Clinical aspects and pathophysiological mechanisms of (systemic) right ventricular failure

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Chapter 1

General introduction and outline of this thesis

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General aspects of the left ventricle and right ventricle

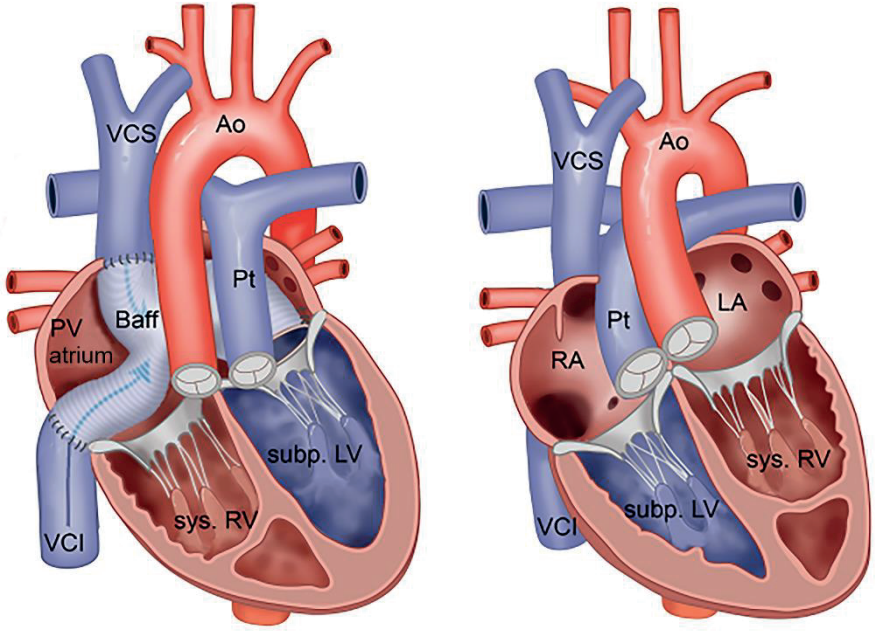
Proper cardiac performance to sustain the body depends heavily on an a well developed biventricular (left and right) anatomy and adequate function. In the normal heart, the right ventricle (RV) provides blood flow to the lungs and the left ventricle (LV) provides (oxygenated) blood flow to the systemic circulation. The LV and the RV are morphologically, developmentally, and functionally different (1). Generally, the RV has a smaller contractile reserve and, for its output, depends more on heart rate than the LV (2). In the past, scientific studies in the field of cardiac disease have initially focused more on the LV than on the RV. However, it has become increasingly clear that knowledge regarding the RV is also of great importance in many settings, such as in the setting of congenital heart disease, where in many patients the RV is the ventricle that is primarily affected. It has been recognized however, that findings derived from studies in the LV, can not be randomly extrapolated to the RV. For example, in cases of heart failure, the RV does not respond the same way to medication as the LV does (3) and information derived from randomized clinical trials based on large patients cohorts, are lacking in many instances. In addition, it is increasingly recognized that RV function may also contribute to prognosis in left sided heart disease. For example, independently of LV function, RV function may be the most important predictor of mortality in patients with ischemic or dilated cardiomyopathy and a reduced LV function (4).

Historical perspective of the systemic right ventricle

In specific cases, the focus on the RV is even more important. In the current thesis, the focus lies on patients with a RV in the systemic position in a biventricular circulation. Patients with a systemic RV comprise two main groups groups. The first group has been diagnosed with transposition of the great arteries (TGA) and received a physiological surgical correction with an atrial switch operation according to Mustard (5) or Senning (6). The second group of patients has been diagnosed with congenitally corrected TGA (ccTGA) (*Figure 1*).

