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Autonomic Heart Rate Control at Rest and During Unloading of the Right Ventricle in Repaired Tetralogy of Fallot in Adolescents

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Abstract

Arrhythmias in patients with repaired tetralogy of Fallot (ToF) might be due in part to altered autonomic heart rate (HR) control caused by altered right ventricle hemodynamics. This study investigated autonomic HR control in ToF adolescents at rest and during unloading of the right ventricle. A total of 17 ToF patients and 56 healthy controls aged 12 to 18 years underwent orthostatic stress with lower body negative pressure (LBNP) of –20 mm Hg. HR, blood pressure and stroke volume were recorded non-invasively. Indices of HR variability were computed in time and frequency domains. All ToF patients also underwent cardiac magnetic resonance imaging, demonstrating pulmonary regurgitation and right ventricular dilation. At rest, HR variability indices of vagal heart rate control were non-significantly lower in the ToF patients compared to controls. During LBNP, HR increased more in controls than ToF patients ($p \leq 0.001$). Further, most HR variability indices decreased among controls, but increased among ToF patients ($p \leq 0.01$ or $p \leq 0.001$ for all variables), suggesting vagal activation in the ToF patients. In conclusion, adolescents after ToF repair have fairly normal HR control at rest despite altered right ventricular hemodynamics. During unloading of the right ventricle, however, vagal HR control increases in the ToF patients and decreases in the controls.

Keywords

Tetralogy of Fallot; autonomic nervous system; heart rate variability; adolescence

Introduction

Arrhythmias in patients with repaired tetralogy of Fallot (ToF) might be due in part to altered autonomic heart rate (HR) control caused by altered right ventricle hemodynamics (1–6). Analysis of HR variability is a well-established non-invasive tool for evaluating autonomic

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HR control (7), whereas lower body negative pressure (LBNP) is a feasible technique for unloading of the right ventricle (8). Combining these approaches can yield information on the neural reflex loops originating from cardiopulmonary baroreceptors. Compared to similar experimental procedures, such as the head-up tilt-test, LBNP has the advantage of being more reproducible within and between subjects, because the subject is immobilized and the effect of the muscle venous pump is eliminated. This study investigated autonomic HR control in repaired ToF adolescents at rest and during LBNP. We put forward the following hypotheses: a) at rest, autonomic HR control would be less altered in this young patient group than what has been reported among older patients, and similar to healthy controls, b) during LBNP-induced unloading of the right ventricle, autonomic HR control would change differently among ToF patients and controls.

Methods

Division of Pediatrics, Rikshospitalet University Hospital, Oslo, Norway, is a national referral centre for congenital heart diseases, serving a population of 4.5 million. Repaired ToF patients were recruited from a locally developed, nation-wide database by the following criteria: a) age 12 to 18 years, b) no known arrhythmia, c) no known neurologic sequelae, and d) no chronic disease apart from their congenital heart defect. Healthy controls 12–18 years volunteered from local schools. Controls having a chronic disease (such as allergy) or using drugs (including contraceptive pills) on a regular basis were excluded. One week prior to the experiments, all participants were instructed not to drink beverages containing alcohol or caffeine, not to take any drugs, and not to use tobacco products. They were instructed to fast overnight the day prior to the experiments. Written, informed consent was obtained from all participants and their parents. The study complied with the Declaration of Helsinki, and was approved by the Regional committee for ethics in medical research.

Symptom assessment and blood biochemistry analyses were carried out in all subjects. In addition, all ToF patients underwent investigations according to a standardized program, featuring cardiac magnetic resonance imaging, echocardiography, 24 hours electrocardiography recording, and exercise tolerance testing. Experiments started at 11 a.m. The participants had been offered a light meal two hours before, but were otherwise not allowed to eat or drink. They lay supine with their lower body in a plastic chamber, in which air could be evacuated very rapidly, reaching a pre-defined negative pressure within milliseconds (9). They were familiarized with the test situations in two pilot experiments. Five minutes were used for baseline recording of cardiovascular variables. Then, LBNP of -20 mm Hg was applied for 6 minutes. In three subjects (one control, two ToF-patients), only one complete run of LBNP was performed, due to dizziness or other discomfort. In all other subjects, the procedure was performed twice with a 5 minute rest period between applications of LBNP.

