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

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Chapter 4

QT interval variability and heart rate turbulence are associated with clinical characteristics in congenital heart disease patients with a systemic right ventricle

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Abstract

Background

QT interval variability (QTV) and heart rate turbulence (HRT) are measures of cardiac autonomic function, which, when abnormal, are correlated with ventricular arrhythmias and worse clinical outcome. This study aims to evaluate QTV and HRT in patients with a systemic right ventricle (RV) and to assess correlations with clinical characteristics.

Methods

In a retrospective cohort study, QTV and HRT were derived from 24-h Holter registrations of patients with a systemic RV and healthy controls. QTV and HRT were compared between groups. In patients, the association between QTV, HRT, and clinical characteristics was assessed.

Results

Holter recordings from 40 patients (mean age 40 years, 16 females) and 37 healthy controls (mean age 42 years, 21 females) were analyzed. Groups were comparable in terms of age and sex. QTV was increased in patients compared with controls ($p < 0.001$), HRT did not differ significantly between the groups. Increased QTV and decreased HRT correlated with medication use, especially of diuretics, and with clinical events, particularly supraventricular arrhythmias. Increased QTV correlated with reduced systemic RV function. Decreased HRT was independently associated with a larger number of past clinical events (estimate −0.33, 95% CI −0.63 to −0.02, $p = 0.037$). QTV was higher in women in both patients and controls ($p = 0.041$ and $p = 0.034$, respectively).

Conclusions

QTV and HRT are associated with clinical factors and events in patients with a systemic RV. Further studies are mandatory to confirm their prognostic value.

Introduction

Patients with congenital heart disease and a systemic right ventricle (RV) have a good mid-term prognosis but long-term complications are frequent, including heart failure and arrhythmias (both supraventricular and ventricular) [1]. The onset of clinical deterioration and the occurrence of complications are hard to predict. In patients with left ventricular disease, non-invasive measures of cardiac autonomic function have potential for use in risk stratification. Abnormal QT interval variability (QTV) and abnormal heart rate turbulence (HRT) are associated with decreased functional capacity, and are predictive of supraventricular and ventricular arrhythmias and mortality [2-8]. Data regarding QTV and HRT in patients with a systemic RV are however lacking.

The duration of the QT interval fluctuates with changes in heart rate, but also spontaneously, independent of heart rate. QTV describes these spontaneous fluctuations. Increased QTV indicates unstable ventricular repolarization and is thus considered to indicate a higher risk for ventricular arrhythmias [9]. Increased QTV may be caused by sympathetic overactivity [10], which can occur as a response to decreased cardiac output in congestive heart failure [4]. Increased QTV is associated with mortality, ventricular tachycardia/fibrillation (VT/VF), and atrial fibrillation in patients with left-sided cardiac disease [2-4].

HRT describes the pattern of acceleration and deceleration of heart rate after a premature ventricular complex (PVC). The transient drop in blood pressure caused by a PVC causes quick parasympathetic withdrawal through activation of the baroreflex. The sympathetic nervous system is activated but with a slight delay. Both mechanisms increase heart rate and blood pressure. The increased blood pressure is registered by the baroreceptors and heart rate is subsequently reduced. In the healthy individual, this response generates an overshoot in both the increase and subsequent decrease in heart rate, which leads to a clear HRT pattern (*Fig. 1*). Normal HRT thus reflects good baroreflex sensitivity, which is an important manifestation of intact parasympathetic function [11]. In patients with left-sided cardiac disease, decreased HRT is associated with mortality, VT/VF, and atrial fibrillation [6-8]. In patients after myocardial infarction, decreased HRT was independently associated with mortality [12] and in patients with operated or unoperated congenital heart disease, HRT was the strongest independent predictor of sudden cardiac death [13]. In the present study, we investigated QTV and HRT in adult patients with a systemic RV and explored the association between QTV and HRT and clinical characteristics and outcomes in this group.

