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

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# Chapter 3

# Association between reduced heart rate variability components and supraventricular tachyarrhythmias in patients with a systemic right ventricle

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**Abstract**

**Background**

Patients with a systemic right ventricle are prone to develop heart failure. Abnormal heart rate variability (HRV), a measure of autonomic dysfunction, is associated with morbidity and mortality in patients with left ventricular failure. The association between HRV and supraventricular arrhythmias (SVTs), which are associated with adverse events in this population, was assessed.

**Methods**

24-Hour Holter recordings of patients with a systemic right ventricle and healthy controls were analysed in a retrospective cohort study. HRV was calculated and compared between groups. Correlation coefficients were determined for HRV variables and clinical characteristics. The relation between HRV and SVTs was investigated with linear regression.

**Results**

The patient group included 29 patients (69%) late after Mustard or Senning correction for transposition of the great arteries, and 13 patients with congenitally corrected transposition of the great arteries (31%). The control group included 38 subjects. HRV was significantly lower in patients compared with controls. In the patient group, lower SDANN (standard deviation of the average NN intervals calculated over 5-minute intervals) was independently associated with a higher number of supraventricular arrhythmias (95% CI −0.03 to −0.0004, p = 0.045). In exploratory correlation analysis, several HRV variables correlated with echocardiographic systemic right ventricular function (rho = 0.36, p = 0.02 for SDANN), and exercise capacity (rho = 0.39, p = 0.05 for SDANN).

**Conclusion**

In patients with a systemic right ventricle, HRV is lower compared with controls and (SDANN) is independently associated with supraventricular arrhythmias.

**Introduction**

Sympathetic and parasympathetic autonomic innervation of vital organs enable adaptation to external circumstances, allowing optimal functioning ranging from 'fight or flight' to 'rest and digest', respectively. However, autonomic nervous system responses to disease states may also eventually contribute to the pathophysiology. Sympathetic overstimulation accompanies left-sided heart failure from the onset, initially leading to restoration of cardiac output but ultimately leading to loss of inotropic reserve and increased susceptibility to arrhythmias (*Franciosi et al., 2017*). Parasympathetic activity is considered to have a protective effect against ventricular arrhythmias, but is often reduced in patients with heart failure (*Brack et al., 2013*).

Adult patients with congenital heart disease with a systemic right ventricle (RV) in a biventricular circulation, i.e. patients with transposition of the great arteries (TGA) after Mustard or Senning correction or patients with congenitally corrected TGA (ccTGA), are prone to develop heart failure and other complications, such as systemic atrioventricular valve regurgitation, impulse formation and conduction disorders, and tachyarrhythmias (*Brida et al., 2018*). Specifically, supraventricular tachyarrhythmias (SVTs) are very common: in patients after Mustard or Senning repair they may be caused by atrial scar tissue and in patients with ccTGA they are often caused by congenital accessory pathways (*Hernandez-Madrid et al., 2018*). SVTs appear to be predictive of mortality and sudden cardiac death in patients with a systemic right ventricle, with most evidence in the Mustard/Senning group (*Connelly et al., 1996; Mongeon et al., 2011; Venkatesh et al., 2019*).

Cardiac autonomic function is disturbed in many congenital heart diseases. This may be a compensatory mechanism but can also be a consequence of surgery or of abnormal development. As autonomic function provides important prognostic information, data regarding autonomic function in systemic RV patients may be valuable in clinical practice.

Cardiac autonomic function can be assessed noninvasively with analysis of heart rate variability (HRV), which is a quantification of spontaneous fluctuations of heart rate. HRV analysis consists of time domain variables and frequency domain variables. Time domain variables quantify the amount of variability in all normal-to-normal (NN) interbeat intervals (excluding non-sinus beats) of a recording (for example a 5-minute electrocardiogram (ECG) or a 24-hour Holter recording). An example is SDNN (standard deviation of all normal-to-normal intervals). Frequency domain variables show how much of the total variance (=power) lies within certain predefined frequency bands.

Variations in heart rate follow many cyclic patterns. Some are known to be caused by autonomic modulation, others are caused by unknown factors. A clarifying example of a well-known cyclic pattern in heart rate is respiratory sinus arrhythmia (RSA). RSA, i.e. fluctuations in heart rate following the frequency of breathing, is caused by parasympathetic output to the sinus node. Parasympathetic stimulation of the sinus node leads to an increase in spontaneous fluctuations, especially on the short term. The frequency domain parameter high-frequency (HF) power, which describes distribution of heart rate variance across the frequency of 0.15–0.4 Hz, which includes breathing frequency, is therefore largely ascribed to vagal modulation (*Akselrod et al., 1981*).

