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

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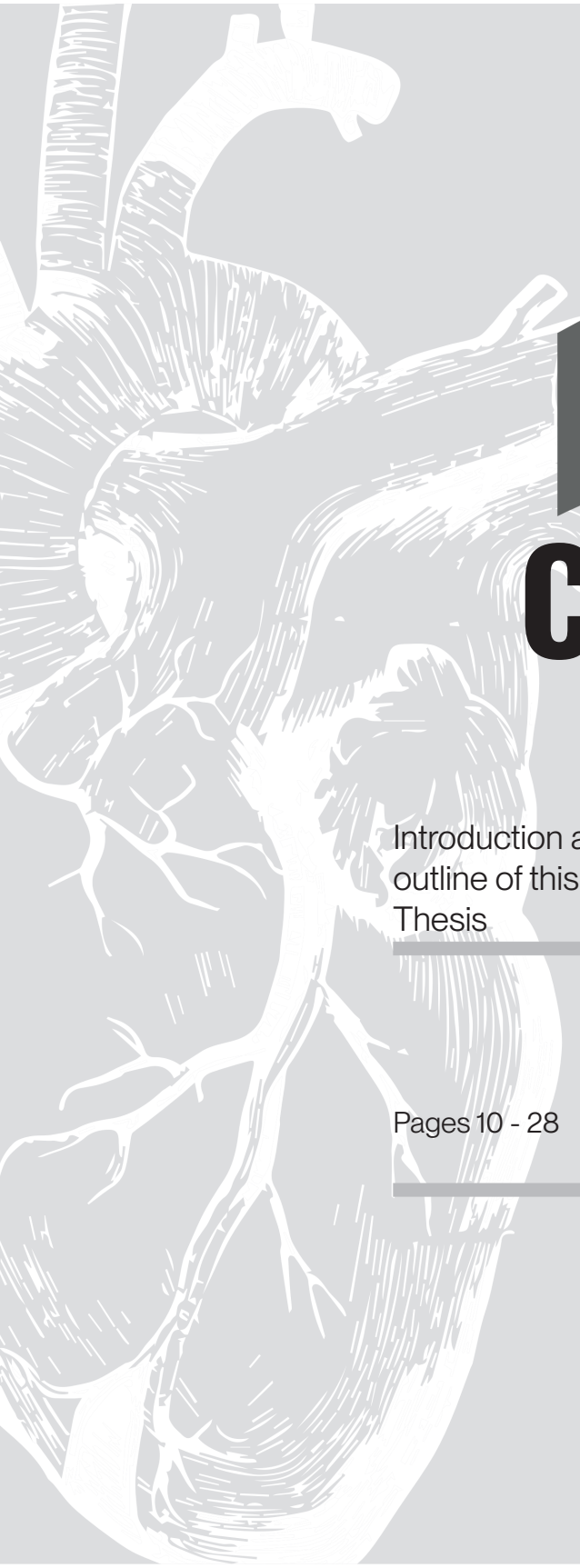


1 CHAPTER

Introduction and outline of this Thesis

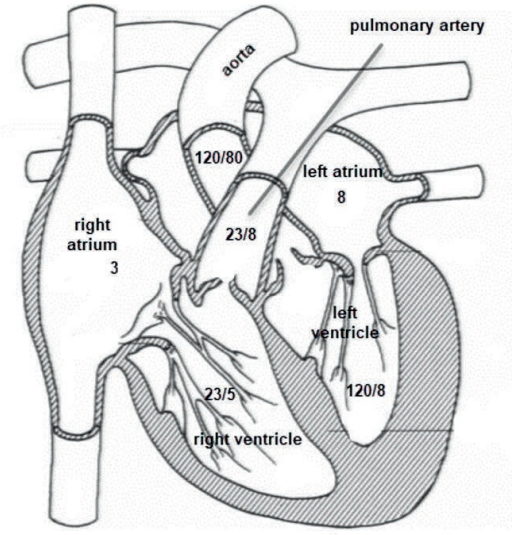
Pages 10 - 28

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)