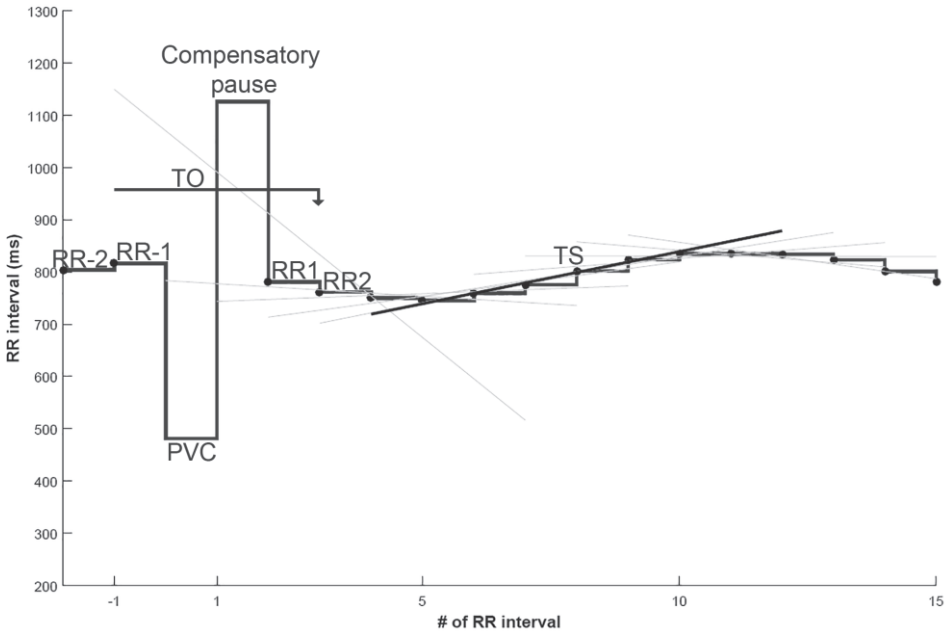

Figure 1. Representative example of heart rate turbulence calculation in a control subject.
PVC, premature ventricular complex; RR-1 and RR-2, the two sinus beats preceding the PVC; RR1 and RR2, the two sinus beats following the PVC; TO, turbulence onset, the percentage of difference between the mean RR intervals of the two sinus beats preceding the PVC and the mean RR intervals of the two sinus beats following the PVC (see also Table 1). TS, turbulence slope, the maximum positive regression slope over any five consecutive RR intervals of the first 15 sinus beats after the PVC (see also Table 1). After the example of [21].

Methods

Design

A retrospective cohort study was conducted. QTV and HRT were calculated from 24-h Holter recordings of congenital heart disease patients with a systemic RV and from healthy controls. Correlation with clinical characteristics and outcomes was investigated. As this was a retrospective study, the need for informed consent was waived by the medical ethical committee of the Leiden University Medical Center.

Inclusion of patients and controls

In the electronic patient record system, 24-h Holter recordings of adult patients with a systemic RV were screened for suitability. The most recent suitable Holter, in which both QTV and HRT analysis could technically be performed, was selected. 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-h 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. Protocols and used reference values for the exercise tests are in accordance with the ACC/AHA guidelines [14].

Exclusion criteria

If no interpretable Holter recordings were available, patients or controls were excluded. Holters with a non-sinus primary rhythm, Holter recordings lasting <18 h, or of insufficient quality were excluded. Patients or controls were excluded if they had clinically relevant diabetes (defined as the use of at least one antidiabetic drug), had rheumatoid arthritis, or were using antidepressant or antipsychotic medication, as these factors may interfere with cardiac autonomic function [15-17]. Additionally, controls were excluded in the case of relevant cardiac disease.

Holter processing

For the patient group, the most recent suitable Holter recording per patient was analyzed (*Table 1*). In the control group, also the most recent and usually the only Holter recording per subject was analyzed. Registrations were manually screened for correct labelling and onset of the QRS-complexes using a dedicated program [MARS, version 8 (GE Healthcare, Milwaukee, WI, USA). Episodes with predominant atrial or ventricular ectopy, atrial pacing, unclear atrial rhythm, inconsistent p-waves or PR intervals, junctional rhythm, or alternating grades of atrioventricular block were manually excluded as they would lead to distorted QTV and HRT calculation.

Table 1: QTV and HRT parameters

Abbreviation	Parameter	Calculation	Represents	Interpretation
VRa	Variability ratio of 5-minute averages	$\frac{SDQTa}{SDANN}$	Sympathetic activity	Higher values associated with adverse outcome
QTVi_a	QT interval variability index of 5-minute averages	$log\frac{QTVaN}{HRVaN}$	Sympathetic activity	Higher values associated with adverse outcome
TO (%)	Turbulence onset	$\frac{(RR_1 + RR_2) - (RR_{-2} + RR_{-1})}{(RR_{-2} + RR_{-1})}$	Parasympathetic activity	Higher (less negative) values associated with adverse outcome
TS (%)	Turbulence slope	The maximum positive regression slope over any five consecutive RR intervals of the first 15 sinus beats after the PVC	Parasympathetic activity	Lower values associated with adverse outcome
HRT 0	Heart rate turbulence category 0	TO<0% and TS>2,5%	Parasympathetic activity	Normal
HRT 1	Heart rate turbulence category 1	TO>0% OR TS<2,5%	Parasympathetic activity	Moderately abnormal
HRT 2	Heart rate turbulence category 2	TO>0% AND TS<2,5%	Parasympathetic activity	Severely abnormal

HRVaN: normalised 5-min averaged heart rate variance; QTVaN: normalised 5-min averaged QT interval variance; RR_1 and RR_2: the two sinus beats following the premature ventricular complex; RR_{-1} and RR_{-2}: the two sinus beats preceding the premature ventricular complex; SDANN: standard deviation of 5-min averaged normal-to-normal/sinus intervals; SDQTa: standard deviation of 5-min averages of all QT intervals; TO: turbulence onset; TS: turbulence slope [9, 19, 20].

Calculation of QT variability

Within MARS, standard QT-analysis was performed, which yields graphs with QT-intervals over time. As MARS does not allow listing of all QT-intervals, dedicated software was designed (by co-author ACM) to extract average values of QT-intervals over 5-min intervals from these graphs. The following variables were recorded or calculated: mean QT interval, mean heart-rate corrected QT interval according to Bazett [18], the standard deviation of the 5-min averaged QT intervals (SDQTa), the 5-min averaged variability ratio (VRa), and the 5-min averaged QTV index (QTVi_a). The VRa was calculated by dividing SDQTa by SDANN (standard deviation of 5-min averaged normal-to-normal/sinus intervals), with the aim of correcting the QTV for variability in heart rate. This is a parameter with the same rationale as the VR coined by Jensen et al. [19], but presently calculated with 5-min averages while Jensen et al. used all QT-intervals and divided them by SDNN (standard deviation of all normal-to-normal intervals). The QTV index (QTVi) as coined by Berger et al. [20] was calculated by taking the logarithm of the ratio of normalized QT variance to heart rate variance, again using the 5-min averages of the QT-intervals and also 5-min averages of heart rate (QTVi_a). See Table 1 for QTV variables. For all QTV parameters, Holter lead 2 was used, as this lead is most similar to electrocardiogram lead II, the use of which is recommended in the position statement by the European Heart Rhythm Association to facilitate comparison between studies [9].