Instantaneous HR was obtained from the RR-interval of the electrocardiogram. Photoplethysmography on the right middle finger was used to obtain a non-invasive, continuous recording of arterial blood pressure (2300 Finapres, Ohmeda, Madison, WI, US) (10,11). Continuous recording of maximum blood flow velocity in the ascending aorta was obtained by a bidirectional ultrasound Doppler velocimeter (SD-100, GE Vingmed Ultrasound, Horten, Norway), operating in pulsed mode at 2 MHz. The ultrasound beam was directed from the suprasternal notch towards the aortic root using a handheld transducer. The sample volume range was adjusted so that measurements were made 1–2 cm above the aortic valve. All recorded signals were transferred on-line to a recording computer running a program for real-time data acquisition (developed by Morten Eriksen, Dep. of Physiology, University of Oslo, Norway). In a separate session, the diameter of the aortic valve orifice was determined by 2D ultrasound imaging, and used to calculate the area of the orifice. However, in some ToF patients, the smallest diameter of the left ventricular outflow tract was significantly less than

the diameter of the aortic orifice, and therefore used to compute a cross sectional area. Beat-to-beat stroke volume was then calculated by multiplying the value obtained by numerical integration of the recorded instantaneous maximal blood flow velocity in the ascending aorta during each RR-interval by the aortic orifice/left ventricular outflow tract cross sectional area. This method has been validated for healthy subjects in a previous study (12). Beat-to-beat mean arterial blood pressure was calculated by numerical integration of the recorded instantaneous blood pressure, whereas systolic blood pressure and diastolic blood pressure were taken as the highest and lowest value, respectively, within subsequent RR-intervals. Beat-to-beat stroke index was obtained by dividing stroke volume by body surface area, estimated from the subject's height and weight. Beat-to-beat cardiac index was calculated as the product of stroke index and HR, and total peripheral resistance index was calculated as mean arterial blood pressure divided by cardiac index for each beat.

From each experimental run, two segments of 120 s length were selected, one prior to LBNP and one during LBNP. In these time segments, the median value of systolic, mean and diastolic pressure, stroke index, cardiac index and total peripheral resistance index were calculated. Beat-to-beat recordings of RR-interval (the inverse value of HR) from the same time segments were converted to 3 Hz time series and subjected to spectral analyses using an autoregressive algorithm. Spectral components were decomposed, and power densities were computed in the low-frequency (LF) band (0.04–0.15 Hz) and the high-frequency (HF) band (0.15–0.5 Hz), and are expressed both in absolute (LF_{abs} , HF_{abs}) and normalized units, where $LF_{norm} = LF_{abs} / (LF_{abs} + HF_{abs})$ and $HF_{norm} = HF_{abs} / (LF_{abs} + HF_{abs})$. In addition, time domain indices of variability were computed: SDNN (the standard deviation of all RR-intervals), pNN50 (the proportion of successive RR-intervals with a difference greater than 50 ms), and r-MSSD (the square root of the mean square differences of successive RR-intervals). For subjects with two experimental recordings, the arithmetical mean for each variable was computed from corresponding experimental time segments.

Statistical analyses were carried out using SPSS statistical software. Results are presented as mean, standard deviation (SD) and range. However, due to occasional outliers, the non-parametric Wilcoxon-Mann-Whitney's test (2-sided) was used to explore differences between the two groups. Multivariate linear regression analyses were performed to investigate the possible confounding role of gender. A p-value of ≤ 0.05 was considered statistically significant.

Results

A total of 21 ToF patients and 56 healthy controls were included. However, echocardiography revealed severe pulmonary stenosis in 2 ToF patients (maximum blood flow velocity of 3.4 and 4.1 m/s, respectively), and both were excluded from further analyses. In 2 other ToF patients, the technical quality of the LBNP data was poor, leaving 17 ToF patients for the final analyses (Table 1). The ToF group had a higher proportion of males than the control group, but they were comparable regarding age and body surface area. All were of Caucasian ethnicity, except one control. Cardiac magnetic resonance imaging of the ToF patients revealed pulmonary regurgitation and increased right ventricular end-diastolic volume (Table 1). ToF patients also had a lower maximum exercise capacity than expected for age. Ambulatory 24 hour electrocardiography recording was considered normal in all patients; isolated ectopic beats were the only arrhythmias detected.