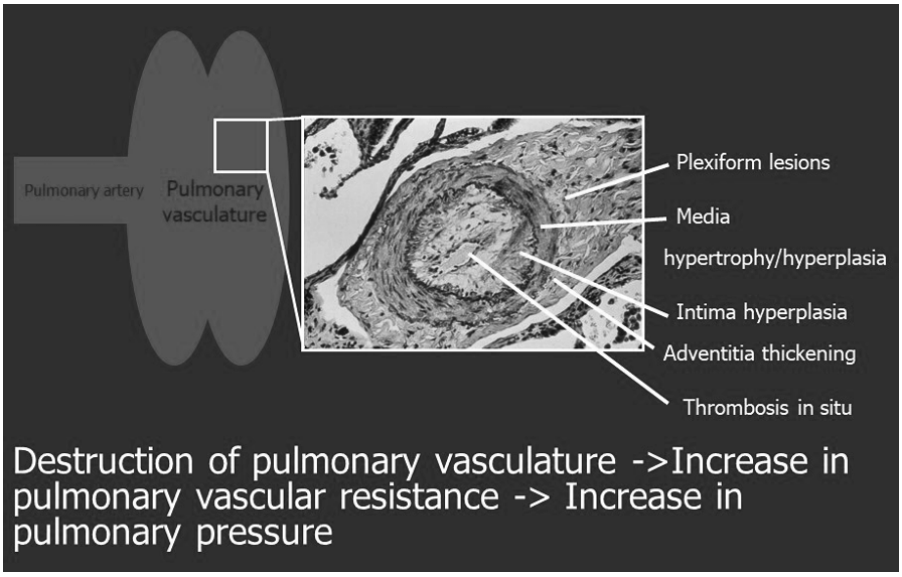
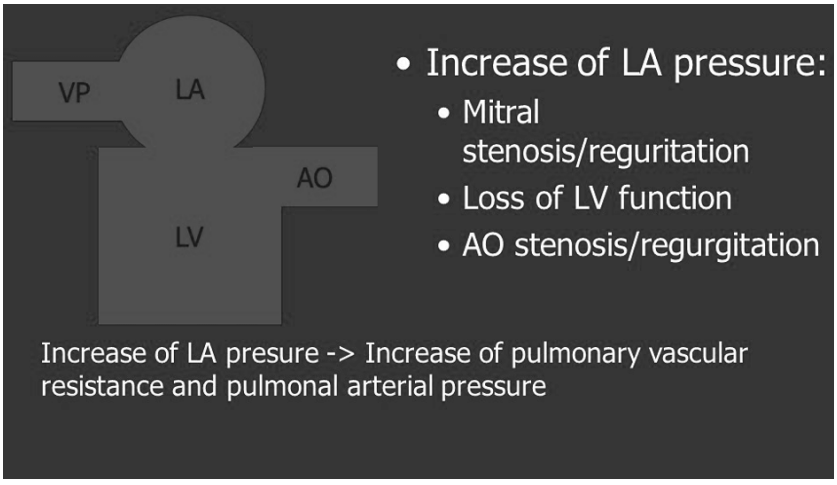


Figure 3. Pathophysiologic response in patients with PH group 2 and in certain cases group 5



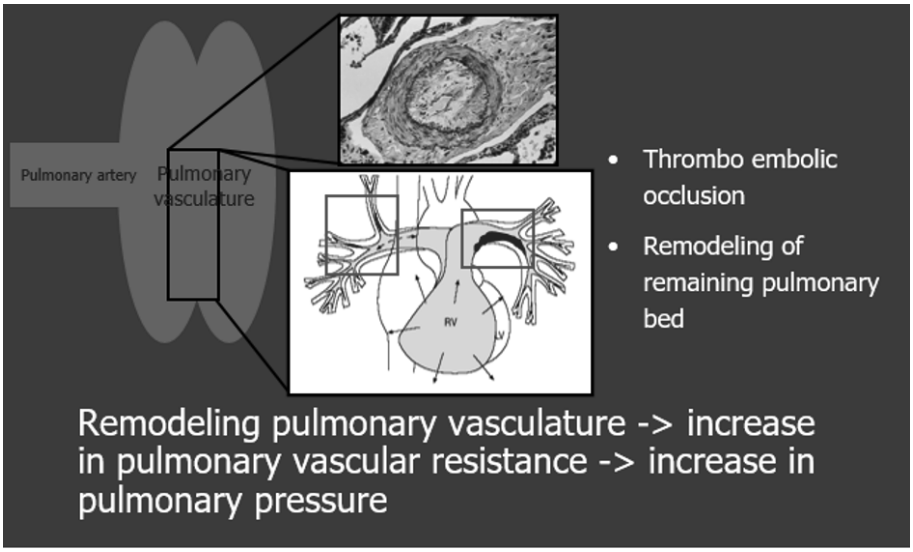
Abbreviations: LA, left atrium; VP, pulmonary veins; LV, left ventricle; Ao, aorta

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

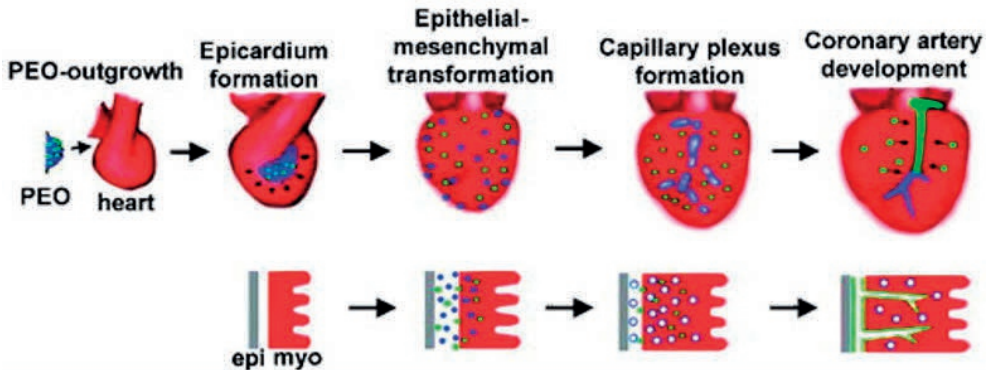
The survival of patients with congenital heart disease (CHD) has markedly improved,

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.