Calculation of heart rate turbulence

For the analysis of HRT, lists of interbeat intervals with appropriate labelling of normal beats, non-sinus supraventricular beats, and PVCs were exported from MARS and processed with dedicated software (written by co-author SM), which identified suitable PVCs according to the consensus statement by the International Society for Holter and Noninvasive Electrophysiology [21]. Most importantly, the PVC should be singular, should be preceded by at least two normal sinus beats, and should be followed by at least 15 normal sinus beats. HRT can reliably be calculated when at least five suitable PVCs have occurred during a recording. Subsequently, turbulence onset (TO) and turbulence slope (TS) were calculated. TO is the percentage of difference between the mean RR intervals of the two sinus beats preceding the PVC and the mean RR intervals of the two sinus beats following the PVC. TS is the maximum positive regression slope over any five consecutive RR intervals of the first 15 sinus beats after the PVC (*Fig. 1*).

Holter recordings were divided into HRT category 0, 1, or 2. Category 0 represents normal HRT and includes patients with TO < 0% and TS > 2,5%, or patients without enough PVCs for valid HRT calculation. Category 1 represents moderately abnormal HRT and includes patients with TO > 0% OR TS < 2,5%, and category 2 represents

severely abnormal HRT and includes patients with TO > 0% AND TS < 2,5%, representing moderately and severely abnormal HRT, respectively [21]. In the present study we made 1 exception: patients with 20 or more PVCs but with <5 PVCs suitable for HRT calculation were classified as 'undefined' instead of category 0. See *Table 1* for HRT variables.

Sick sinus syndrome may theoretically influence QTV and HRT calculation. However, because (episodes of the) Holters exhibiting signs of sinus node dysfunction were thus manually excluded, and because both QTV and HRT are calculated by averaging a multitude of values, the effect of sinus node dysfunction is minimized. Therefore, we did not specifically assess its influence on QTV and HRT in this study.

Clinical characteristics and endpoints

The event score was defined as the sum of all relevant clinical events per patient up until the time of the Holter. The following events were scored: supraventricular arrhythmias (SVT) for which treatment was initiated, or persistent and accepted supraventricular arrhythmias; (attempted) ablation of supraventricular arrhythmia; ventricular arrhythmias lasting >30 s or adequate implantable cardioverter-defibrillator (ICD) therapy; (attempted) ablation of ventricular arrhythmia; implantation of ICD (grouped under tachy-arrhythmia); implantation of pacemaker (categorized as brady-arrhythmia); hospital admission for cardiac decompensation; start or increase in dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARBs), diuretics, β-blockers, or other medication indicated due to heart failure (temporary increase in dose of e.g. diuretics, was included if the increase was for longer than 1 day) (grouped as heart failure); tricuspid valve repair or replacement (TVP/TVR). See also *Online Table 1*. As the relative impact of these events on QTV and HRT are unknown, each event was weighed equally. Other clinical data were collected dating from the same time or no more than 1 year apart (before or after) from the Holter recording and included age, length, weight, body surface area, New York Heart Association (NYHA) functional classification, results of bicycle exercise tests in terms of maximum achieved Watts and percentage of predicted number of Watts, and echocardiographic global systemic ventricular function. Offline measurement of global longitudinal strain of the systemic ventricle in the apical four-chamber view was performed [22]. Echocardiograms had been obtained with commercially available ultrasound systems and offline analysis was performed in EchoPac, GE Medical Systems (Little Chalfont, UK).

Statistical analysis

IBM SPSS statistics version 23 (Armonk, NY, USA) was used. Data were reported as mean ± SD or median-interquartile range as appropriate. The independent samples T-test, Mann-Whitney-U test, chi-square test, or Fisher's exact test were used for the comparison of clinical characteristics, QTV, and HRT between patients and controls, as appropriate. Spearman's rho correlation coefficients were calculated to assess correlations between QTV/HRT and clinical characteristics or events. Multivariate linear regression was used to assess the associations of QTV and HRT with the clinical event score. For all analyses, a p-value <0.05 was considered statistically significant.

Results

Patient selection and baseline characteristics

QTV and HRT were calculated for 40 patients (*Fig.* 2). QTV and HRT were calculated for 37 consecutive controls. The patient and control groups were comparable in terms of age and sex. The patient group used more medication, had a worse exercise capacity, and reduced echocardiographic function of the systemic ventricle compared with controls. Most patients were in NYHA class 1 or 2. The vast majority of controls was in NYHA class 1 (*Table* 2).

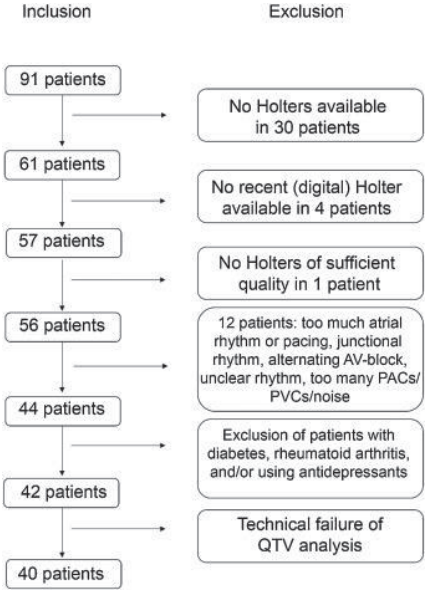

Figure 2. Flowchart for patient selection.
AV, atrioventricular; PAC, premature atrial complex; PVC, premature ventricular complex; QTV, QT interval variability.

