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

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Chapter 10

Summary, conclusions, and future perspectives

The aims of this thesis were to clarify the physiology and pathophysiology of the systemic right ventricle, with a specific focus on autonomic function (part I: physiology and mechanisms) in relation to clinical outcome, and to explore diagnostic and treatment options (part II: clinical applications). Below, the chapters will be summarized and placed within the context of current literature. Future perspectives will be given per topic.

Part I: (patho)physiology and mechanisms

In the first three chapters, several mechanisms underlying (systemic) ventricular physiology and disease were explored. In **chapter 1**, current knowledge regarding asymmetry and heterogeneity in cardiac autonomic innervation was reviewed. Knowledge about the cardiac autonomic nervous system is necessary to understand and to treat cardiac disease. The heart is an asymmetrical organ, and also cardiac autonomic innervation demonstrates left-right as well as regional differences in anatomy and function. This may have relevant clinical implications. For example, the left and right stellate ganglia and the left and right vagus nerves innervate different areas of the heart or have different effects on the same area (1, 2). In particular, the left stellate ganglion appears to play an important role in ventricular arrhythmias and is an important treatment target, which is not the case for the right stellate ganglion (3, 4).

In **chapter 2 and 3**, three categories of ambulatory ECG-derived measures of cardiac autonomic function were investigated in patients with a systemic right ventricle: *heart rate variability*, *QT-interval variability*, and *heart rate turbulence*. In **chapter 2**, we conclude that in patients with a systemic RV, the heart rate variability component of SDANN (standard deviation of the average normal-to-normal intervals calculated over 5-minute intervals) was independently associated with the occurrence of supraventricular tachycardias. This is clinically relevant as previous studies show that supraventricular arrhythmias are independently associated with sudden cardiac death and mortality in patients with a systemic RV (5-7). Several components of heart rate variability were also correlated with systemic RV function, while in the cohort as a whole, the systemic RV function was relatively preserved. This may indicate the usefulness of heart rate variability to predict clinically overt systemic RV failure. In **chapter 3**, we conclude that components of both QT interval variability and heart rate turbulence were also associated with supraventricular tachycardias. Medication use, including flecainide, diuretics, and ACE inhibitors/ARBs, was also associated with QT variability and heart rate turbulence components, which may indicate that a worse clinical status of these patients is reflected in their autonomic function. Interestingly, heart rate turbulence was worse in patients who underwent recent thoracic surgery but not in patients who underwent one or multiple thoracic surgeries longer ago,

indicating the ability of the cardiac innervation to regenerate after surgical trauma. Future studies might investigate the effects of autonomic modulation, for example vagus nerve stimulation, in patients with a systemic RV. Currently, carefully optimistic results are available for patients with LV disease (8). Heart rate variability, QT interval variability, and heart rate turbulence may be investigated further for their potential to predict clinical deterioration and their possible response to autonomic modulation therapies.

Part II: clinical applications

In **chapter 5**, we concluded that, while echocardiographical assessment of systemic RV function is challenging, several echocardiographic variables are highly feasible and perform well compared with cardiac magnetic resonance, which is considered the gold standard. These variables include *visual estimation of global function*, *fractional area change*, and especially *global longitudinal strain*. Conceptually sound variables such as the *myocardial performance index* may also perform well in patients with LV disease (9) or selected, less complex groups of patients with a systemic RV (10). However, the population we describe reflects the heterogeneous and complex population that is seen in daily clinical practice. The measurement of fractional area change, global longitudinal strain, and the visual estimation of RV function may be implemented in routine echocardiographic protocols for the follow-up of patients with a systemic RV.

In **chapter 6**, the clinical course of patients long after Mustard or Senning correction of TGA was characterized and a risk score to predict major clinical events was distilled from the data. The score requires the often readily available information regarding current age, age at atrial switch operation, prior ventricular arrhythmia, moderate or severe systemic RV dysfunction, severe tricuspid valve regurgitation, and mild or greater subpulmonary LV dysfunction. This risk score may be used in the counseling of patients in the outpatient clinic or in the process of deciding the frequency and intensity of follow-up. Previous studies addressing risk stratification have mainly focused on the group of adults of congenital heart disease as a whole, for example in the need for implantable cardioverter-defibrillator therapy (11), or heart failure (12). However, since the group of adults with congenital heart disease is very heterogeneous, the risk score described in chapter 6 may be more useful in the group of systemic RV patients after Mustard or Senning correction.

Chapter 7 describes the first results of the treatment of systemic right ventricular failure with sacubitril/valsartan. After six months of follow-up, NT-pro-BNP was significantly decreased, echocardiographic systemic RV function showed a small but significant improvement, and 6-minute walking distance and some aspects of quality of

life also showed improvement. Considering that the current ESC guidelines do not recommend specific medical treatment of systemic RV failure yet (13), these results are an important step forward towards expanding and standardizing the medical treatment of systemic RV failure. More evidence is needed to translate these preliminary results into standard clinical practice. In the future, hopefully, the options for medical treatment of systemic RV failure will be expanded with other medications such as SGLT2-inhibitors (14).

Chapter 8 describes the experience of the application of eHealth smart technology in the titration of sacubitril/valsartan in the cohort of **Chapter 7** consisting of patients with systemic RV failure. The patient adherence was high: 83,3% of patients submitted measurements twice a week during the titration process. The satisfaction with the implementation of this technology was 95,5%. For the 24 patients included, 68 trips to the hospital were prevented when compared with the conventional titration process. In one patient (4,2%) a heart failure-related hospital admission was not prevented despite sending in measurements and subsequent contact moments, according to protocol. The possibilities of eHealth are not limited to the measurement of blood pressure, weight, daily steps taken, and the detection of arrhythmias, as described here, but measurement of oxygen saturation and even remote physical activity interventions are being tested in patients with congenital heart disease (15, 16)

In **chapter 9**, we report the first two cases of implantation of a ventricular assist device into a failing systemic RV. At the time of writing, both patients were doing well and had experienced no more complications than can be expected in the usual patient category of LV failure (two early reoperations, one ischemic stroke with mild cognitive sequelae, and a hemodynamically well-tolerated VT, for both patients in total). The implantation of a ventricular assist device may be an attractive option for patients with end stage systemic RV failure. Due to factors such as a complex anatomy or the presence of pulmonary hypertension, they are likely to be rejected for cardiac transplantation, and the function of the subpulmonary LV function is often preserved. In the future, the number of systemic RV patients who might benefit from implantation of a ventricular assist device (either as bridge to transplant or as destination therapy) is expected to increase as the generation of systemic RV patients becomes older and the shortage of donor organs is expected to persist. For patients with concomitant subpulmonary LV dysfunction, a total artificial heart might also become a feasible treatment modality (17).

In conclusion, adult congenital heart disease patients with a systemic RV comprises a complex patient group in whom a myriad of long-term complications can be observed. The work highlighted in this thesis will form the base for ongoing studies aimed at improving outcome and quality of life of this vulnerable group.

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