After the era of Mustard and Senning, due to improved surgical techniques, the arterial switch operation became feasible, providing patients diagnosed with TGA with an anatomical correction, resulting in a systemic LV. During this procedure the great arteries are "switched", making the native aortic root, a neo-pulmonary trunk, whereas the pulmonary root becomes the neo-aorta, with re-implanted coronary arteries (7). For the ccTGA group, nowadays a "double switch operation" (i.e. performing both an atrial as well as arterial switch) is an option in selected patients, which also leads to the

restoration of the LV as the systemic ventricle. Despite these new treatment options, there are still several generations of patients with a systemic RV, currently mostly in their 30s, 40s, and 50s. Every new decade that this group faces, brings new clinical challenges which were unseen before. To be able to provide this group of patients with optimal health care, continuous monitoring and research efforts are necessary. This also encompasses the exploration of new management techniques that have proven efficient in patients with LV failure, but that have often not been evaluated yet in the smaller group of patients with (systemic) RV failure.



*(**Figure 1**): **TGA after atrial switch correction and ccTGA***
Ao: aorta; Baff: systemic venous baffle; LA: (morphologically) left atrium; Pt: pulmonary trunk; PV tunnel: pulmonary venous atrium; RA: (morphologically) right atrium; Subp. LV: subpulmonary LV; Sys. RV: systemic RV; VCI: inferior vena cava; VCS: superior vena cava

Development and epidemiology of TGA and ccTGA

TGA, representing about 5-8% of all adult congenital heart disease (8), is characterized by a concordant atrioventricular connection (i.e. the morphological right atrium drains to the morphological right ventricle, and the morphological left atrium drains to the morphological left ventricle) and a discordant ventriculo-arterial connection (i.e. the morphological right ventricle drains to the aorta and the morphological left ventricle drains to the pulmonary trunk). In complex forms, a hemodynamically relevant

ventricular septal defect and/or left ventricular outflow tract obstruction are also present. The course of great arteries and their outflow tracts is usually parallel in TGA, often with a right anterior position of the aortic orifice, which is a distinctive feature on for example echocardiography. During normal embryonic development, the entire outflow tract (later to be separated into left and right) is initially positioned above the RV. Due to asymmetric contributions of cells from the second heart field (the splanchnic mesoderm posterior to the heart, that contributes a.o. myocardium to the heart during development), the right ventricular outflow tract grows and thereby "pushes" the pulmonary trunk to its normal left anterior position, as related to the aorta (9-12). Variations/errors in this process of the so-called "pulmonary push" and anomalous development of the subpulmonary myocardium are thought to give rise to congenital heart defects with abnormal position of the great arteries, such as TGA, double outlet right ventricle, or tetralogy of Fallot (10, 12).

CCTGA is rarer than TGA, representing only about 1% of all adult congenital heart defects (13). It is characterized by both a discordant atrioventricular connection as well as a discordant ventriculo-arterial connection. As such, in uncomplicated cases, although the systemic ventricle is a RV, a functioning circulation is present at birth and problems may not arise until decades later (14). However, ventricular septal defects and left ventricular outflow tract stenosis are often present, and the tricuspid valve is regularly found to be structurally abnormal and may have Ebstein-like characteristics, making it prone to dysfunction. These associated anomalies can negatively influence the disease course of ccTGA (15). Less is known about the embryology of ccTGA. The heart defect is thought to (partly) arise through faulty looping of the primitive heart tube.

Autonomic function and cardiac disease

Function and dysfunction of the autonomic nervous system play an important role in cardiac disease and many treatments rely on its modification. The sympathetic system optimizes heart function for active or stress situations (fight or flight) and is responsible for increases in heart rate, conduction speed, and contractility. The parasympathetic system optimizes heart function for restorative states (rest and digest) by lowering these parameters, thus conserving energy. Generally, decreased cardiac autonomic function is associated with adverse prognosis in both primary and secondary prevention settings (16).

Cardiac autonomic innervation is involved in the pathophysiology of heart failure and arrhythmias, both of which are important problems in patients with a systemic RV.

Regarding heart failure, as a response to reduced cardiac output, the sympathetic branch of the autonomic nervous system becomes activated. Initially, sympathetic activation leads to restoration of cardiac output through increased inotropy on the cardiac level. On the long term, chronically increased catecholamine levels lead to downregulation of cardiac β-adrenergic receptors as a protective mechanism against myocardial norepinephrine toxicity, but this desensitization also leads to loss of adrenergic functional reserve (17, 18).