Table 2. Baseline characteristics based on most recent Holter for QT interval variability

Characteristics	Patients N (%)	Mean±SD or median [IQR]	*Controls*	Mean±SD or median [IQR]	p-value
Total/females	40/16 (100%/40%)		37/21 (100%/57%)		0.141
Primary condition:					
TGA (Mustard)	10 (25%)		n.a.		
TGA (Senning)	18 (45%)		n.a.		
ccTGA	12 (30)		n.a.		
Age (years)		40±9		42 (±13)	0.451
NYHA class					
1	20 (50%)		35 (95%)		<0.001
2	16 (40%)		2 (5%)		
3	4 (10%)		0 (0%)		
BSA (m^2)		2.0±0.2		1.9 (±0.2)	0.098
Medication use:					
β-blocker	6 (15%)		0 (0%)		0.026*
ACEi or ARB	17 (43%)		1 (3%)		<0.001*
Diuretic	9 (23%)		1 (3%)		0.010*
Bm/AC	2 (5%)		5 (14%)		0.251
Digoxin	1 (3%)		0 (0%)		1.000
Amiodarone	1 (3%)		0 (0%)		1.000
Flecainide	2 (5%)		0 (0%)		0.494
Watts (ergometry)		160 [120-200]		200 [160-236]	0.007*
Validity (%)(ergometry)		93 [75-112]		123 [108-142]	<0.001*
Systemic ventricular GLS[1] (echocardiography)		-15.0±2.0		-20.2±2.7	<0.001*
Systemic ventricular function by eyeballing[2]					<0.001*
good (1)	2 (5%)		35 (97%)		
mildly reduced (2)	26 (70%)		1 (3%)		
moderately reduced (3)	9 (25%)		0 (0%)		
severely reduced (4)	0 (0%)		0 (0%)		
Number of previous thoracic surgeries					
0	8 (20%)		37 (100%)		<0.001*
1	16 (40%)				
2	12 (30%)				
3	4 (10%)				

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II 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; NYHA, New York Heart Association classification of heart failure; SD, standard deviation; TGA (Mustard/Senning), after Mustard/Senning correction for transposition of the great arteries.

**significant p-value; 1: 3 patients and 1 control excluded: no (qualitatively sufficient) available images; 2: 2 patients and 1 control excluded: no (qualitatively sufficient) available images.*

QTV and HRT in patients and controls

QT intervals were significantly longer in patients. QTV was significantly increased in the patient group. HRT did not differ significantly between patients and controls (*Table 3*).

Of note, VRa was higher in women in the patient group (p = 0.041) and QTVi_a was higher in women in the control group (p = 0.034). There were no sex differences in QT intervals, QTc intervals, or HRT in either group (see *Online Table 2* for detailed information). There were no significant differences in QTV or HRT between patients after the atrial switch (Mustard or Senning) procedure for TGA and patients with ccTGA (see *Online Table 3* for detailed information).

Table 3. QT interval variability and HRT in patients and controls

		N	mean	±SD	*p*-value
Mean QT (ms)	Patients	40	425	±36	<0.001*
	Controls	37	394	±24	
Mean QTc (ms)	Patients	40	460	±28	<0.001*
	Controls	37	436	±17	
SDQTa	Patients	40	36	±11	0.032*
	Controls	37	31	±7	
VRa	Patients	40	0.30	±0.08	<0.001*
	Controls	37	0.22	±0.04	
QTVi_a	Patients	40	-0.51	±0.17	<0.001
	Controls	37	-0.74	±0.13	
TO[1] (%)	Patients	34	-2.5	±1.7	0.116
	Controls	14	-3.4	±2.3	
TS[1] (%)	Patients	34	8.6	±5.2	0.071
	Controls	14	12.4	±8.8	
			Count	%	
HRT category 0	Patients	40	36	90	
HRT category 1			2	5	
HRT category 2			2	5	
					0.611
HRT category 0	Controls	37	36	97	
HRT category 1			1	3	
HRT category 2			0	0	

**significant p-value; 1: 6 patients and 13 controls excluded because an insufficient number of suitable premature ventricular complexes was available for calculation of TO and TS; HRT, heart rate turbulence; 2: concerning the difference in HRT category between patients and controls; QTVi_a, QTV index of 5-minute averaged QT intervals; TO, turbulence onset; TS, turbulence slope; VRa, variability ratio of 5-minute averaged QT intervals.*

QTV, HRT, and clinical characteristics in patients with a systemic RV

Several types of medication correlated with increased QTV and/or more abnormal HRT, especially diuretics and flecainide. Decreased systemic RV function (less negative global longitudinal strain) correlated with increased QTV. Increased QTV and decreased HRT correlated with a higher event score (*Table 4*). Correlations between clinical events that occurred up until the time of the analyzed Holter recording (i.e. the components of the event score) are also shown in *Table 4*. Types of events were grouped in categories (see *Online Table 1* for detailed information). Increased QTV and decreased HRT correlated with a higher number of tachy-arrhythmia-related events (which were mainly SVTs). The correlations between tachy-arrhythmias (category within the event score) and QTV/HRT were similar to the correlations between solely SVTs (part of tachy-arrhythmias) and QTV/HRT (*Table 4* and *Online Table 1*). Decreased HRT correlated with heart failure (including hospitalization for decompensated heart failure and increases in heart failure medication) and TVP/TVR. The TVP/TVR procedures occurred 2 months, 2 months, and 6 years before the Holters of the respective patients. Of the other thoracic surgical procedures, none occurred more recently than 15 years before the Holter. Neither QTV nor HRT correlated with the number of previous thoracotomies (excluding the 3 TVP/TVR patients).