Generally, considerable variation in heart rate is a sign of health and decreased HRV is a sign of disease. In healthy, resting humans, parasympathetic tone predominates. A predominating sympathetic tone, however, leads to a decrease in the time-domain variables of HRV. Regarding frequency domain variables, both sympathetic and parasympathetic influences modulate a part of the low-frequency (LF) power, but other and unknown factors also influence this peak, therefore the exact composition of the LF peak is unclear (*Camm et al., 1996*).

Several studies (for example (*La Rovere et al., 1998*)) have demonstrated decreased HRV in patients with congestive heart failure, which is an independent risk factor for mortality in this group. Most data are derived from studies in patients with left ventricular (LV) failure based on ischemic or non-ischemic cardiomyopathy. Recently, it has become clear that autonomic dysfunction also plays an important role in diseases involving primarily RV dysfunction. For example, in patients with pulmonary hypertension, HRV is decreased and correlated with disease progression (*Bienias et al., 2015*). In (young) adult patients late after repair of tetralogy of Fallot, abnormal HRV is correlated with pulmonary valve regurgitation and with the number of years after repair (*Davos et al., 2002*). Importantly, abnormal HRV patterns are also associated with ventricular arrhythmias and sudden cardiac death, both in left ventricular (LV) and RV disease (*Davos et al., 2002; Valkama et al., 1995*).

The aims of the current study were to gain insight in the patterns of autonomic (dys) function of the systemic RV and to study whether HRV is correlated with SVTs in this group, as SVTs are an important marker of clinical status and may provide indirect information about clinical outcome. We hypothesised that worse HRV would be associated with SVTs and other clinical characteristics reflective of cardiac deterioration, such as exercise capacity and echocardiographic systemic RV function.

## Methods

### Design

A retrospective cohort study was performed. HRV analysis was carried out in systemic RV patients and healthy controls. Correlation of HRV with clinical factors was investigated. The need for informed consent was waived by the Leiden University Medical Center's medical ethical committee. The study protocol conforms to the ethical guidelines of the 2013 Declaration of Helsinki.

### Selection of patients and controls

All files of adult patients with a systemic RV and a biventricular circulation under current/past follow-up in our center were screened for the presence of digitally available 24-hour Holter registrations. A control group was formed by consecutive patients referred for cardiac screening because of possible genetic cardiac abnormalities. As part of the screening protocol, 24-hour Holter monitoring, echocardiography, genetic testing, and (bicycle) exercise test were conducted. Control subjects were eligible for inclusion if no genetic abnormalities and no abnormalities in the cardiac investigations were found. For both patients and controls, protocols for the exercise tests are in accordance with the guidelines of the American College of Cardiology/American Heart Association (*Fletcher et al., 2013*).

### Exclusion criteria

Patients or controls were excluded if there were no available/interpretable Holter monitoring records. Holter recordings were excluded if the primary rhythm was not sinus rhythm or if the quality was insufficient, if the patient had clinically relevant diabetes (defined as the use of at least one antidiabetic drug), had rheumatoid arthritis, or was using antidepressant or antipsychotic medication, due to potential interference with cardiac autonomic function (*Benichou et al., 2018; Koopman et al., 2016; O'Regan et al., 2015*). Control subjects were excluded if they had a history of relevant cardiac disease, or if they were using β-blockers.

### Holter processing and variables

For each patient or control subject, the most recent 24-hour Holter registrations were analysed. Processing and HRV calculations were performed with the specialised program MARS, version 8 (GE Healthcare, Milwaukee, United States). In line with standard HRV settings in MARS, RR interval ratios <0.8 and >1.2 (probably indicating a sinus pause or an ectopic beat) were automatically excluded. RR intervals >1500 ms (40 beats per minute) were also automatically excluded because this amount of bradycardia affects HRV calculation and is furthermore more likely to be ectopic atrial

rhythm or a consequence of sinus node dysfunction rather than autonomic modulation. Registrations were thoroughly manually reviewed for correct labelling and correct onset of the QRS-complexes. Episodes with non-sinus ectopic atrial rhythm or unreliable signals were excluded. The rhythm was considered to be sinus rhythm in cases with positive p-waves on Holter lead II and III. This was always confirmed with 12-lead ECGs. In all cases, consensus was reached by discussion with experienced congenital cardiologists (HV, PK, AE, MJ). Registrations with <18 h of analysable time (due to either noise or large proportion of non-sinus rhythm) were excluded, in accordance with HRV guidelines (*Camm et al., 1996*). All in all, Holters from patients with sick sinus syndrome, or the parts of the Holters displaying these features, were likely to be excluded. Therefore, sick sinus syndrome was not analysed in the context of HRV in this study.

The HRV function in MARS was used for calculation of the following variables: SDNN (standard deviation of all normal-to-normal, or NN intervals), SDANN (standard deviation of the average NN intervals calculated of all 5-minute intervals), ASDNN (average standard deviation of all NN intervals for all 5-minute intervals, pNN50 (percentage of adjacent NN intervals that differ by >50 milliseconds), rMSSD (square root of the mean squared differences of successive NN intervals)), (time domain), VLF (very low-frequency power, 0.003–0.04 Hz), LF (low-frequency power, 0.04–0.15 Hz), and HF (high-frequency power, 0.15–0.4 Hz) (frequency domain) (*Camm et al., 1996*).