Compared to sympathetic involvement in heart failure, less is known about parasympathetic involvement. It is generally thought that, in contrast to sympathetic activity, parasympathetic activity in heart failure is cardioprotective, but that this is downregulated through pathophysiological mechanisms. Clinically, reduced parasympathetic tone can be observed for example as reduced baroreflex sensitivity, impaired heart rate deceleration after exercise, or reduced heart rate variability (HRV) in patients with heart failure (19-22). Briefly, HRV analysis quantifies the spontaneous fluctuations in heart rate. These are mainly caused by parasympathetic modulation, so generally, higher indices of HRV indicate higher parasympathetic activity which implies intact parasympathetic innervation, at least of the sinus node (23). Furthermore, heart rate turbulence (HRT) also provides information about parasympathetic function: HRT describes the pattern of acceleration and deceleration of heart rate after a premature ventricular complex, and reflects baroreflex function (24).

Regarding arrhythmias, the left atrial area around the pulmonary veins contains many ganglionated plexuses which receive sympathetic as well as parasympathetic output (25). Atrial fibrillation can be triggered by stimulation of these areas, and can be successfully treated with ablation of these sites. Atrial fibrillation can be sympathetically or parasympathetically mediated (26, 27). Changes in autonomic tone appear to immediately precede ventricular arrhythmias, as becomes clear through HRV analysis of ICD or Holter records (28-34). However, the direction of the changes and the exact parameters concerned are inconsistent and probably highly dependent on patient factors and specific etiology of the arrhythmia. Only an increase in heart rate preceding arrhythmias is consistently seen in these recordings (28-34).

Specifically in congenital heart disease, abnormal autonomic function is common and may result from abnormal development of innervation, altered hemodynamics, or thoracic surgery (35-37, 38). Abnormal autonomic function as a consequence of altered hemodynamics can for example be seen in patients with an atrial septal defect, where stretch of the sinoatrial node alters HRV (39). Another example is in coarctation of the aorta: here, renal hypoperfusion may lead to neurohumoral activation and

subsequently increased sympathetic output, despite adequate left ventricular function (40). Heart failure can also cause reduced autonomic function: for example, in adults with tetralogy of Fallot, reduced heart rate turbulence is correlated with reduced LVEF and RVEF (41). Cardiac nerves can be damaged and hemodynamics can be stressed during surgery, which may lead to a decrease in HRV immediately after surgery and an increase at longer follow-up, indicating nerve recovery and improved hemodynamic status (38). Generally, knowledge regarding asymmetry and heterogeneity in cardiac autonomic innervation, which is especially relevant in patients with a systemic RV, is scattered. In this thesis, **chapter 2** aims to link and summarize existing literature. Furthermore, in patients with a systemic RV, cardiac autonomic function has not yet systematically been quantified and correlated with clinical features and outcomes, such as arrhythmias, in adult patients. In this thesis, **chapters 3 and 4** address these gaps in current knowledge.

The systemic right ventricle in adult patients: (patho)physiology and complications

In the past decades, survival of patients with a systemic right ventricle has shown a vast improvement thanks to improved surgical and percutaneous techniques, expertise, routine follow-up, and focus on early detection of complications (42-44). This has confronted clinicians with problems previously unencountered as patients with complex cardiac anatomy and physiology reached the adult age and became older. Challenges have been posed by progressive heart failure, baffle leakage/stenosis, valvular defects, arrhythmias, and conduction disorders. These problems and their urgency in this group of relatively young patients with serious risks of morbidity and mortality have been increasingly recognized by the research agenda (44, 45).