At baseline, systolic blood pressure was significantly lower in ToF patients than in controls ($p \leq 0.05$) (Table 2). All absolute HR variability indices, including total power, LF_{abs} , HF_{abs} , SDNN, pNN50 and r-MSSD, were observed to be non-significantly lower among ToF patients than controls. During LBNP, HR increased more among controls than ToF patients ($p \leq 0.001$),

and stroke index decreased more ($p \leq 0.01$) (Table 2). Total power, HF_{abs} , SDNN, pNN50 and r-MSSD all decreased among controls, but increased among ToF patients. The differences were highly significant ($p \leq 0.01$ or $p \leq 0.001$ for all variables). All hemodynamic variables were consecutively subjected to a multivariate linear regression analysis featuring group (ToF, control) and gender as independent variables. These analyses did not substantially alter the established differences between ToF patients and controls in the bivariate analyses.

Discussion

The most important findings from this study are: a) at rest, there are few significant differences in hemodynamic variables among ToF patients and controls, despite pulmonary regurgitation and right ventricular dilation in the ToF patients, and b) during LBNP-induced unloading of the right ventricle, there are significantly different responses for HR and HR variability between the ToF patients and controls, indicating improved vagal HR control during LBNP in the ToF patients.

Spectral power densities of HR are usually computed in three frequency bands: very low frequency (≤ 0.04 Hz), low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.5 Hz) (7). The sum of power densities constitutes total power. Variability of HR in the HF region is mediated by variations of efferent vagal (parasympathetic) neural activity only, whereas HR variability in the LF region is due to the combined effect of cardiac vagal and sympathetic activity (13,14). Power spectral density in the HF-band correlates strongly with both r-MSSD and pNN50; these variables serve as indices of vagal modulation of HR.

At rest, all the absolute HR variability indices were (non-significantly) lower in ToF patients than controls. Thus, vagal HR control seems to be mildly reduced, corresponding to previous findings (2,4–6). However, the values reported here are generally less abnormal than those reported in prior studies, even though the degree of pulmonary regurgitation and right ventricular dilatation in our group was similar to that reported by Davos (4). This discrepancy might indicate that vagal HR control decreases over time. Such a change could be related to the detrimental effect of persistent right heart hemodynamic disturbances. The patients in our study were also repaired at a younger age and had fewer ventriculotomies than in the Davos study (4), possibly accounting for some of the findings (15).

Low levels of LBNP (–10 to –15 mm Hg) reduce central volume and cardiac output, and activate the cardiopulmonary baroreflex (8,16–18). Typically, this low level of activation leads to a sympathetically mediated increase in peripheral resistance which maintains arterial pressure, and also leads to simultaneous increases in cardiac sympathetic and vagal activity which offset each other leading to no change in HR. The term “Baibridge reflex” is used to describe these volume related HR changes (19). Moderate levels of LBNP (–20 to –25 mm Hg) reduce central volume further and typically lead to additional arterial baroreflex activation and an increase in HR.

In this study, a moderate level of LBNP led to very different HR responses in the two groups. Normal controls had a relatively large increase in HR and decrease in stroke index, while the ToF patients had almost no increase in HR, and a much smaller decrease in stroke index than the controls, consistent with a previous study (20). These changes suggest that the controls had a larger sympathetic than vagal component in the response to cardiopulmonary deactivation, while the ToF patients had a larger vagal than sympathetic component. The HR variability data strongly supports these conclusions since all absolute HR variability parameters decreased in the controls and increased in the ToF group, indicating vagal activation in the ToF group. These differences might be explained by permanent damage to the reflex loops and/or the sinus node caused by the surgical procedure. An alternative explanation may lie in the overall

physiological response to decreased central volume and LBNP described above and qualitatively drawn in Figure 1. LBNP in control subjects reduced the preload to levels at which the arterial baroreflex elicited a significant HR increase due to sympathetic activation and vagal withdrawal. However, LBNP in the ToF patients, who had higher pre-load at rest, caused a shift towards the inflection point of the curve, leading to primarily cardiopulmonary reflex activation dominated by the Bainbridge response.