**Clinical characteristics and outcomes**

For each patient or control, length, weight, body surface area (BSA), medication use, and age at the time of the Holter registration were noted. Values of N-terminal brain natriuretic peptide (NT-pro-BNP) and results of exercise tests closest to the time of Holter registration were noted when available, including: the number of maximum achieved Watts, exercise capacity (percentage of the predicted number of Watts), and the percentage of the predicted maximum heart rate (220-age) that was achieved. The global systemic RV function as noted in the report by the supervising imaging cardiologist was scored. Global longitudinal strain of the systemic ventricle was assessed offline in the apical four-chamber view (*Rudski et al., 2010*). Echocardiograms had been obtained with commercially available ultrasound systems and offline analysis was performed in EchoPac, GE Medical Systems.

To examine the role that HRV plays in current clinical context, a surrogate endpoint was constructed in the form of the number of supraventricular arrhythmias (SVTs) which occurred up until the time of the Holter recording. This methodology was chosen because assessment of the predictive power of HRV in the context of sudden cardiac

death or mortality was not feasible, and because SVTs are an important marker of clinical condition in patients with a systemic right ventricle (*Connelly et al., 1996; Mongeon et al., 2011; Venkatesh et al., 2019*). SVTs were scored when they led to initiation of treatment or when they were persistent and accepted. So for example, an episode of atrial flutter was counted when it was followed by a change in anti-arrhythmic medication, but several episodes of paroxysmal flutter in a short period of time which were not treated, were not counted.

**Statistical analysis**

All statistical analyses were performed with IBM SPSS statistics version 23. Normally distributed data are reported as mean ± SD and non-normally distributed data are reported as median and interquartile range (IQR). For the comparison of baseline characteristics and Holter variables between patients and controls, a t-test or Mann-Whitney-U for independent samples was used for continuous data and the Chi-square or Fisher's exact test were used for categorical data, as appropriate. To assess correlations of clinical factors with HRV, Spearman's rho correlation coefficient was calculated. For all analyses, p-values<0.05 were considered statistically significant. Spearman's rho correlation coefficient was also calculated for clinical characteristics and HRV variables in the control group. Holm's correction method for multiple comparisons (*Holm, 1979*) was applied to the correlation analyses. In this method, the p-values are sorted smallest to largest and ranked accordingly. All raw p-values are then compared to 0.05*(number of tests-rank+1). If the raw p-value is smaller than the newly calculated threshold, the hypothesis can be accepted. If larger, it is rejected.

To assess whether HRV was associated with clinical outcome, linear regression was performed with the number of SVTs which occurred up until the Holter recording as outcome variable. Predictor variables were selected as follows: All HRV variables which had a statistically significant Spearman's correlation coefficient with the number of SVTs were included in the univariate analysis. Other clinical factors were also included when they were expected to be potentially clinically relevant. The multivariate model was constructed with stepwise forward addition of variables, starting with the most significant variables in univariate analysis. Addition of variables was terminated after addition of the last variable that improved the model significantly.

## Results

### Subjects and baseline characteristics

Holter recordings were analysed for 42 systemic RV patients (*Figure 1*) and 38 healthy controls. Both groups were comparable in terms of age and gender. Patients had worse exercise capacity, reduced chronotropic competence, and reduced systemic ventricular function (*Table 1*).