Systemic right ventricular failure and tricuspid valve (systemic atrioventricular valve) regurgitation may arise in the course of the years due to progressive dilatation caused by the high systemic pressure to which the RV is exposed. Especially in ccTGA, this can be exacerbated by Ebstein-like structural valve defects. Endocarditis may cause additional valve damage. In patients post Mustard or Senning procedures, the atrial kick contributing to ventricular filling is virtually absent, due to the usually stiff baffle between the pulmonary veins and the systemic RV. Surgery may be considered in patients with progressive tricuspid valve regurgitation. Due to a high relapse rate of valve regurgitation after valvuloplasty, valve replacement is the preferred option (46).

Baffle-related complications may occur in patients after the atrial switch operation (Mustard/Senning). Obstruction of the systemic venous baffle may be chronic or acute. Chronic obstruction is usually accompanied by the formation of a collateral circulation and may therefore be asymptomatic (47). Balloon dilation with/without stenting or

surgical correction are possible treatments. Obstruction of the pulmonary venous conduit may be suspected in the case of turbulent high flows at the pulmonary veins as shown by Doppler echocardiography. Pulmonary venous obstruction may lead to pulmonary hypertension and should be surgically relieved (48). Baffle leakage can lead to shunting and puts the patient at risk for paradoxical emboli. The diagnosis can usually be made with transoesophageal echocardiography. The leakage may be treated interventionally or surgically (48).

Arrhythmias in patients with a systemic right ventricle, apart from bradycardias and other arrhythmias caused by conduction system damage/maldevelopment (see paragraph below), mostly consist of atrial flutter. Scarring at the atrial level can create areas prone to slow conduction, increased automaticity, and re-entry, predisposing to atrial flutter. These arrhythmias may be difficult to treat and further exacerbate systemic RV dysfunction (49). Specifically in ccTGA, arrhythmias may also be a consequence of congenital accessory pathways (49).

Conduction disorders in patients with a systemic right ventricle may also be due to scarring on the atrial level as a late complication of Mustard or Senning surgery. In patients with ccTGA, complete atrioventricular block is highly prevalent due to an anatomically abnormal and fragile conduction system, and may be caused by fibrosis of conduction fibres or a greater distance between the AV-node and the septum (50).

Generally, since major clinical events are common in patients with a systemic RV, a relatively simple risk score for the prediction of these events would be useful in follow-up and counselling. In this thesis, **chapter 6** incorporates data from multiple centers to address this question.

Routine follow-up, treatment, and imaging in patients with a systemic RV

In the 2020 ESC guidelines on congenital heart disease in adults, at least annual follow-up in a specialized adult congenital heart disease center is recommended, where special attention can be paid to the possible complications described above (48). For follow-up of the systemic RV function, echocardiography is described as the first-line diagnostic modality, which can provide information about a.o. the systemic RV size and function. Cardiac magnetic resonance imaging may provide more robust quantification of systemic RV function when compared with echocardiography. Echocardiography is more readily available and is also feasible in patients with devices and potentially present epicardial or abandoned leads, in contrast with cardiac magnetic resonance imaging (48, 51, 52). However, the complex three-dimensional shape of the systemic RV, its pronounced trabeculations, and the presence of a moderator band limits the

assessment of systemic RV function with echocardiography (53) which complicates routine assessment. Global longitudinal strain is a promising variable to quantify systemic RV function, as recent studies show (54). However, echocardiographic protocols for the routine follow-up of patients with a systemic RV have not been standardized, as it is currently unclear which echocardiographic variables correlate best with cardiac magnetic resonance imaging and are also feasible across the whole, heterogeneous group of patients with a systemic RV. In this thesis, this subject will be addressed in **chapter 5**.

Regarding medical treatment, no specific recommendations are currently made in the ESC guidelines. There is no strong evidence that heart failure medication improves outcome in patients with a systemic RV (48), although the angiotensin receptor blocker valsartan may slow the progression of systemic RV failure (55, 56), and the cautious use of ACE inhibitors and β-blockers may be beneficial in symptomatic patients (57). The European guidelines recommend considering diuretics for symptom relief and to prescribe heart rate-lowering drugs with caution because of the risk of brady-arrhythmias (48). For patients with heart failure with a normal biventricular circulation, sacubitril/valsartan has recently proven to improve outcome (58). For patients with a systemic RV, this drug has not yet been investigated. In this thesis, this subject will be addressed in **chapter 7**.

