OPEN ACCESS

GAVIN PUBLISHERS

Family Medicine and Primary Care: Open Access

Research Article

Reiner B and Julia B. J Family Med Prim Care Open Acc 4: 149.
DOI: 10.29011/2688-7460.100049

Excessive Heart Rate Increments during Active Standing Test in Children with Anorexia Nervosa: An Indicator of a Postural Orthostatic Tachycardia Syndrome and a New Therapeutic Target?

Reiner Buchhorn[1,2*], Julia Buchhorn [3]

[1]Caritas-Krankenhaus Bad Mergentheim, Department of Pediatrics, Uhlandstraße 7, Bad Mergentheim, Germany

[2]University of Wuerzburg, Medical Faculty, Josef-Schneider-Straße 2, Würzburg, Germany

[3]Pädagogische Hochschule Weingarten, Studiengang Bewegung und Ernährung, Kirchplatz 2, 88250 Weingarten, Germany

***Corresponding author:** Buchhorn Reiner, Caritas-Krankenhaus Bad Mergentheim, Department of Pediatrics, Uhlandstraße 7, Bad Mergentheim, Germany

Citation: Buchhorn R, Buchhorn J (2020) Excessive Heart Rate Increments during Active Standing Test in Children with Anorexia Nervosa: An Indicator of a Postural Orthostatic Tachycardia Syndrome and a New Therapeutic Target? J Family Med Prim Care Open Acc 4: 149. DOI: 10.29011/2688-7460.100049

Received Date: 07 June, 2020; **Accepted Date**: 03 July, 2020; **Published Date:** 10 July, 2020

Abstract

Background: Abnormalities in Heart Rate Variability analysis (HRV) and orthostatic intolerance have been found in patients with anorexia nervosa (AN), indicating impaired autonomic function.

Methods: The patients were 34 adolescents with AN, who were hospitalized (mean age=16.4±1.8 years; body mass index (BMI) =16.3±1.9 kg/m^2) compared to a healthy control group (N=32; mean age=15.4±3.7 years; BMI=20.6±2.9 kg/m^2). All adolescents had an active standing test with continuous measurement of heart rate during 5 minutes in supine position and ten minutes during active standing using the HRV Scanner™. 13 patients with AN have a second tilt test after 4 weeks refeeding on average. Using a questionnaire, physical activity (Hours of sport/week), nausea and dizziness were queried.

Results: We found nearly no differences of HRV between AN and control in the supine position but significantly higher heart rate increments in AN while standing (5 minutes: 26.4±15.1 versus 16.1±7.3** bpm, p<0,001; 10 minutes: 31.6±14.1 versus 20.1±8.0*** bpm, p<0.0001). Heart rate increment while standing are significantly related to the stress index (R^2=0.916***). Heart rate increment while 5-minutes standing are related to the BMI (r=-0.304*), physical activity (r=-0.376**) and orthostatic dizziness (r=-0.479**). 13 patients after one-month refeeding have significantly reduced heart rate increments (20.9±9.4 versus 35.7±16.3***, p<0.001).

Conclusion: AN have significantly enhanced heart rate increment while standing that are related to the stress index and clinical symptoms.

Keywords: Anorexia nervosa; Postural orthostatic tachycardia syndrome; Heart rate variability; Ivabradine; Omega-3-fatty acids; Adolescence

Abbreviations: AN: Anorexia nervosa; bpm: Beats per Minute; cm: Centimeter; d: Day; HRV: Heart Rate Variability; kg: Kilogram; ms: Milliseconds; POTS: Postural Orthostatic Tachycardia Syndrome; y: Year

Introduction

Anorexia Nervosa (AN) is an eating disorder and a growing health problem characterized by a low BMI and calorie restriction associated with a desire to be thin. AN affects approximately 1-4% of women and 0.3-0.7% of men in Europe [1]. The cause of AN is still unknown. There appear to be environmental and genetic components in the etiology of AN. The primary risk factors for developing AN could be stress inducing events in early life and a genetic predisposition. Often AN comes along with severe medical complications such as pericardial effusion, gastroparesis or hypokalemia. Among psychiatric disorders anorexia nervosa has the highest mortality rate [2]. Apart from suicidal events cardiac complications are the leading causes of death in AN patients.