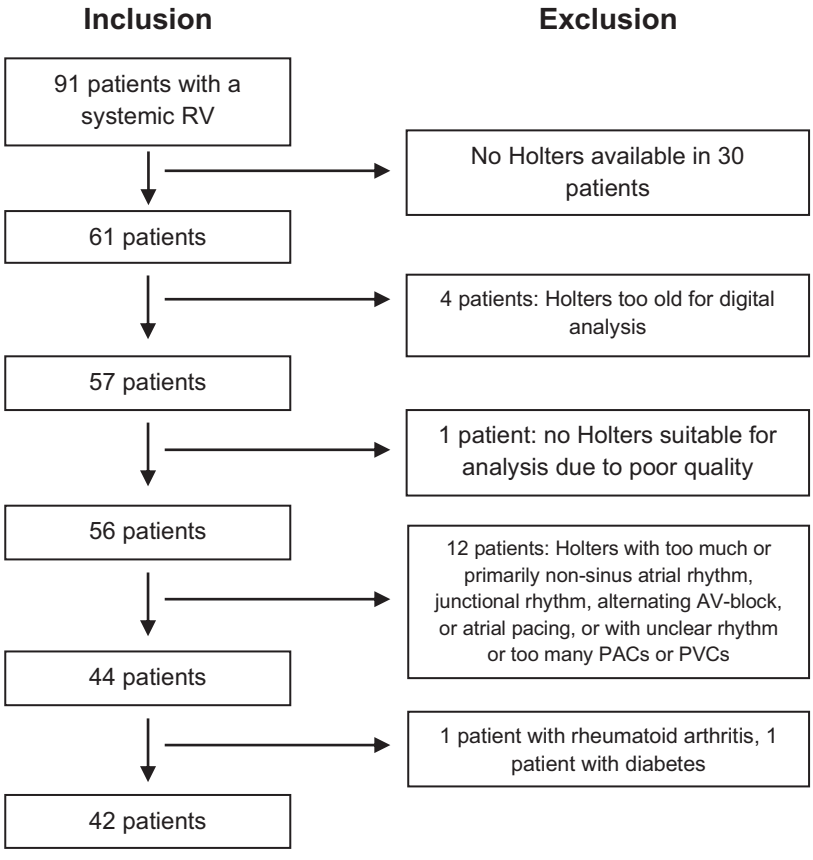


***Figure 1: Flowchart patient Holter selection.***
*PACs: premature atrial complexes; PVCs: premature ventricular complexes; RV: right ventricle*

**Table 1: Baseline characteristics patients (at most recent Holter) and controls**

| Characteristics | Patients N (%) | | Mean (±SD) or median (IQR) | | Controls N (%) | | Mean (±SD) or median (IQR) | | p-value |
|---|---|---|---|---|---|---|---|---|---|
| Total number | 42 | (100%) | | | 38 | (100%) | | | |
| Females | 18 | (43%) | | | 21 | (55%) | | | 0.27 |
| Alive | 40 | (95%) | | | 38 | (100%) | | | 0.50 |
| Primary condition: | | | | | | | | | |
| Mustard | 11 | (26%) | | | n.a. | | | | |
| Senning | 18 | (43%) | | | n.a. | | | | |
| ccTGA | 13 | (31%) | | | n.a. | | | | |
| Age (years) | | | 40 | (±9.5) | | | 42 | (±12.9) | 0.49 |
| BSA ($m^2$) | | | 2.0 | (±0.19) | | | 1.9 | (±0.23) | 0.15 |
| Holters per patient | | | 2.0 | (1.0–4.0) | 1 | | | | |
| Patients with > 1 Holter | 29 | (69%) | | | 0 | | | | |
| Time first-last Holter (years) | | | 3.3 | (0.0-8.4) | | | | | |
| Medication use: | | | | | | | | | |
| Beta-blocker | 7 | (17%) | | | 0 | (0%) | | | **0.01*** |
| ACEi or ARB | 18 | (43%) | | | 1 | (3%) | | | **<0.01*** |
| Diuretic | 10 | (24%) | | | 1 | (3%) | | | **0.01*** |
| Bm/AC | 2 | (5%) | | | 5 | (13%) | | | 0.24 |
| Digoxin | 1 | (2%) | | | 0 | (0%) | | | 1.00 |
| Amiodarone | 2 | (5%) | | | 0 | (0%) | | | 0.50 |
| Class I anti-arrhythmic drug | 2 | (5%) | | | 0 | (0%) | | | 0.50 |
| Watts | | | 160 | (110-200) | | | 200 | (160-240) | **0.05*** |
| Exercise capacity (%) | | | 92 | (80-115) | | | 123 | (±108-142) | **<0.01*** |
| % of predicted heart rate | | | 87 | (±17) | | | 97 | (±7) | **0.011*** |
| Systemic ventricular GLS[1] | | | 14.7 | (±2.3) | | | 20.1 | (±2.8) | **<0.01*** |
| Systemic ventricular function[1] | | | | | | | | | **<0.01*** |
| good (1) | 1 | (3%) | | | 36 | (97%) | | | |
| mildly reduced (2) | 29 | (72%) | | | 1 | (3%) | | | |
| moderately reduced (3) | 10 | (25%) | | | 0 | (0.0%) | | | |
| severely reduced (4) | 0 | (0.0%) | | | 0 | (0.0%) | | | |
| TR grade | | | | | | | | | **<0.01*** |
| 1 or less | 20 | (48%) | | | 38 | (100%) | | | |
| 2 | 22 | (52%) | | | 0 | (0%) | | | |
| 3 | 0 | (0%) | | | 0 | (0%) | | | |
| 4 | 0 | (0%) | | | 0 | (0%) | | | |
| Number of previous surgeries | | | | | | | | | **<0.01*** |
| 0 | 9 | (21%) | | | 38 | (100%) | | | |
| 1 | 16 | (38%) | | | 0 | (0%) | | | |
| 2 | 13 | (31%) | | | 0 | (0%) | | | |
| 3 | 4 | (10%) | | | 0 | (0%) | | | |

**Significant p value; 1: no echo available in 2 patients and in 1 control; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor antagonist; Bm/Ac: betamimetic or anticholinergic drug; BSA: body surface area; ccTGA: congenitally corrected transposition of the great arteries; GLS: global longitudinal strain; IQR: interquartile range; SD: standard deviation; TR: tricuspid regurgitation*

**Comparison of HRV between patients and controls**

*Table 2* shows ECG characteristics and HRV data of patients compared with controls. Patients often had a right axis deviation of the QRS complex, and had significantly longer PR intervals, QRS durations, and QTc intervals compared with controls. SDNN, SDANN, and LF power were significantly reduced in the patient group. *Figure 2* shows SDNN and SDANN in patients and controls.