In adult patients with congenital heart disease, including patients with a systemic RV, it may be especially valuable to integrate home monitoring through eHealth in the follow-up routine: these patients are younger compared to the general population of cardiac patients, are likely to own a smartphone device, and have a high degree of digital literacy (59). In this thesis, the experience of titration of sacubitril/valsartan using eHealth smart technology in the cohort of **chapter 7** will be described in **chapter 8**.

For selected patients with a systemic RV and end-stage heart failure , ventricular assist device implantation in the failing systemic RV may be an option (60). In this thesis, **chapter 9** describes the first two cases in the Netherlands where this treatment was used.

Aim and outline

The aim of this thesis is to explore the systemic right ventricle from different interrelated angles. In part I, (patho)physiology and mechanisms, we have studied the anatomy and function of the autonomic nervous system in the setting of CHD with a systemic RV, as related to outcome. In part II, clinical applications, we aimed to predict and monitor clinical deterioration, and to explore treatment options of complications

accompanying the circulation with a systemic right ventricle. **Part I** of this thesis consists of **chapters 2-4**. In **chapter 2**, the differences between the LV and the RV regarding cardiac autonomic innervation are reviewed. In **chapters 3 and 4,** noninvasive measures of cardiac autonomic function are investigated in a group of patients with a systemic RV and related to clinical outcome. **Part II** of this thesis consists of **chapters 5-8**. In **chapter 5**, different imaging modalities are compared and from these data, the most reliable and practical echocardiographic measures of systemic RV function are extracted. In **chapter 6**, the patterns of the clinical course and a prediction model of clinical outcome in patients with a systemic RV are described. **Chapter 7** reports on the first results of the treatment of systemic RV failure with the drug sacubitril/valsartan. **Chapter 8** describes the experience of titration of sacubitril/valsartan using eHealth smart technology in the cohort of **Chapter 7**. Finally, **chapter 9** describes the first two cases of implantation of a ventricular assist device in patients with a systemic RV in the Netherlands.

References

1. Dykes IM. Left Right Patterning, Evolution and Cardiac Development. J Cardiovasc Dev Dis. 2014;1(1):52-72.

2. Groepenhoff H, Westerhof N, Jacobs W, Boonstra A, Postmus PE, Vonk-Noordegraaf A. Exercise stroke volume and heart rate response differ in right and left heart failure. European journal of heart failure. 2010;12(7):716-20.

3. Borgdorff MA, Bartelds B, Dickinson MG, Steendijk P, Berger RM. A cornerstone of heart failure treatment is not effective in experimental right ventricular failure. International journal of cardiology. 2013;169(3):183-9.

4. Bleasdale RA, Frenneaux MP. Prognostic importance of right ventricular dysfunction. Heart (British Cardiac Society). 2002;88(4):323-4.
5. Mustard WT. Succesful two-stage correction of transposition of the great vessels. Surgery. 1964;55:469-72.

6. Senning A. Surgical correction of transposition of the great vessels. Surgery. 1959;45(6):966-80.

7. Jatene AD, Fontes VF, Paulista PP, Souza LCB, Neger F, Galantier M, et al. Anatomic correction of transposition of the great vessels. The Journal of thoracic and cardiovascular surgery. 1976;72(3):364-70.

8. Samánek M, Slavík Z, Zborilová B, Hrobonová V, Voríšková M, Skovránek J. Prevalence, treatment, and outcome of heart disease in live-born children: a prospective analysis of 91,823 live-born children. Pediatric cardiology. 1989;10(4):205-11.

9. Gittenberger-de Groot AC, Calkoen EE, Poelmann RE, Bartelings MM, Jongbloed MRM. Morphogenesis and molecular considerations on congenital cardiac septal defects. Ann Med. 2014;46(8):640-52.

