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Author M.M. Winter
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ONE

Introduction and outline of this thesis

INTRODUCTION

Congenital heart disease is the most common congenital malformation, and accounts for approximately 8 cases per 1,000 life births.[1] Five to eight percent of patients with congenital heart disease is diagnosed with a transposition of the great arteries (TGA). TGA is defined by a concordant atrio-ventricular connection, and a discordant ventriculo-arterial connection, creating two parallel circulations. Until the mid 1980s, most patients with TGA were palliated with an atrial switch operation, leaving the right ventricle (RV) responsible for the systemic circulation.[2, 3] Patients with congenitally corrected transposition of the great arteries (ccTGA) have a double discordance; the atria are connected to the opposite ventricles, and the ventricles to the opposite arteries. Circulation is not impaired, and surgery early in life mostly unnecessary. However, in patients with a ccTGA too, the RV is responsible for the systemic circulation.

Mid-term survival is relatively good, with more than 80% of TGA patients reaching adulthood.[4] However, complications, such as arrhythmias, tricuspid valve regurgitation, and reduced exercise capacity, are common, and frequently relate to systemic RV dysfunction.[5] Accurate diagnostic tools are essential for the clinical follow-up of systemic RV function, and evidence based treatment regimens are crucial to halt the deterioration of systemic RV function, and provide these young patients with a better future.

Systemic RV dysfunction

Many pathophysiological pathways have been described to play a role in the development of systemic RV dysfunction. Already early in life, the myocardium becomes severely damaged due to extensive cardiac surgery. As a result of the atrial switch operation, the RV becomes responsible for the systemic circulation, and is therewith exposed to a constant pressure overload. The RV hypertrophies, causing demand ischemia, with subsequent further deterioration of systemic RV function. [6] Morphologic abnormalities of the tricuspid valve are frequent, especially

in patients with a ccTGA, leading to a high incidence of tricuspid valve regurgitation. The systemic RV dilates, due to the increased volume load, and its function deteriorates even further.[7, 8] Although neuroendocrinal activation compensates for the diminished contractility at first, it will eventually overstrain the already failing ventricle. [9]

Therapy

Although treatment regimens of patients with left ventricular failure are well established, clinical management of patients with systemic RV dysfunction remains challenging. In theory, patients with systemic RV dysfunction would benefit from treatment with diuretics, β-blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin II receptor antagonists (ARBs). However, conclusive evidence on the effect of these medications is lacking. This is mainly due to the rarity of the condition, and the heterogeneity of the patient group, which makes prospective and sufficiently powered research difficult.

Diagnostic imaging modalities

For careful follow-up of adult patients with a systemic RV, accurate diagnostic tools are essential. Echocardiography remains the first choice imaging modality for the systemic RV, as it is non-invasive, widely available, and cost-effective. Systemic RV deterioration has been extensively studied by means of echocardiography, and it is known that both systolic and diastolic RV function are diminished in adult TGA patients.[10, 11] Notwithstanding the diminished function of the systemic RV, it remained unclear which echocardiographic parameters best predicted a patient's clinical condition. Currently, Cardiovascular Magnetic Resonance (CMR) Imaging is considered to be the gold standard for the evaluation of systemic RV volumes and function. CMR can provide any desired imaging plane, and does not rely on geometric assumptions to calculate systemic RV ejection fraction.[12, 13] However, 20% of patients with a systemic RV is pacemaker or ICD dependent, and an increasing number of patients with a failing systemic RV benefits from cardiac

resynchronization therapy.[14-16] As most intra-cardiac devices are currently considered to be CMR incompatible, these patients are unsuitable to undergo CMR. Multidetector Row Computed Tomography (MDCT) provides a reliable alternative for CMR in these patients.

The objectives of this thesis are to obtain more insight in the cardiac pathophysiology of adult patients with a systemic RV due to an atrially switched TGA, or a ccTGA. In addition, we aim to outline the therapeutic possibilities for these patients, and to assess which imaging modalities are best suited to evaluate the systemic RV. In addition, we aim to evaluate whether physical exercise adds to patients' clinical and psychological well-being.