Table 4 Correlations between patient QTV/HRT, medication, and clinical characteristics

		VRa	QTVi_a	TO	TS	HRT category
β-blocker	Rho	0.24	0.23	0.09	-0.09	0.08
	P	0.131	0.152	0.617	0.617	0.617
ACEi/ARB	Rho	0.31	**0.33**	0.15	-0.12	**0.39**
	P	0.052	**0.040***	0.394	0.507	**0.014***
Digoxin	Rho	0.21	0.16	0.26	-0.29	**0.51**
	P	0.213	0.325	0.142	0.093	**0.001***
Amiodarone	Rho	0.13	0.19	-	-	-0.05
	P	0.418	0.247			0.744
Flecainide	Rho	**0.33**	0.29	0.31	-0.26	**0.33**
	P	**0.039***	0.071	0.079	0.146	**0.041***
Diuretic	Rho	0.27	**0.35**	**0.39**	**-0.53**	**0.41**
	P	0.089	**0.029***	**0.022***	**0.001***	**0.009***
Bm/Ac	Rho	-0.06	0.14	0.05	0.00	-0.08
	P	0.715	0.392	0.775	1.000	0.640
Thoracic surgeries[1]	Rho	-0.14	0.03	0.07	-0.14	0.09
	P	0.415	0.868	0.712	0.453	0.583
Watts	Rho	-0.29	-0.24	-0.39	0.39	-0.38
	P	0.178	0.269	0.087	0.093	0.072
Validity	Rho	-0.12	-0.33	-0.39	0.25	-0.35
	P	0.594	0.129	0.087	0.282	0.098
RV-GLS	Rho	0.25	**0.33**	0.35	-0.26	0.16
	P	0.134	**0.048***	0.055	0.163	0.343
Event score	Rho	0.26	**0.43**	**0.38**	**-0.48**	**0.40**
	P	0.099	**0.006***	**0.027***	**0.004***	**0.011***
Components of event score						
Tachy-arrhythmia	Rho	**0.43**	**0.45**	0.32	**-0.46**	**0.36**
	P	**0.005***	**0.004***	0.064	**0.007***	**0.023***
Brady-arrhythmia	Rho	0.01	0.22	0.18	-0.13	-0.11
	P	0.930	0.180	0.317	0.463	0.495
Heart failure	Rho	0.21	0.31	0.30	-0.30	**0.47**
	P	0.188	0.052	0.089	0.090	**0.002***
TVP/TVR	Rho	0.11	0.10	**0.46**	**-0.42**	**0.54**
	P	0.495	0.528	**0.006***	**0.014***	**<0.001***

**significant p-value; 1: excluding 3 patients who underwent tricuspid valve replacement or repair. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; Bm/Ac, betamimetic or anticholinergic drug; GLS, global longitudinal strain; HRT, heart rate turbulence; QTV, QT interval variability; QTVi_a, QTV index of 5-minute averaged QT intervals; RV, right ventricular; TO, turbulence onset; TS, turbulence slope; TVP/TVR, tricuspid valve repair or replacement; VRa, variability ratio of 5-minute averaged QT intervals.*

When patients without PVCs were excluded (N = 6), patients with a higher number of PVCs had a significantly higher HRT category (p = 0.026) (*Fig. 3*).

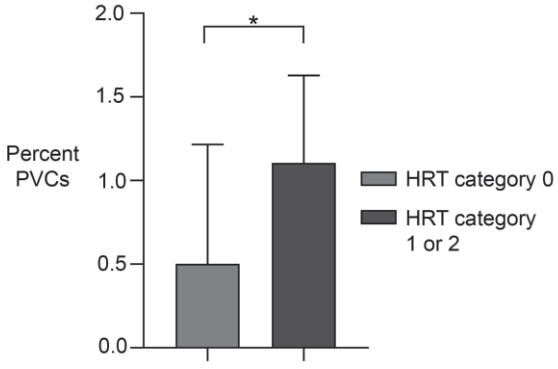

Figure 3. HRT category and percentage of PVCs in the patient group.

HRT, heart rate turbulence; PVC, premature ventricular complex. Patients in HRT category 1 or 2 (reduced HRT) have more PVCs than patients in HRT category 0 (normal HRT).

Factors associated with the event score

To investigate the association between QTV and HRT and clinical outcome, linear regression for the event score was performed. In the univariate analysis, higher QTV and worse HRT are associated with a higher event score. In the multivariate analysis, TS remains independently associated with the event score, in addition to exercise capacity and the use of ACE inhibitors/ARBs (*Table 5*).

Correlation between QTV and HRT

VRa and QTVi_a were not correlated with either TO or TS. TO and TS were strongly correlated, and VRa and QTVi_a were strongly correlated. Thus, QTV variables correlated with each other and HRT parameters correlate with each other, but QTV and HRT do not correlate with each other. This indicates that QTV and HRT reflect two different pathways (data in *Online Table 4*).