10. Scherptong RWC, Jongbloed MRM, Wisse LJ, Vicente-Steijn R, Bartelings MM, Poelmann RE, et al. Morphogenesis of outflow tract rotation during cardiac development: The pulmonary push concept. 2012;241(9):1413-22.

11. Bajolle F, Zaffran S, Kelly RG, Hadchouel J, Bonnet D, Brown NA, et al. Rotation of the myocardial wall of the outflow tract is implicated in the normal positioning of the great arteries. Circulation research. 2006;98(3):421-8.

12. Parisot P, Mesbah K, Théveniau-Ruissy M, Kelly RG. Tbx1, subpulmonary myocardium and conotruncal congenital heart defects. Birt Defects Res A Clin Mol Teratol. 2011;91(6):477-84.

13. Ferencz C, Rubin JD, McCarter RJ, Brenner JI, Neill CA, Perry LW, et al. Congenital heart disease: prevalence at livebirth. The Baltimore-Washington Infant Study. Am J Epidemiol. 1985;121(1):31-6.

14. Kumar TKS. Congenitally corrected transposition of the great arteries. Journal of thoracic disease. 2020;12(3):1213-8.

15. Connelly MS, Liu PP, Williams WG, Webb GD, Robertson P, McLaughlin PR. Congenitally corrected transposition of the great arteries in the adult: functional status and complications. Journal of the American College of Cardiology. 1996;27(5):1238-43.

16. Lauer MS. Autonomic function and prognosis. 2009;76(4 suppl 2):S18-S22.

17. Bristow MR, Ginsburg R, Minobe W, Cubicciotti RS, Sageman WS, Lurie K, et al. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. The New England journal of medicine. 1982;307(4):205-11.

18. Brodde OE, Bruck H, Leineweber K. Cardiac adrenoceptors: physiological and pathophysiological relevance. Journal of pharmacological sciences. 2006;100(5):323-37.

19. Billman GE, Schwartz PJ, Stone HL. Baroreceptor reflex control of heart rate: a predictor of sudden cardiac death. Circulation. 1982;66(4):874-80.

20. La Rovere MT, Bigger JT, Jr., Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet

(London, England). 1998;351(9101):478-84.

21. Bauer A, Kantelhardt JW, Barthel P, Schneider R, Makikallio T, Ulm K, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet (London, England). 2006;367(9523):1674-81.

22. Olshansky B, Sabbah HN, Hauptman PJ, Colucci WS. Parasympathetic nervous system and heart failure: pathophysiology and potential implications for therapy. Circulation. 2008;118(8):863-71.

23. Camm AJ, Malik M, Bigger JT, Jr., Breithardt G, Cerutti S, Cohen RJ, et al. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. European heart journal. 1996;17(3):354-81.

24. Bauer A, Malik M, Schmidt G, Barthel P, Bonnemeier H, Cygankiewicz I, et al. Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus. Journal of the American College of Cardiology. 2008;52(17):1353-65.

25. Pauza DH, Skripka V, Pauziene N, Stropus R. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. The Anatomical record. 2000;259(4):353-82.

26. Vaitkevicius R, Saburkina I, Rysevaite K, Vaitkeviciene I, Pauziene N, Zaliunas R, et al. Nerve supply of the human pulmonary veins: an anatomical study. Heart rhythm. 2009;6(2):221-8.
27. Wickramasinghe SR, Patel VV. Local innervation and atrial fibrillation. Circulation. 2013;128(14):1566-75.

28. Huikuri HV, Valkama JO, Airaksinen KE, Seppanen T, Kessler KM, Takkunen JT, et al. Frequency domain measures of heart rate variability before the onset of nonsustained and sustained ventricular tachycardia in patients with coronary artery disease. Circulation. 1993;87(4):1220-8.

29. Huikuri HV, Seppanen T, Koistinen MJ, Airaksinen J, Ikaheimo MJ, Castellanos A, et al. Abnormalities in beat-to-beat dynamics of heart rate before the spontaneous onset of life-threatening ventricular tachyarrhythmias in patients with prior myocardial infarction. Circulation. 1996;93(10):1836-44.