**Table 2. Comparison ECG and Holter data between patients and controls**

| ECG | Patients (n=42) Mean±SD or median (IQR) | | Controls (n=38) Mean±SD or median (IQR) | | p value |
|---|---|---|---|---|---|
| Axis[1] (N, %) | | | | | **<0.01*** |
| Normal | 8 | (21%) | 33 | (87%) | |
| Right axis deviation | 20 | (51%) | 1 | (3%) | |
| Left axis deviation | 6 | (15%) | 4 | (10%) | |
| Extreme axis deviation | 5 | (13%) | 0 | (0%) | |
| PR interval | 184 | ±36 | 153 | ±21 | **<0.01*** |
| QRS[1] duration | 113 | (103 – 121) | 100 | (90 – 111) | **<0.01*** |
| RBTB[1] (N, %) | 8 | (21%) | 3 | (8%) | 0.19 |
| LBTB[1] (N, %) | 3 | (8%) | 1 | (3%) | 0.62 |
| QTc interval[1] | 423 | ±25 | 399 | ±17 | **<0.01*** |
| Holter | | | | | |
| Mean HR | 72 | (±7) | 75 | (±9) | 0.07 |
| SDNN (ms) | 139 | (±46) | 161 | (±36) | **0.02*** |
| SDANN (ms) | 122 | (±44) | 144 | (±32) | **0.02*** |
| ASDNN (ms) | 59 | (±20) | 66 | (±22) | 0.13 |
| pNN50 (%) | 9.4 | (6.2 – 14.8) | 9.8 | (4.3 – 19.0) | 0.81 |
| rMSSD (ms) | 33 | (27-42) | 34 | (25-44) | 0.87 |
| VLF ($ms^2$) | 1072 | (540-1290) | 1140 | (778-1776) | 0.13 |
| LF ($ms^2$) | 383 | (234-757) | 669 | (425-1164) | **0.01*** |
| HF ($ms^2$) | 165 | (99-313) | 199 | (103-385) | 0.53 |

**Significant p value; 1: 3 patients with ventricular pacing not included; ASDNN: average standard deviation of all NN intervals for all 5-minute intervals; HF: high-frequency power: HR: heart rate; IQR: interquartile range; LBTB: left bundle branch block morphology; LF: low-frequency power; ms: milliseconds; PAC: premature atrial complex; pNN50: percentage of adjacent NN intervals that differ by more than 50 ms; PVC: premature ventricular complex; QTc; heart rate corrected QT interval; RBTB: right bundle branch block morphology; rMSSD: square root of the mean squared differences of successive NN intervals; SD: standard deviation; SDANN: standard deviation of the average NN intervals calculated over 5-minute intervals; SDNN: standard deviation of all normal-to-normal (NN) intervals; VLF: very low-frequency power*

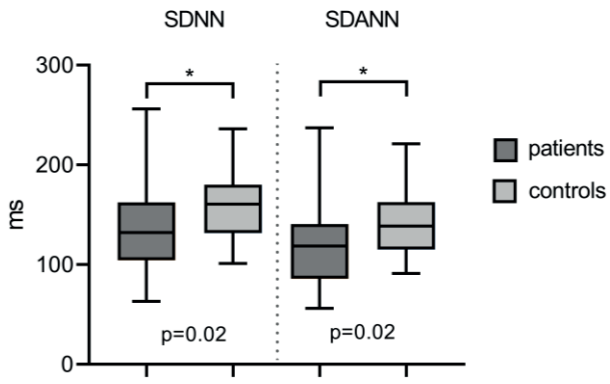


***Figure 2: SDNN and SDANN in patients and controls.***
*SDANN: standard deviation of the average normal-to-normal (NN) intervals calculated over 5-minute intervals; SDNN: standard deviation of all NN intervals.*

**Correlation between HRV and clinical factors**

Spearman's rho correlation coefficient was calculated to assess the correlation between the HRV variables and clinical factors, including the number of SVTs (*Table 3*). Higher age, worse echocardiographic RV function (higher GLS) (*Figure 3*), worse exercise capacity, and a higher number of SVTs correlated with lower HRV in several variables. The percentage of predicted maximum heart rate that was reached during exercise testing positively correlated with LF power. Higher exercise capacity correlated with higher HRV. NT-pro-BNP is not listed as very few values were available. After correction of the p-values according to Holm's method, only the correlations between SDNN and SVTs and SDANN and SVTs remained significant ($p=0.00033 <$ calculated norm of 0.00063, and $p=0.00024 <$ calculated norm of 0.00063, respectively).

