenomen voor de opleiding Cardiologie (onder opleider Ton Slagboom en inmiddels Jean Paul Herrman).