OUTLINE OF THIS THESIS

Treatment regimens in patients with systemic RV dysfunction remain equivocal. **Chapter 2** reviews the pathophysiology of systemic RV dysfunction, and describes all therapeutic possibilities for these patients. It concludes that little evidence is available on the treatment of systemic RV dysfunction, and that large-scale, prospective research is warranted to overcome this hiatus. In response to chapter 2, Szymañski argued that most studies on treatment regimens in patients with a systemic RV remain inconclusive, due to vague inclusion criteria, and heterogeneous patient populations. [16] We agree with Szymañski, although we argue that the absolute number of adult patients with a systemic RV does not allow for narrow inclusion criteria. To overcome the lack of evidence based therapy, we set-up a multi-center, double-blind, randomized controlled trial to evaluate the effect of Angiotensin-II receptor antagonists on systemic RV function, of which we present the rationale and design in **chapter 3**.

In **chapter 4** we describe the different mechanisms in which patients with an atrially switched TGA, and patients with a ccTGA increase their cardiac output during exercise. Whereas ccTGA patients increase both stroke volume and heart rate during exercise, patients with an atrially switched TGA lack the ability to

increase stroke volume, and are primarily dependent on an increase in heart rate. To conserve a normal cardiac response to stress seems crucial, as those patients who show abnormal response to stress Cardiovascular Magnetic Resonance (CMR) Imaging, have a substantially higher risk of adverse outcome, as is stated in **chapter 5**. Physical exercise could positively effect cardiac function in patients with a systemic RV. **Chapter 6** demonstrates that daily physical exercise is positively associated with increased exercise capacity and favorable quality of life. We recommend to alleviate current conservative guidelines regarding physical exercise in patients with a systemic RV. To definitely prove the value of exercise and its safety, we conducted an international, prospective randomized controlled trail, in which patients were randomized to participate in an exercise training program, or to refrain from such a program. As described in **chapter 7**, exercise training increases exercise capacity in patients with a systemic RV, and can be performed safely.

The role of several diagnostic imaging modalities in the evaluation of the systemic RV had not been properly evaluated. Currently, CMR is considered the gold standard for the evaluation of systemic RV volumes and function. However, methods of delineating the cavity relative to the hypertrophied trabeculations and papillary muscles were inconsistent. In **chapter 8** we state that cavity delineation inside the myocardium of the RV, but outside the trabeculations and papillary muscles is the method of preference, as this approach takes less time and gives more reproducible values. Twenty percent of patients with a systemic RV are dependent on intra-cardiac devices, and therefore unsuitable to undergo CMR. The reliability of Multirow Detector Computed Tomography (MDCT) as an alternative to CMR is discussed in **Chapter 9**. Indeed, MDCT provides a reliable alternative for CMR for the evaluation of volumes and function in patients with a systemic right ventricle, although larger variability between measurements should be taken into account. However, patient selection should be restrictive, to avoid unnecessary exposure to radiation and contrast agents. Although CMR is considered the gold standard to assess systemic right ventricular function, echocardiography remains

the first choice imaging modality in these patients. In **chapter 10** we determine that qualitative assessment of systemic RV function and tricuspid annulus plane systolic excursion (TAPSE), as measured by echocardiography, best predict a patient's clinical condition.

The majority of patients with a systemic RV has undergone surgery early in life. Late complications, such as tricuspid valve regurgitation, are frequently seen and often require additional surgical intervention. Surgical correction of the leaking tricuspid valve increases a patient's functional status, as is described in **chapter 11**. In comparison with tricuspid valve replacement, tricuspid valvuloplasty is associated with an increased risk of recurrence of regurgitation.

Sexuality is receiving increased attention in patients with acquired heart disease, in whom it is affected. **Chapter 12** describes that many aspects of sexuality are affected in adult patients with four different types of congenital heart disease. As sexuality is an important aspect of quality of life in these patients, we advise physicians to be receptive to discuss the issue and provide patients with adequate therapy.

Mackie et al. published an article stating that 61% of patients with congenital heart disease are lost to follow-up at the age of 18, in the Canadian province of Quebec. In response to this publication, we outline the Dutch situation in **chapter 13**. There are approximately 25,000 adult patients with congenital heart disease in the Netherlands. Thanks to the success of the CONCOR database, the Dutch national registry and DNA-bank of adult patients with congenital heart disease, we know that a mere third of adult patients with congenital heart disease fail to receive cardiac care in the Netherlands.

In **chapter 14** all studies presented in this thesis are summarized, and future directions for research on adult patients with a systemic RV are discussed.

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