**Table 3: Correlations between HRV and clinical factors in most recent patient Holters**

| | | SDNN | SDANN | ASDNN | pNN50 | rMSSD | VLF | LF | HF |
|---|---|---|---|---|---|---|---|---|---|
| Age | rho | -0.34 | -0.35 | -0.26 | -0.04 | -0.07 | -0.34 | -0.28 | -0.20 |
| | p | **0.03*** | **0.02*** | 0.10 | 0.81 | 0.66 | **0.03*** | 0.07 | 0.22 |
| Gender | rho | -0.03 | -0.04 | -0.01 | 0.11 | 0.08 | -0.04 | 0.00 | 0.17 |
| | p | 0.85 | 0.79 | 0.93 | 0.49 | 0.64 | 0.78 | 0.98 | 0.28 |
| Thoracotomies[a] | rho | -0.16 | -0.16 | -0.07 | -0.12 | -0.11 | -0.08 | -0.21 | -0.24 |
| | p | 0.33 | 0.34 | 0.66 | 0.46 | 0.52 | 0.64 | 0.21 | 0.14 |
| β-blocker use | rho | -0.24 | -0.30 | 0.01 | 0.07 | 0.08 | -0.08 | 0.01 | 0.09 |
| | p | 0.13 | 0.06 | 0.96 | 0.64 | 0.60 | 0.63 | 0.93 | 0.58 |
| QRS duration | rho | 0.14 | -0.14 | -0.09 | 0.14 | 0.14 | -0.23 | -0.06 | -0.01 |
| | p | 0.40 | 0.40 | 0.58 | 0.39 | 0.40 | 0.17 | 0.70 | 0.96 |
| QTc duration | rho | -0.14 | -0.18 | -0.04 | 0.21 | 0.20 | -0.22 | -0.02 | 0.04 |
| | p | 0.40 | 0.28 | 0.83 | 0.19 | 0.23 | 0.18 | 0.88 | 0.79 |
| % of predicted | rho | 0.11 | 0.04 | 0.27 | -0.16 | -0.06 | 0.27 | **0.47** | 0.08 |
| heart rate[b] | p | 0.63 | 0.85 | 0.25 | 0.51 | 0.80 | 0.25 | **0.04*** | 0.73 |
| Watts | rho | 0.49 | 0.50 | 0.15 | -0.41 | -0.31 | 0.23 | 0.23 | -0.25 |
| | p | **0.01*** | **0.01*** | 0.47 | **0.04*** | 0.12 | 0.28 | 0.27 | 0.24 |
| RV GLS | rho | -0.49 | -0.50 | -0.29 | -0.04 | -0.06 | -0.43 | -0.34 | -0.08 |
| | p | **<0.01*** | **<0.01*** | 0.07 | 0.82 | 0.70 | **<0.01*** | **0.04*** | 0.62 |
| SVTs | rho | **-0.53** | **-0.54** | -0.28 | -0.02 | -0.03 | **-0.39** | **-0.31** | -0.13 |
| | p | **<0.01*** | **<0.01*** | 0.07 | 0.88 | 0.85 | **0.01*** | **0.05*** | 0.40 |

*ASDNN: average standard deviation of all NN intervals for all 5-minute intervals; HF: high-frequency power; LF: low-frequency power; pNN50: percentage of adjacent NN intervals that differ by >50 ms; rMSSD: square root of the mean squared differences of successive NN intervals; RV GLS: (systemic) right ventricular global longitudinal strain; SDANN: standard deviation of the average NN intervals calculated over 5-minute intervals; SDNN: standard deviation of all normal-to-normal (NN) intervals; VLF: very low-frequency power. *Significant p-value; a: excluding patients who underwent TVP/TVR; b: excluding β=blocker users*

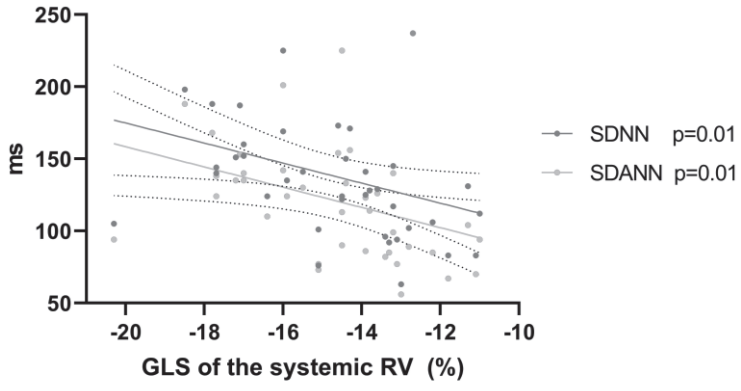


***Figure 3: SDNN/SDANN and GLS of the systemic RV.***
*SDANN: standard deviation of the average normal-to-normal (NN) intervals calculated over 5-minute intervals; SDNN: standard deviation of all NN intervals; GLS: global longitudinal strain.*