Table 5 Linear regression for the event score

Linear regression	Estimate univariate (95% CI)		p-value univariate	Estimate multivariate (95% CI)		*p*-value multivariate
Variable						
Age	0.11	(-0.02 – 0.24)	0.096			
Gender	0.98	(-1.57 – 3.53)	0.441			
Watts	-0.06	(-0.09 - -0.03)	**0.001***			NS
RV GLS	1.10	(0.52 – 1.68)	**<0.001***	0.99	(0.35 – 1.63)	0.004*
BSA	4.61	(-2.31 – 11.52)	0.185			
VRa	18.72	(4.12 – 33.31)	**0.013***			NS
QTVi_a	9.88	(3.16 – 16.61)	**0.005***			NS
TO	1.00	(0.21 – 1.79)	**0.015***			NS
TS	-0.36	(-0.61 - -0.12)	**0.005***	-0.24	(-0.46 - -0.03)	<0.001*
HRT category	3.29	(0.88 – 5.69)	**0.009***			NS
Use of:						
β-blocker	4.10	(0.84 – 7.35)	**0.015***			NS
ACEi/ARB	3.94	(1.75 – 6.14)	**0.001***	3.34	(1.22 – 5.47)	<0.001*
Digoxin	0.15	(-7.91 – 8.21)	0.969			
Amiodarone	2.21	(-5.82 – 10.23)	0.581			
Flecainide	1.74	(-4.01 – 7.48)	0.544			
Diuretic	6.07	(3.81 – 8.33)	**<0.001***			NS

**significant p-value. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; BSA, body surface area; CI, confidence interval; HRT, heart rate turbulence; NS, not significant; QTVi_a, QT interval variability index of 5-min averaged QT intervals; RV GLS, right ventricular global longitudinal strain; TO, turbulence onset; TS, turbulence slope; VRa, variability ratio of 5-min averaged QT intervals.*

Discussion

Key findings of this study are: in patients with a systemic RV, both QTV and HRT were associated with clinical events (TS independently), including tachy-arrhythmias (mainly SVTs). QTV was increased in patients compared with controls.

Both QTV and HRT appear related to deteriorating clinical condition in patients with a systemic RV. TS was independently associated with clinical (mainly arrhythmia- and heart failure related) events. Increased QTV correlated with reduced systemic RV function. The use of flecainide, diuretics, and ACE inhibitors/ARBs correlated with increased QTV and decreased HRT. Digoxin correlated with decreased HRT. These results may indicate that worse clinical status, translating into medication requirement, is associated with abnormal QTV and HRT. Medication may also influence autonomic function directly. While flecainide may enhance sympathetic function [23], ACE inhibition and diuretic treatment tend to restore autonomic function [24, 25], and digoxin increases parasympathetic activity [26]. The observations are in line with previous research: in children with atrial septal defect, QTV was increased and correlated with the left-to-right shunt ratio [27]. In adults with tetralogy of Fallot, abnormal HRT was related to both worse left ventricular and right ventricular function and worse exercise capacity [5].

In patients with a systemic RV, QTV and HRT correlated with SVTs. In this population, SVTs are an important predictor of mortality [28, 29]. Several mechanisms might explain this observation. Systemic RV failure leads to increased sympathetic output, which is reflected in QTV and HRT and predisposes to atrial tachycardias or fibrillation [30]. SVTs by themselves can further decrease systemic RV function, resulting in progressive autonomic adaptation, also causing changes in QTV and HRT. In addition, intrinsic atrial abnormalities, which predispose to SVTs, are common in patients with a systemic RV due to atrial scar tissue or congenital conduction abnormalities [31]. These can cause abnormal QTV as atrial refractoriness is a component of the QT interval [32]. Previous research in patients with left-sided cardiac disease also show associations between QTV/HRT and SVTs [2, 8].

The increased QTV may indicate repolarization instability and possibly a higher risk for ventricular arrhythmias [9]. The mechanism is probably spontaneous variable diastolic calcium release caused by sympathetic stimulation following reduced systemic RV function [33]. This leads to variable action potential duration [34] and therefore increased QTV [9]. However, autonomic innervation of the systemic RV may also be inherently different as a result of abnormal cardiac development. This might differ

between individual patients, as the group is heterogeneous. If so, this might partly explain why not all ventricular arrhythmias occur in patients with reduced systemic RV function [35], which makes it difficult to estimate which patients benefit from ICD implantation. In a large cohort of patients with structural heart disease and an ICD, increased QTV predicted ventricular arrhythmias [3].

In the studied population, surgical denervation may have occurred. This could theoretically have influenced the observed results. However, we showed no differences in QTV and HRT between patients with TGA after atrial switch and ccTGA patients. The number of previous (early) thoracotomies was not correlated with either QTV or HRT. Indeed in previous studies, recovery of autonomic function was usually seen in a matter of months after thoracic surgery, indicating functional re-innervation [36, 37]. Also, in contrast to the currently used arterial switch procedure, in the atrial switch procedure, the great arteries, and therefore the nerves alongside them, are not transected [38].