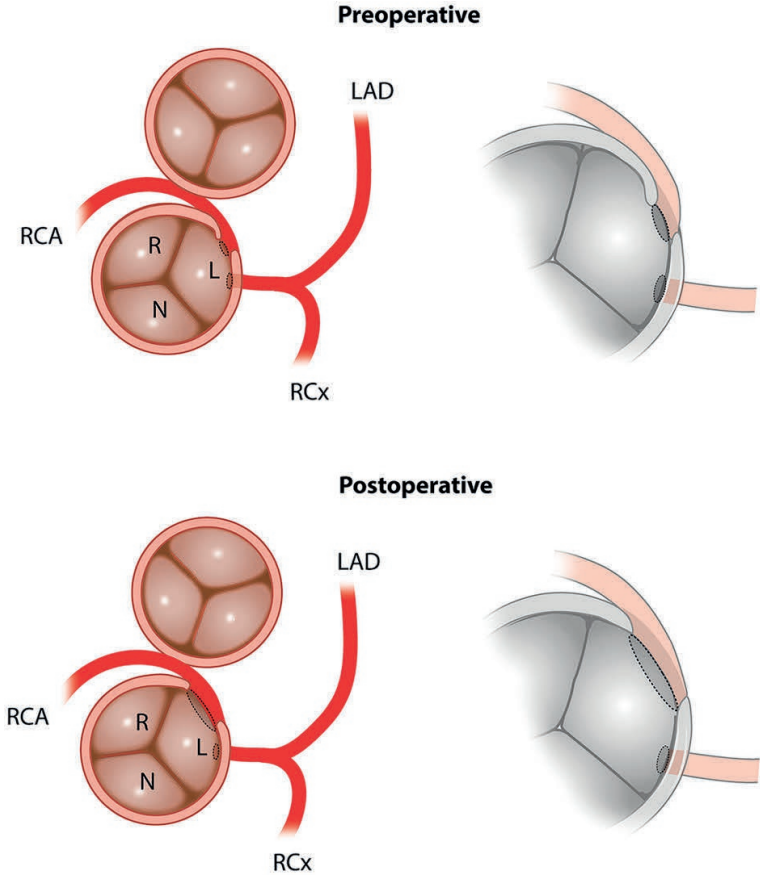
Reimplantation, as in the case of AAORCA from the left coronary sinus with inter-arterial course and intramural segment, is possible41. The RCA is divided immediately distal to the intramural segment and reimplanted end-to-side into the right sinus of Valsalva without a button [42].

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)

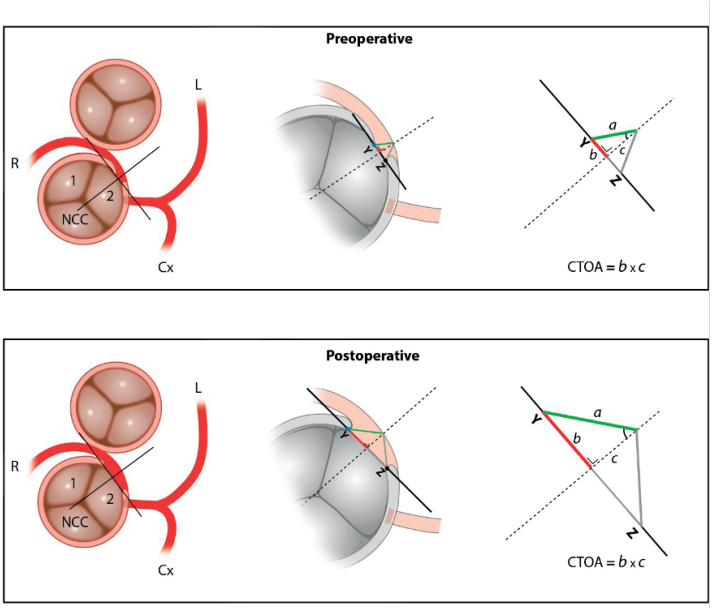


AAORCA, anomalous aortic origin of a right coronary artery; RCA, right coronary artery; LAD, left anterior descending artery; RCx, ramus circumflex artery; R, right coronary cusp; L, left coronary cusp; N, non coronary cusp

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.

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