The first therapeutic step to treat patients with AN is refeeding to reverse malnutrition and its complications. However, improving weight gain must be balanced against fatal complications such as cardiac arrhythmias, heart failure, delirium, seizures, coma and sudden death. All these complications are summarized by the term refeeding syndrome, but pathophysiology is highly unclear. Studies suggest that some of these abnormalities result from a dysfunction of the autonomic nervous system [3].

Over the last few years the measurement of Heart Rate Variability (HRV) has become an important tool to gain knowledge of the autonomic nervous system. The autonomic nervous system is one of the most important regulators of the heart rate. Under normal resting conditions parasympathetic activity prevails sympathetic tone. According to demands of physical mental or metabolic activity the sympathetic system is released by reduction of vagal tone. HRV measures the variations in the interbeat intervals and reflects an extraordinarily complex interplay of feedback loops, thermogenesis, parasympathetic and sympathetic tone.

Mazurak, et al. conducted a review of the literature to this topic in 2010 and found contradicting results [4]. The majority of twenty publications reviewed found an autonomic imbalance with parasympathetic dominance in AN patients. However, others could not replicate these findings and could not identify any autonomic imbalance or instead described sympathetic dominance. We introduced HRV monitoring in all patients with AN admitted to the department of pediatrics for in hospital refeeding in 2005. We compared the HRV data of children with anorexia nervosa, constitutional thinness and obesity and found a clear pathophysiological principle to explain HRV changes according to the caloric intake [5]. In summary, our 24 hours HRV analysis clearly indicate low heart rates and high HRV in AN during starvation at hospital entry. After successful nutritional refeeding the mean heart rates significantly increase and HRV decrease. According to these date we modified our refeeding protocol with respect to the autonomic nervous system and could recently publish a significantly improved weight gain in a retrospective analysis [6].

For a better understanding of heart rate regulation in AN we now introduce short time HRV analysis during an active standing test. In 2014 Y. Takimoto, et al. found autonomic dysfunction in response to head-up active standing in AN [7]. These data may indicate that patients with AN suffer from postural orthostatic tachycardia syndrome. This syndrome has received more attention in recent years as it explains symptoms that go beyond orthostatic intolerance like chronic fatigue, abdominal pain, nausea, dizziness, and lightheadedness. In this context gastrointestinal symptoms have an approximately 69% prevalence in patients with postural orthostatic tachycardia syndrome due to delayed gastric emptying and impaired gastrointestinal motility [8]. However, the definition of postural orthostatic tachycardia syndrome with an orthostatic heart increment of at least 30 bpm of active standing in adults or 40 bpm in adolescents has many methodological limitations [9].

We decide for a 15 minutes active standing test with continuous heart rate registration for HRV analysis in 34 patients with anorexia nervosa and 32 healthy controls. The active standing test and head-up tilt test are comparable methods for the assessment of the postural orthostatic tachycardia syndrome [10].

Methods

Patients

We included 34 adolescents with AN, who were hospitalized for nutritional refeeding (mean age=16.4±1.8 years; Body Mass Index (BMI) =16.3±1.9 kg/m^2) in the pediatric department of the Caritas Hospital in Bad Mergentheim and the Schön Klinik Bad Arolsen - a specialized clinic for psychosomatics for adolescents and adults. The healthy control group included 32 heathy adolescents (mean age=15.4±3.7 years; BMI=20.6±2.9 kg/m^2) without any somatic or psychosomatic diseases.

The author ensure that the work described has been carried out in accordance with "The Code of Ethics of the World Medical Association (Declaration of Helsinki") for experiments involving humans. Informed consent was obtained for the active standing test in all patients and the off label use of pharmacotherapy with ivabradine for the postural orthostatic tachycardia syndrome in two patients.

Active Standing Test

All adolescents had at least one active standing test with continuous measurement of heart rate during 5 minutes in supine position and ten minutes during active standing. We perform blood pressure measurements in the supine position and each 2 minutes during standing. Patients with blood pressures of more than 135 mmHg at rest were excluded. 13 patients with AN have a second active standing test after 4 weeks refeeding on average.

