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

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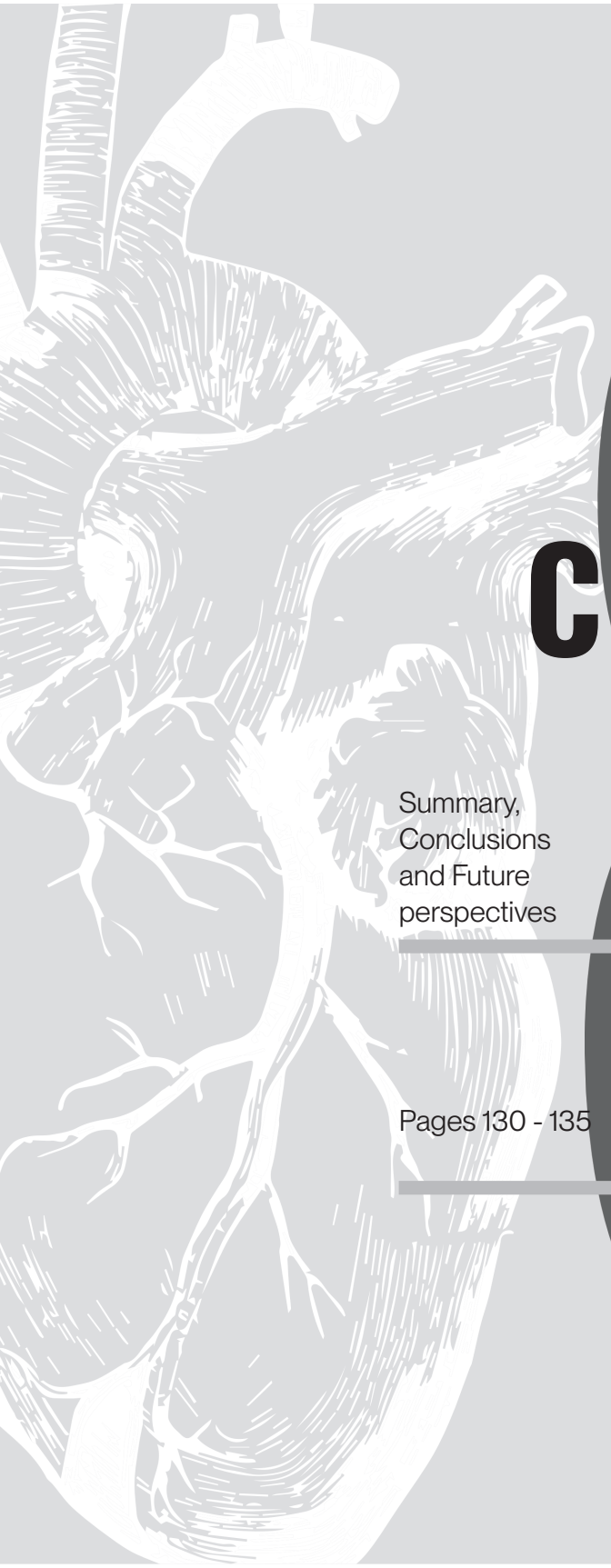

CHAPTER 8

Summary, Conclusions and Future perspectives

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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.