**Linear regression: association between HRV and SVTs**

Regression analyses with SVTs as the outcome variable are shown in *Table 4*. As SDNN, SDANN, VLF, and LF correlated with SVTs (*Table 3*), they were assessed in univariate linear regression (*Table 4*). Other potentially clinically relevant variables were also assessed. SDNN and SDANN were significantly associated with SVTs in univariate analysis, as were the number of Watts derived from bicycle exercise testing, the echocardiographic systemic RV GLS, the QTc interval, and β-blocker use. In multivariate analysis, only SDANN and the systemic RV GLS were independently associated with SVTs (*Table 4*). The percentage of predicted heart rate was not significantly associated with SVTs. However, chronotropic incompetence may affect HRV and therefore theoretically its association with SVTs, and the percentage of predicted heart rate is highly dependent on β-blocker use. Therefore, to explore these associations, another multivariate model was composed with SVTs as the outcome variable and the percentage of predicted heart rate, β-blocker use, and SDANN as predictor variables. Thus correcting for chronotropic incompetence and β-blocker use, SDANN remained significantly associated with SVTs (estimate −0.02, 95% CI −0.04 to −0.003, p = 0.025). The percentage of predicted heart rate and β-blocker were not significantly associated with SVTs in this model (data not shown).

**Table 4. Determinants of SVTs in systemic RV patients.**

| Linear regression variable | Estimate univariate (95% CI) | p-value univariate | Estimate multivariate (95% CI) | p-value multivariate |
|---|---|---|---|---|
| Watts | −0.02 (−0.03 to −0.002) | 0.033* | | NS |
| % of predicted heart rate | −0.04 (−0.09–0.01) | 0.079 | | NS |
| RV GLS | 0.58 (0.29–0.88) | <0.001* | 0.47 (0.17–0.77) | 0.03* |
| SDNN | −0.02 (−0.03 to −0.004) | 0.015* | | NS |
| SDANN | −0.02 (−0.04 to −0.01) | 0.009* | −0.02 (−0.03 to −0.0004) | 0.045* |
| VLF | −0.001 (−0.002–0.000) | 0.105 | | |
| LF | −0.001 (−0.002–0.001) | 0.492 | | |
| QRS duration | 0.03 (−0.004–0.06) | 0.080 | | NS |
| QTc interval | 0.03 (0.004–0.06) | 0.028* | | NS |
| β-Blocker use | 2.03 (0.20–3.86) | 0.031* | | NS |

*CI: confidence interval; LF: low-frequency power; NS: not significant; RV GLS: (systemic) right ventricular global longitudinal strain; SDANN: standard deviation of the average NN intervals calculated over 5-minute intervals; SDNN: standard deviation of all normal-to-normal intervals; VLF: very low-frequency power; QTc interval: corrected QT interval. *Significant p-value.*

## Discussion

The current results show that HRV differs between patients with a systemic RV and controls, and is related to clinical factors in the patient group. SDANN was independently associated with SVTs. This is clinically relevant as SVTs are independently associated with sudden cardiac death and mortality in patients with a systemic RV (*Connelly et al., 1996; Mongeon et al., 2011; Venkatesh et al., 2019*).

Next to the association between SDANN and SVTs, multiple time- and frequency domain variables of HRV correlated with SVTs, which were common in this cohort. They are usually attributed to scar tissue after Mustard or Senning procedures or macro-re-entrant circuits (*Hernandez-Madrid et al., 2018*). SVTs may furthermore be due to dilated atria because of tricuspid valve regurgitation, or re-entrant tachycardias through congenital accessory bundles in ccTGA patients (*Andrade et al., 2020; Daliento et al., 1986*). However, a disbalance between sympathetic and parasympathetic influence, as indicated by a change in HRV, can also be a trigger for SVTs (*Carnagarin et al., 2019*). SVTs predispose to heart failure and mortality through inducing tachycardiomyopathy and contributing to ischemia and are therefore an important clinical marker in patients with a systemic RV (*Connelly et al., 1996; Mongeon et al., 2011; Venkatesh et al., 2019*).

In this study, patients showed reduced SDNN, SDANN, and LF power compared with controls. These variables, together with VLF power, also appeared to be correlated with echocardiographic systemic RV function and with SVTs. These components of HRV reflect a mix of sympathetic, parasympathetic, and baroreflex activity. Variables known from previous evidence to primarily reflect parasympathetic activity, namely pNN50 and rMSSD, did not differ between patients and controls and did not correlate with clinical events. These results are striking, since heart failure is generally characterized by increased sympathetic activity and decreased parasympathetic activity.