Altogether, our results indicate that the slight abnormalities of autonomic heart rate control in adolescent ToF patients at rest are reversed by unloading of the right ventricle, demonstrating a normal cardiopulmonary reflex activation. These findings support a causal link between right heart hemodynamic disturbances and abnormal autonomic heart rate control, which appears to be reversible in young patients. Thus, our findings might provide a basis for prophylactic strategies: reconstructive surgery to improve right heart anatomy, or diuretics to provide a continuous unloading of the right ventricle.

Respiratory activity has been shown to change during LBNP and could influence cardiovascular variability (21); however, ventilation was not controlled for in this study. Blood pressures were recorded using the Finapres finger technique only, which is less reliable than direct intra-arterial measurements. The methods for continuous stroke volume measurements have not been validated in ToF patients. The proportion of males vs. females was higher among patients than controls, but a multivariate analysis did not support gender as a confounding variable. Finally, we have only studied 17 ToF patients, reducing the statistical power and the generalizability of our results.

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Figure 1.

Gross outline of heart rate responses as a function of preload. A moderate decrease in preload causes a marked increase in heart rate, as observed among healthy controls (red lines).

However, when preload is reduced from slightly high to slightly low levels, heart rate changes in the same direction (Bainbridge-reflex), as observed among the ToF patients (blue lines).

Table 1

Subject characteristics

Variable	Fallot (n = 17)		Control (n = 56)	
Male gender	11 (65 %)		23 (41 %)	
Palliation	12 (71 %)			
Ventriculotomy at repair	4 (27 %) ^a			
Transannular patch at repair	7 (41 %)			
Reoperations after repair	5 (29 %) ^b			
	<i>Median</i>	<i>Range</i>	<i>Median</i>	<i>Range</i>
Age (years)	16	(13–18)	16	(13–18)
Age at repair (years)	2.8	(1.1–4.2)		
Interval since repair (years)	13.2	(10.7–16.4)		
Body surface area (m ²)	1.68	(1.42–1.84)	1.70	(1.40–2.21)
Pulmonary stenosis (m/s)	1.8	(1.3–2.4)		
Pulmonary regurgitation (%)	12	(0–60)		
Right ventricle end diastolic volume (ml/m ²)	117	(58–189)		
Right ventricle ejection fraction (%)	45	(36–66)		
pro Brain Natriuretic Peptide (pmol/L)	7.9	(3.8–24.3)	5.3	(1.2–19.8)
Maximum exercise capacity (% of expected O ₂ -consumption)	73	(50–97)		

^a In 2 patients, the records didn't explicitly state whether ventriculotomy was performed at repair or not.

^b A pulmonary homograft was inserted in 4 of these 5 patients.

Table 2
Hemodynamic variables before and during lower body negative pressure (LBNP). Mean±SD (Range)