HRV

Short time HRV analysis was performed using the HRV Scanner™ (BioSign GmbH, Germany) at three time periods: 1) Supine position. 2) First 5 minutes standing. 3) 5-10 minute standing. HRV-measurements are based on the RR intervals of normal QRS complexes (NN intervals) of the three 5 minute's intervals except eight patients who have prematurely stopped the active standing test after 5 minutes because of dizziness. In HRV- analyses a differentiation is made between time-domain and frequency-domain parameters, which are briefly outlined below [11-14]:

Time domain HRV

- Average heart rates = mean heart rates of each 5 minute interval. SDNN in milliseconds = Standard deviation of NN; reflects general variability of HR influenced by ANS but also endocrine and thermoregulatory mechanisms

- pNN50 = Percent of NN intervals which differ more than 50 ms from the prior interval; reflects mainly the parasympathetic influence rMSSD in milliseconds = Root mean square of differences between successive NN intervals; reflects mainly the parasympathetic influence.

Stress Index

$$Stress\,index = \frac{Amo}{2 \times Mo \times MxDMn}$$

Mo: Modal value, most common value of the RR intervals; Amo: number of RR intervals corresponding to the mode as a percentage of the total number of all readings; MxDMn: variability width, difference between the maximum and minimum RR intervals.

The stress index is calculated based on Prof. Baevsky, who had developed and validated this parameter in the context of Russian space medicine. The stress index is becoming increasingly popular because it reacts sensitively to shifts in the vegetative balance between the sympathetic and parasympathetic nerves.

Frequency domain HRV

The Fourier transformation shows that HRV- signals are concentrated into four different frequency bands:

- Very low frequency power (VLF=0.00-0.04Hz) in ms^2 – uncertain physiological meaning.
- Low-frequency power (LF=0.04-0.15Hz) in ms^2 – mediated by sympathetic tone, however interpretation controversial, may represent both sympathetic and parasympathetic activity.
- High-frequency power (HF=0.15-0.4Hz) in ms^2 – 'sinus arrhythmia', mediated by alternating levels of parasympathetic tone.
- LF/HF ratio - Often referred to as the balance between sympathetic and parasympathetic tone.
- Total power (TP) in ms^2 – measures the total variance in HRV.

Questionnaire

To compare the data measured during the active standing test with clinical symptoms each patients get a questionnaire with which we asked the following points: 1) Pharmacotherapy 2) Physical activity (Hours of sport/week) 3) Nausea 4) Concentration deficits and 5) Dizziness and in an ordinal manner. The questionnaire was filled by 55 patients but we have asked sports data from all patients.

Statistics

We used SPSS version 25.0 for statistical analysis. For descriptive statistics data were expressed as mean±standard deviation. As most variables exhibited a normal distribution, between-group differences were assessed using parametric statistics. First, we compared mean heart rates HRV parameters of each 5-minute segment before and after standing (0-5 and 5-10 Minute standing) using paired student t-test. Secondly, we performed a Pearson correlation analysis between changes of heart rate and HRV indices. The statistical significance threshold accounted for p=0.05.

Results

Clinical data are shown in Table 1. Absolute values as well as percentiles of body weight and body mass index are highly significantly different between the two groups as expected by the diagnosis. Patients with AN have significantly lower systolic blood pressures (105.9±12.4 versus 115.9±7.9***; p<0.0001) compared to the healthy control group but nearly the same diastolic blood pressures. There is a trend to lower heart rates at rest in AN patients. However, we found nearly no differences of HRV between AN and healthy controls in the supine position except a slightly lower standard deviation of heart rates (Table 2). In contrast, there are significantly higher heart rate increments in AN while standing (5 minutes: 26.4±15.1 versus 16.1±7.3** bpm, p<0.001; 10 minutes: 31.6±14.1 versus 20.1±8.0*** bpm, p<0.0001 (Figure 1). The excessive heart rate increase in AN seems to be related to global heart rate variability indicated by SDNN and Total Power, but these changes are not clearly attributable to the sympathetic or parasympathetic branch of the autonomic nervous system (Table 2). The Pearson correlation coefficients of the heart rate increments after 5 and 10 minutes are not related to the HRV parameters in the supine position (Table 3). However, many of the HRV parameters during the first and second 5-minute segment are significantly related to the heart rate increments. But again, these significant correlations are related to global HRV (SDNN) as well as to the classic vagus parameters (pNN50 and RMSSD). However, frequency domain analysis show no consist correlation of heart rate increases to the high frequency power that indicates the vagus (Figure 2, Table 3).