30. Maier P, Toepfer M, Dambacher M, Theisen K, Roskamm H, Frey AW. Heart rate variability and its relation to ventricular tachycardia in patients with coronary artery disease. Clinical science (London, England : 1979). 1996;91 Suppl:67.

31. Shusterman V, Aysin B, Gottipaty V, Weiss R, Brode S, Schwartzman D, et al. Autonomic nervous system activity and the spontaneous initiation of ventricular tachycardia. ESVEM Investigators. Electrophysiologic Study Versus Electrocardiographic Monitoring Trial. Journal of the American College of Cardiology. 1998;32(7):1891-9.

32. Lombardi F, Porta A, Marzegalli M, Favale S, Santini M, Vincenti A, et al. Heart rate variability patterns before ventricular tachycardia onset in patients with an implantable cardioverter defibrillator. Participating Investigators of ICD-HRV Italian Study Group. The American journal of cardiology. 2000;86(9):959-63.

33. Meyerfeldt U, Wessel N, Schutt H, Selbig D, Schumann A, Voss A, et al. Heart rate variability before the onset of ventricular tachycardia: differences between slow and fast arrhythmias. International journal of cardiology. 2002;84(2-3):141-51.

34. Wollmann CG, Gradaus R, Bocker D, Fetsch T, Hintringer F, Hoh G, et al. Variations of heart rate variability parameters prior to the onset of ventricular tachyarrhythmia and sinus tachycardia in ICD patients. Results from the heart rate variability analysis with automated ICDs (HAWAI) registry. Physiological measurement. 2015;36(5):1047-61.

35. Brown CB, Feiner L, Lu MM, Li J, Ma X, Webber AL, et al. PlexinA2 and semaphorin signaling during cardiac neural crest development. Development (Cambridge, England). 2001;128(16):3071-80.

36. Sanchez-Castro M, Pichon O, Briand A, Poulain D, Gournay V, David A, et al. Disruption of the SEMA3D Gene in a Patient with Congenital

Heart Defects. Human Mutation. 2015;36(1):30-3.

37. Epstein JA, Aghajanian H, Singh MK. Semaphorin signaling in cardiovascular development. Cell metabolism. 2015;21(2):163-73.

38. Nederend I, Jongbloed M, de Geus E, Blom N, ten Harkel A. Postnatal Cardiac Autonomic Nervous Control in Pediatric Congenital Heart Disease. Journal of Cardiovascular Development and Disease. 2016;3(2):16.

39. Bakari S, Koca B, Öztunç F, Abuhandan M. Heart rate variability in patients with atrial septal defect and healthy children. J Cardiol. 2013;61(6):436-9.

40. Polson JW, McCallion N, Waki H, Thorne G, Tooley MA, Paton JF, et al. Evidence for cardiovascular autonomic dysfunction in neonates with coarctation of the aorta. Circulation. 2006;113(24):2844-50.

41. Davos CH, Moutafi AC, Alexandridi A, Petropoulou E, Varela E, Chamakou AC, et al. Heart rate turbulence in adults with repaired tetralogy of Fallot. International journal of cardiology. 2009;135(3):308-14.

42. Said SM, Burkhart HM, Schaff HV, Dearani JA. Congenitally Corrected Transposition of Great Arteries: Surgical Options for the Failing Right Ventricle and/or Severe Tricuspid Regurgitation. World journal for pediatric & congenital heart surgery. 2011;2(1):64-79.

43. Duncan BW, Mee RB. Management of the failing systemic right ventricle. Semin Thorac Cardiovasc Surg. 2005;17(2):160-9.

44. Vejlstrup N, Sorensen K, Mattsson E, Thilen U, Kvidal P, Johansson B, et al. Long-Term Outcome of Mustard/Senning Correction for Transposition of the Great Arteries in Sweden and Denmark. Circulation. 2015;132(8):633-8.