In contrast, previous TVP/TVR did correlate with decreased HRT. As these procedures were more recent, surgical denervation may have played a role. A study in patients without congenital heart disease, after undergoing mitral valve replacement, also showed depressed autonomic function. However, follow-up time was relatively short and therefore did not allow assessment of long-term recovery [39]. Next to surgical denervation, autonomic adaptation due to hemodynamic factors may also play a role. Systemic RV patients after TVP/TVR have experienced a period of volume overload due to tricuspid valve regurgitation, followed by relative pressure overload after surgery. This may induce autonomic adaptation similar to heart failure.

In both patients and controls, QTV (and not the QT and QTc intervals) was increased in women, suggesting a potentially higher arrhythmic risk. Previous literature is conflicting. Some studies report no gender differences [40], while others report higher QTV in women [41].

HRT was not significantly different in patients and controls. There was a trend toward lower TS in the patient group. The lack of a significance is likely due to the limited sample size, as previous research indicates a clear difference in HRT between (non-congenital) heart failure patients and controls [6].

To our knowledge, this is the first study to describe QTV and HRT in a cohort of patients with a systemic RV. They may be suitable monitoring tools for heart failure and arrhythmia risk in these patients and have potential use in ICD-related decision making.

Assessment of both QTV and HRT is likely more valuable than either alone, as they were not correlated and thus likely reflect different pathways. This study was limited by the required sinus rhythm for analysis of both QTV and HRT: this may have caused selection bias. However, QTV and HRT may be especially useful early in disease progression, when most patients are in sinus rhythm and do not have clear signs and symptoms of heart failure yet. Analysis of the association between QTV/HRT and ventricular arrhythmias was limited by the small number of events. QTV analysis was performed on 5-min averaged values instead of from consecutive QT intervals. This limits comparability with other studies. TO and TS could not be calculated in all subjects because of a lack of suitable PVCs. In the future, this could be overcome in patients with intracardiac leads or during a percutaneous cardiac procedure, with induced HRT: calculation of HRT after a 'PVC' simulated by intracardiac pacing [42]. The likelihood of finding enough suitable PVCs can also be increased by using 48-h Holter monitoring or continuous monitoring through implantable or wearable devices.

In conclusion, QTV and HRT are associated with clinical factors and events in congenital heart disease patients with a systemic RV. Prospective research is needed to confirm their prognostic value. Monitoring of QTV and HRT might be useful in the assessment of arrhythmia risk and clinical deterioration in this patient group.

References

[1] Brida M, Diller G-P, Gatzoulis MA. Systemic right ventricle in adults with congenital heart disease. Circulation 2018;137:508-18.

[2] Magnano M, Gallo C, Bocchino PP, Briguglio M, Rivetti A, Gaita F, et al. QT prolongation and variability: new ECG signs of atrial potentials dispersion before atrial fibrillation onset. J Cardiovasc Med 2019;20:180-5.

[3] Tereshchenko LG, Fetics BJ, Domitrovich PP, Lindsay BD, Berger RD. Prediction of ventricular tachyarrhythmias by intracardiac repolarization variability analysis. Circ Arrhythm Electrophysiol 2009;2:276-84.

[4] Dobson CP, La Rovere MT, Pinna GD, Goldstein R, Olsen C, Bernardinangeli M, et al. QT variability index on 24-hour Holter independently predicts mortality in patients with heart failure: analysis of Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) trial. Heart Rhythm 2011;8:1237-42.

[5] Davos CH, Moutafi AC, Alexandridi A, Petropoulou E, Varela E, Chamakou AC, et al. Heart rate turbulence in adults with repaired tetralogy of Fallot. Int J Cardiol 2009;135:308-14.

[6] Yin DC, Wang ZJ, Guo S, Xie HY, Sun L, Feng W, et al. Prognostic significance of heart rate turbulence parameters in patients with chronic heart failure. BMC Cardiovasc Disord 2014;14:50.

[7] Lombardi F, Tundo F, Abukwaik A, Tarricone D. Heart rate turbulence and variability in patients with ventricular arrhythmias. Heart Int 2007;3:51.

[8] Park SJ, On YK, Kim JS, Jeong DS, Kim WS, Lee YT. Heart rate turbulence for predicting new-onset atrial fibrillation in patients undergoing coronary artery bypass grafting. Int J Cardiol 2014;174:579-85.

[9] Baumert M, Porta A, Vos MA, Malik M, Couderc JP, Laguna P, et al. QT interval variability in body surface ECG: measurement, physiological basis, and clinical value: position statement and consensus guidance endorsed by the European Heart Rhythm Association jointly with the ESC Working Group on Cardiac Cellular Electrophysiology. Europace 2016;18:925-44.

[10] Piccirillo G, Magri D, Ogawa M, Song J, Chong VJ, Han S, et al. Autonomic nervous system activity measured directly and QT interval variability in normal and pacing-induced tachycardia heart failure dogs. J Am Coll Cardiol 2009;54:840-50.

[11] Marine JE, Watanabe MA, Smith TW, Monahan KM. Effect of atropine on heart rate turbulence. Am J Cardiol 2002;89:767-9.

[12] Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999;353:1390-6.

[13] Lammers A, Kaemmerer H, Hollweck R, Schneider R, Barthel P, Braun S, et al. Impaired cardiac autonomic nervous activity predicts sudden cardiac death in patients with operated and unoperated congenital cardiac disease. J Thorac Cardiovasc Surg 2006;132:647-55.

[14] Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training. Circulation 2013;128:873-934.

[15] Benichou T, Pereira B, Mermillod M, Tauveron I, Pfabigan D, Maqdasy S, et al. Heart rate variability in type 2 diabetes mellitus: A systematic review and meta-analysis. PLoS One 2018;13:e0195166.