Previously (*Malik and Camm, 1993*), it was pointed out that when either sympathetic or parasympathetic activity increases within the physiological range, their corresponding HRV components increase. However, when they are pathologically increased, for example in the case of sympathetic hyperactivity in heart failure, the sinus node may be saturated with sympathetic input and thus may not respond to the other sources of modulation anymore, leading to a decrease in sympathetically mediated HRV components.

The current cohort shows relatively preserved systemic RV function and relatively few heart failure related events, and thus likely represents a group of patients in a compensated state of (pre-)heart failure. Acute pathological sympathetic activity such as has been demonstrated in patients admitted with decompensated heart failure was very rare in this group, and Holter monitoring was usually conducted in steady states. However, the systemic RV is not equally equipped compared to the systemic LV to provide systemic pressure, and therefore, it is possible that the hearts of the current cohort have already been functioning under increased sympathetic stimulation since birth. From current literature it is as of yet unknown how such a pattern of autonomic activity reflects in HRV but a possible explanation of the presented findings may be that this activity also provides saturating sympathetic outflow to the sinus node.

A pattern similar to our findings was seen by Patel et al. in a group of healthy individuals with normal cardiac anatomy that would later develop heart failure (*Patel et al., 2017*): they demonstrated a.o. reduced SDNN, SDANN, LF power, and normal or even slightly increased measures of parasympathetic activity (rMSSD and HF power). This study indicates that our findings may indeed be reflective of a state of compensated (pre-)heart failure.

In the current cohort, a higher number of previous thoracotomies and therefore potentially a higher risk of surgical denervation, was not correlated with any of the studied HRV variables. This is in line with previous investigations: although thoracic

surgery may damage autonomic pathways to and from the heart on the short term, it has been demonstrated that full recovery usually takes place in a matter of months (*Kiseleva et al., 2002*). Furthermore, contrary to the arterial switch procedure (*Kondo et al., 1998*), during the Mustard or Senning procedures, the cardiopulmonary nerves coursing along the origin of the great arteries are not likely to be transsected as the great arteries are left intact.

The percentage of predicted heart rate that was achieved during exercise testing was positively correlated with LF power (only before p-value correction, however). This is in line with previous literature, showing a decreased LF power in the presence of chronotropic incompetence (*Fei et al., 1996*). However, the percentage of predicted heart rate did not affect the association between SDANN and SVTs. This suggests that, regardless of chronotropic (in)competence, HRV may still provide useful information about SVTs.

**Study limitations**

The current study was limited by its retrospective design, the limited patient numbers, and the heterogeneous population in which for example differing surgical factors may have influenced HRV. Also, it is unknown how HRV changes over time in relation to clinical events in this patient group. Therefore, the usefulness of HRV analysis in the individual patient still has to be confirmed by longitudinal studies in systemic RV patients. Studies with devices measuring HRV in patients with a structurally normal heart and heart failure are promising: a decline in HRV was observed in patients who progress from stable to unstable heart failure and the need for hospitalization (*Adamson, 2009*). Whether HRV can predict sudden cardiac death or mortality in patients with a systemic RV remains to be investigated, as the current limited sample size and limited number of events did not allow this. However, within the published studies regarding HRV in populations with specific complex congenital heart disease, this is one of the largest cohorts of adult patients. Most literature concerns either (mostly) children or consists of a heterogeneous group with different types of congenital heart disease (*Massin and von Bernuth, 1998; McLeod et al., 1999*).

HRV analysis requires sinus rhythm causing a selection bias since patients with overt sick sinus syndrome were excluded. Theoretically, it is possible that preclinical sinus node dysfunction affected the HRV in more subtle ways that did not lead to exclusion of the recording or the patient. Therefore, sinus node dysfunction may have influenced the current results to some extent. However, as sick sinus syndrome probably leads to an increase in HRV (pNN50, rMSSD, and SDNN) (*Butta et al., 2019*), the finding of a

decreased SDNN and LF power in the current cohort is probably unrelated to sinus node dysfunction and can be attributed to heart failure.

After Holm's correction of the p-values for the correlation coefficients between HRV variables and clinical factors (*Table 3*), only the association between SDNN/SVTs and SDANN/SVTs remained significant. However, pre-correction, there were more significant correlations (15) than would be expected purely by chance with a p-value cut-off of 0.05 (about 4, i.e. 1 in 20). Therefore, although the results need to be interpreted with caution, it might be too rigorous to reject all other correlations in *Table 3* besides SDNN/SVTs and SDANN/SVTs. It could be appropriate to use such results to guide formation of new hypotheses and the design of further studies (Perneger, 1998; Rothman, 1990).

**Conclusion**

In conclusion, HRV is associated with clinical factors and events in patients with a systemic RV. HRV analysis in this population may be useful to detect disease progression before this is clinically overt, and may provide indirect information about outcome. Further longitudinal research is needed.

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