45. Filippov AA, Del Nido PJ, Vasilyev NV. Management of Systemic Right Ventricular Failure in Patients With Congenitally Corrected Transposition of the Great Arteries. Circulation. 2016;134(17):1293-302.

46. Scherptong RW, Vliegen HW, Winter MM, Holman ER, Mulder BJ, van der Wall EE, et al. Tricuspid valve surgery in adults with a dysfunctional systemic right ventricle: repair or replace? Circulation. 2009;119(11):1467-72.

47. Muzzarelli S, Ordovas KG, Higgins CB, Meadows AK. Collateral flow measurement by phase-contrast magnetic resonance imaging for the assessment of systemic venous baffle patency after atrial switch repair for transposition of the great arteries. J Thorac Imaging. 2012;27(3):175-8.

48. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, et al. 2020 ESC Guidelines for the management of adult congenital heart disease. European heart journal. 2021;42(6):563-645.

49. Hernandez-Madrid A, Paul T, Abrams D, Aziz PF, Blom NA, Chen J, et al. Arrhythmias in congenital heart disease: a position paper of the European Heart Rhythm Association (EHRA), Association for European Paediatric and Congenital Cardiology (AEPC), and the European Society of Cardiology (ESC) Working Group on Grown-up Congenital heart disease, endorsed by HRS, PACES, APHRS, and SOLAECE. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2018;20(11):1719-53.

50. Anderson RH, Becker AE, Arnold R, Wilkinson JL. The Conducting Tissues in Congenitally Corrected Transposition. 1974;50(5):911-23.

51. Helbing WA, Rebergen SA, Maliepaard C, Hansen B, Ottenkamp J, Reiber JH, et al. Quantification of right ventricular function with magnetic resonance imaging in children with normal hearts and with congenital heart disease. American heart journal. 1995;130(4):828-37.

52. Winter MM, Bernink FJ, Groenink M, Bouma BJ, van Dijk AP, Helbing WA, et al. Evaluating the systemic right ventricle by CMR: the importance of consistent and reproducible delineation of the cavity. J Cardiovasc Magn Reson. 2008;10(1):40.

53. Iriart X, Roubertie F, Jalal Z, Thambo J-B. Quantification of systemic right ventricle by echocardiography. Archives of cardiovascular diseases. 2016;109(2):120-7.

54. Woudstra OI, van Dissel AC, van der Bom T, de Bruin-Bon R, van Melle JP, van Dijk APJ, et al. Myocardial Deformation in the Systemic Right

Ventricle: Strain Imaging Improves Prediction of the Failing Heart. The Canadian journal of cardiology. 2020;36(9):1525-33.

55. van der Bom T, Winter MM, Bouma BJ, Groenink M, Vliegen HW, Pieper PG, et al. Effect of valsartan on systemic right ventricular function: a double-blind, randomized, placebo-controlled pilot trial. Circulation. 2013;127(3):322-30.

56. van Dissel AC, Winter MM, van der Bom T, Vliegen HW, van Dijk APJ, Pieper PG, et al. Long-term clinical outcomes of valsartan in patients with a systemic right ventricle: Follow-up of a multicenter randomized controlled trial. International journal of cardiology. 2019;278:84-7.

57. Woudstra OI, Kuijpers JM, Jongbloed MRM, van Dijk APJ, Sieswerda GT, Vliegen HW, et al. Medication in adults after atrial switch for transposition of the great arteries: clinical practice and recommendations. European heart journal Cardiovascular pharmacotherapy. 2022;8(1):77-84.

58. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. The New England journal of medicine. 2014;371(11):993-1004.

59. Treskes RW , Koole M , Kauw D , Winter MM, , Monteiro M , Dohmen D , Abu-Hanna A , Schijven MP , Mulder BJ , Bouma BJ , Schuuring MJ. Adults with congenital heart disease: ready for mobile health? Neth Heart J 2019;27:152–160.

60. Brida M, Diller G-P, Gatzoulis MA. Systemic Right Ventricle in Adults With Congenital Heart Disease. Circulation. 2018;137(5):508-18.