[16] Koopman FA, Tang MW, Vermeij J, de Hair MJ, Choi IY, Vervoordeldonk MJ, et al. Autonomic dysfunction precedes development of rheumatoid arthritis: a prospective cohort study. EBioMedicine 2016;6:231-7.

[17] O'Regan C, Kenny RA, Cronin H, Finucane C, Kearney PM. Antidepressants strongly influence the relationship between depression and heart rate variability: findings from The Irish Longitudinal Study on Ageing (TILDA). Psychol Med 2015;45:623-36.

[18] Bazett HC. An analysis of the time-relations of electrocardiograms. Ann Noninvasive Electrocardiol 1997;2:177-94.

[19] Jensen BT, Larroude CE, Rasmussen LP, Holstein-Rathlou N-H, Hojgaard MV, Agner E, et al. Beat-to-beat QT dynamics in healthy subjects. Ann Noninvasive Electrocardiol 2004;9:3-11.

[20] Berger RD, Kasper EK, Baughman KL, Marban E, Calkins H, Tomaselli GF. Beat-to-beat QT interval variability: novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. Circulation 1997;96:1557-65.

[21] 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. J Am Coll Cardiol 2008;52:1353-65.

[22] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713.

[23] Stramba-Badiale M, Lazzarotti M, Facchini M, Schwartz PJ. Malignant arrhythmias and acute myocardial ischemia: interaction between flecainide and the autonomic nervous system. Am Heart J 1994;128:973-82.

[24] Cody RJMD. The sympathetic nervous system and the renin angiotensin aldosterone system in cardiovascular disease. Am J Cardiol 1997;80:9J-14J.

[25] Tomiyama H, Nakayama T, Watanabe G, Shiojima K, Sakuma Y, Yamamoto A, et al. Effects of short-acting and long-acting loop diuretics on heart rate variability in patients with chronic compensated congestive heart failure. Am Heart J 1999;137:543-8.

[26] Watanabe AM. Digitalis and the autonomic nervous system. J Am Coll Cardiol 1985;5:35A-42A.

[27] Eryu Y, Hata T, Nagatani A, Funamoto Y, Uchida H, Fujino M, et al. Electrocardiographic RR and QT interval variability in patients with atrial septal defect and healthy children. Pediatr Cardiol 2017;38:582-7.

[28] Venkatesh P, Evans AT, Maw AM, Pashun RA, Patel A, Kim L, et al. Predictors of late mortality in D-transposition of the great arteries after atrial switch repair: systematic review and meta-analysis. J Am Heart Assoc 2019;8:e012932.

[29] McCombe A, Touma F, Jackson D, Canniffe C, Choudhary P, Pressley L, et al. Sudden cardiac death in adults with congenitally corrected transposition of the great arteries. Open Heart 2016;3:e000407.

[30] Chen P-S, Chen LS, Fishbein MC, Lin S-F, Nattel S. Role of the autonomic nervous system in atrial fibrillation. Circ Res 2014;114:1500-15.

[31] 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 2018;20:1719-53.

[32] Nguyen KT, Gladstone RA, Dukes JW, Nazer B, Vittinghoff E, Badhwar N, et al. The QT interval as a noninvasive marker of atrial refractoriness. Pacing Clin Electrophysiol 2016;39:1366-72.

[33] Bers DM. Cardiac sarcoplasmic reticulum calcium leak: basis and roles in cardiac dysfunction. Annu Rev Physiol 2014;76:107-27.

[34] Johnson DM, Heijman J, Bode EF, Greensmith DJ, van der Linde H, Abi-Gerges N, et al. Diastolic spontaneous calcium release from the sarcoplasmic reticulum increases beat-to-beat variability of repolarization in canine ventricular myocytes after beta-adrenergic stimulation. Circ Res 2013;112:246-56.

[35] Zeppenfeld K. Ventricular tachycardia in repaired congenital heart disease. Herzschrittmacherther Elektrophysiol 2016;27:131-6.

[36] Kiseleva IV, Riabykina GV, Sobolev AV, Agapov AA, Akchurin RS. Heart rate variability before and after coronary artery bypass surgery

in patients with ischemic heart disease. Kardiologiia 2002;42:16-20.

[37] Komatsu T, Kimura T, Nishiwaki K, Fujiwara Y, Sawada K, Shimada Y. Recovery of heart rate variability profile in patients after coronary artery surgery. Anesth Analg 1997;85:713-8.

[38] Kondo C, Nakazawa M, Momma K, Kusakabe K. Sympathetic denervation and reinnervation after arterial switch operation for complete transposition. Circulation 1998;97:2414-9.

[39] Zaunseder S, Riedl M, Kurths J, Malberg H, Bauernschmitt R, Wessel N. Impact of cardiac surgery on the autonomic cardiovascular function. J Comput Surg 2014;1:9.

[40] Dobson CP, La Rovere MT, Olsen C, Berardinangeli M, Veniani M, Midi P, et al. 24-hour QT variability in heart failure. J Electrocardiol 2009;42:500-4.

[41] Krauss TT, Mauser W, Reppel M, Schunkert H, Bonnemeier H. Gender effects on novel time domain parameters of ventricular repolarization inhomogeneity. Pacing Clin Electrophysiol 2009;32 (Suppl. 1):S167-72.

[42] Watanabe MA. Heart rate turbulence: a review. Indian Pacing Electrophysiol J 2003;3:10-22.