	Healthy Control	**Anorexia Nervosa**	***P-Value***
N	32	34	
female	21	32	
male	11	2	
Age [Years]	15.4±3.7	16.4±1.8	0.15
Height [cm]	163.3±12.1	166.6±7.5	0.20
Height Percentile [%]	51.3±19.8	52.6±27.8	0.83
Weight [kg]	55.4±13.0	45.2±7.6***	<0.0001
Weight Percentile [%]	56.5±25.0	12.6±15.3***	<0.0001
Body Mass Index [kg/m²]	20.6±2.9	16.3±1.9*	0.013
BMI Percentile [%]	56.0±2.7	6.6±9.9***	<0.0001
Heart Rate [bpm]	73.3±13.7	66.6±14.0	0.052
Systolic Blood Pressure [mmHg]	115.9±7.9	105.9±12.4***	<0.0001
Diastolic Blood Pressure [mmHg]	64.8±10.9	66.4±9.7	0.51

Table 1: Descriptive Statistics of Body Measurement at rest.

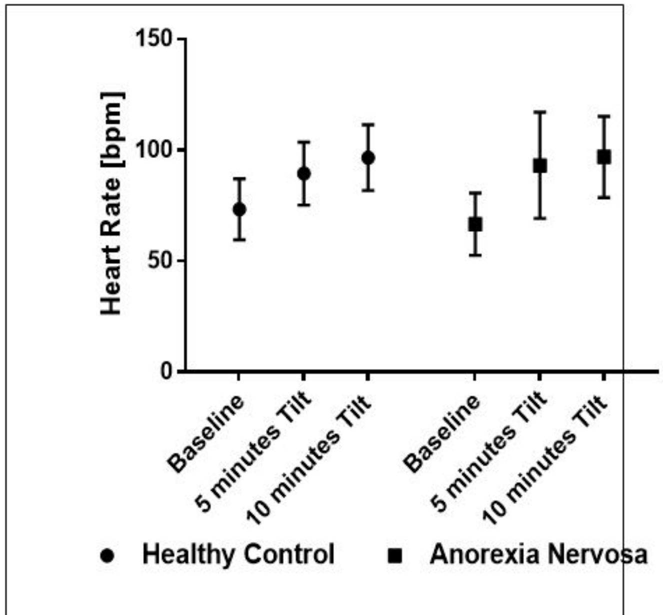
	Healthy Control	**Anorexia nervosa**	**p-Value**
	Baseline: 5 minutes lying position		
Heart Rate [bpm]	73.3±13.7	66.6±14.0	0.052
Standard Deviation [bpm]	6.61±2.57	5.26±2.04*	0.022
SDNN [ms]	80.2±39.2	72.9±37.1	0.442
PNN50 [%]	43.2±23.5	43.5±24.7	0.961
RMSSD [ms]	87.5±61.6	81.6±53.0	0.680
Stressindex [Pt]	99.9±93.0	111.7±121.0	0.502
Power HF Band [ms²]	3174±5005	2317±2513	0.389
Power LF-Band [ms²]	1700±3321	1355±1357	0.588
Power VLF-Band [ms²]	1522±2089	923±762	0.134
Power Total [ms²]	6397±7110	4596±3945	0.213
5 minutes Tilt Test			
Heart Rate Increment [bpm]	**16.1±7.3**	**26.4±15.1****	**0.001**
Heart Rate[bpm]	89.4±14.2	93.1±23.9	0.452
Standard Deviation HR [bpm]	7.2±2.3	6.3±2.1	0.117
SDNN [ms]	60.8±26.1	53.2±35.1	0.322
PNN50 [%]	16.2±14.7	12.5±16.6	0.344
RMSSD [ms]	39.1±19.8	34.9±26.3	0.464

Stressindex [Pt]	169.1±117.4	360.8±457.2*	0.023
Power HF Band [ms^2]	831±979	687±988	0.553
Power LF-Band [ms^2]	1207±992	878±907	0.166
Power VLF-Band [ms^2]	1380±1694	1224±2168	0.745
Power Total [ms^2]	3419±3007	2790±3612	0.944
10 Minutes Tilt Test			
Heart Rate Increase [bpm]	**20.1±8.0**	**31.6±14.1*****	**<0.0001**
Heart Rate[bpm]	96.6±14.8	96.9±18.3	0.455
Standard Deviation HR [bpm]	6.8±2.2	5.6±1.6*	0.022
SDNN [ms]	51.6±20.6	39.0±14.1**	0.008
PNN50 [%]	11.1±12.2	7.42±10.6	0.215
RMSSD [ms]	32.0±16.7	26.0±13.7	0.137
Stressindex [Pkt]	206.6±142.5	396.7±595.6	0.116
Power HF Band [ms^2]	529±594	311.5±352.0	0.091
Power LF-Band [ms^2]	1072±944	657±480*	0.037
Power VLF-Band [ms^2]	1293±1534	588±460*	0.02
Power Total [ms^2]	2894±2329	1557±1026**	0.006

Table 2: HRV data during active standing test.