Variable	Baseline		LBNP		Delta (LBNP-Baseline)	
	Control (n=56)	Fallot (n=17)	Control (n=56)	Fallot (n=17)	Control (n=56)	Fallot (n=17)
Systolic blood pressure (mm Hg)	118.7±15.3 (82.8–160.1)	109.4±10.2 ^a (93.4–129.0)	118.0±14.2 (83.6–156.9)	111.2±7.5 (96.9–124.0)	-0.8±7.0 (-15.6–16.2)	1.8±6.5 (-7.4–15.6)
Mean arterial blood pressure (mm Hg)	79.7±8.1	78.7±7.2	81.0±7.6	79.9±6.1	1.3±3.8	1.2±3.3
Diastolic blood pressure (mm Hg)	(62.9–104.9)	(69.2–94.3)	(69.0–100.0)	(68.2–92.3)	(-5.4–11.4)	(-5.8–6.4)
	64.6±7.4	63.8±6.2	66.9±6.9	65.7±5.7	2.4±3.8	1.9±3.3
Heart rate (HR) (beats/min)	(50.5–86.1)	(55.6–74.3)	(53.2–86.3)	(53.2–73.8)	(-5.4–13.2)	(-6.1–7.1)
	65.2±10.7	67.3±9.2	72.1±14.0	68.2±9.2	7.0±5.9	0.9±3.8 ^c
Stroke index (ml/m ²)	(42.1–89.4)	(51.1–92.7)	(44.8–101.2)	(58.6–94.8)	(-5.7–23.3)	(-8.2–7.5)
	41.3±8.7	38.7±10.9	30.6±7.2	32.4±7.9	-10.7±5.1	-6.3±4.9 ^b
Cardiac index (l/min/m ²)	(22.6–62.5)	(19.4–59.3)	(16.8–46.2)	(17.1–42.9)	(-26.8–1.2)	(-17.1–1.0)
	2.67±0.68	2.62±0.92	2.16±0.52	2.23±0.73	-0.51±0.32	-0.39±0.33
Total peripheral resistance index (mm Hg/l/min/m ²)	(1.48–4.16)	(1.39–4.45)	(1.21–3.46)	(1.05–4.04)	(-1.63–0.02)	(-1.26–0.06)
	11.5±5.4	12.8±4.9	14.4±7.0	15.1±5.2	2.9±2.2	2.3±2.3
Total power (ms ²)	(5.3–41.7)	(6.6–21.3)	(6.5–54.1)	(7.5–26.2)	(-0.1–12.4)	(-1.9–7.7)
	4611±4519	3220±4028	4001±3175	5144±3651	-610±3467	1325±3202 ^b
Low frequency HR variability, absolute values (LF _{abs}) (ms ²)	(274–23276)	(289–14416)	(375–16036)	(630–13702)	(-16398–6526)	(-7268–8221)
	1375±2091	946±1009	1325±1309	1632±1122	-50±1939	686±1089
High frequency HR variability, absolute values (HF _{abs}) (ms ²)	(40–13134)	(15–3537)	(44–6103)	(276–4057)	(-10795–4646)	(-975–3121)
	1804±1789	980±1162	1059±1246	1376±1226	-745±1281	396±1260 ^c
Low frequency HR variability, normalized values (LF _{norm}) (nu)	(61–6001)	(25–4518)	(40–4341)	(112–4399)	(-5158–2220)	(-1970–4184)
	44±19	48±23	58±18	58±15	15±20	10±20
High frequency HR variability, normalized values (HF _{norm}) (nu)	(5–80)	(6–85)	(15–89)	(35–88)	(-44–53)	(-31–42)
	55±19	50±22	41±18	41±15	-14±20	-9±20
	(19–90)	(15–90)	(10–85)	(11–62)	(-48–44)	(-40–32)

Variable	Baseline		LBNP		Delta (LBNP-Baseline)	
	Control (n=56)	Fallot (n=17)	Control (n=56)	Fallot (n=17)	Control (n=56)	Fallot (n=17)
LF _{norm} / HF _{norm}	1.2±1.1 (0.1–4.6)	1.6±1.5 (0.1–5.8)	2.7±2.6 (0.2–13.3)	2.4±2.2 (0.6–8.1)	1.5±2.4 (–2.7–11.2)	0.8±1.7 (–2.0–5.3)
Standard deviation of all RR-intervals (SDNN) (ms)	62.0±29.6 (15.9–162.3)	52.9±27.7 (16.9–102.3)	58.3±24.2 (16.5–127.0)	65.8±25.1 (24.8–115.0)	–3.7±22.7 (–93.6–47.9)	12.9±17.7 ^b (–15.4–52.6)
Proportion of successive RRs with a difference greater than 50 ms (pNN50) (%)	16.7±12.4 (0.0–41.1)	11.3±9.6 (0.0–32.7)	10.0±10.7 (0.0–37.9)	13.0±9.4 (0.5–31.4)	–6.6±7.9 (–35.4–9.1)	1.7±6.9 ^c (–12.2–13.6)
Square root of the mean square differences of successive RRs (r-MSSD) (ms)	64.3±41.9 (11.9–184.0)	48.9±30.8 (8.4–127.7)	44.3±30.9 (11.8–121.6)	57.1±29.2 (15.7–102.5)	–20.0±27.6 (–169.9–21.6)	8.2±23.2 ^c (–33.0–61.7)

^a p ≤ 0.05 for differences between groups, Wilcoxon-Mann-Whitney's test (2-sided)

^b p ≤ 0.01 for differences between groups, Wilcoxon-Mann-Whitney's test (2-sided)

^c p ≤ 0.001 for differences between groups, Wilcoxon-Mann-Whitney's test (2-sided)