	Baseline		**5 Minutes Tilt**		**10 Minutes Tilt**	
Heart Rate Increase after	5 min	10 min	5 min	10 min	5 min	10 min
Mean Heart Rate	0.053	0.03	.698**	.663**	.442**	.568**
SDNN	-0.187	-0.066	-.344**	-0.254	-.452**	-.459**
PNN50	-0.192	-0.165	-.534**	-.459**	-.425**	-.455**
RMSSD	-0.162	-0.06	-.523**	-.399**	-.430**	-.462**
Stressindex	.269*	.305*	.803**	.740**	.520**	.605**
HF - Power	-0.145	-0.065	-.289*	-0.152	-0.243	-0.253
LF - Power	-0.007	0.032	-.363**	-.319*	-.311*	-.306*
VLF - Power	-0.075	-0.095	-0.118	-0.078	-0.248	-.259*
**Pearson correlation $p < 0.01$; *Pearson correlation $p < 0.05$						

Table 3: Pearson correlation coefficients between heart rate increase after 5 and 10 minutes and absolute HRV parameters.



Heart Rate Increments during Tilt Test	Healthy Control	Anorexia nervosa	p-Wert
after 5 Minutes	16.1 ± 7.3	26.4 ± 15.1**	0.001
after 10 Minutes	20.1 ± 8.0	31.6 ± 14.1***	<0.0001

Figure 1: Heart Rates during Tilt Test.

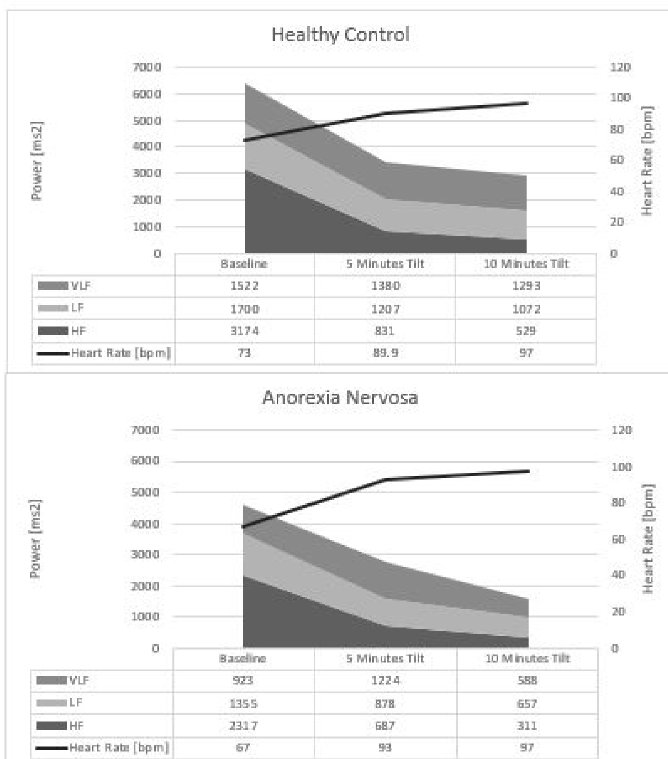


Figure 2: Spectral Analysis of Heart Rate Variability during the Tilt Test.

The most impressive correlations of the heart rate increments while standing are related to the stress index (R^2=0.916***). Figure 3 shows a steep increase of the stress index if the orthostatic heart rate increment exceeds 30 bpm, the classical threshold for the diagnosis of a postural orthostatic stress syndrome. Thirteen patients with AN had an orthostatic heart rate increment higher than 30 bpm and probably suffer from postural orthostatic stress syndrome, but no healthy control patient. However, we found a high standard deviation of the stress index in patients with AN while standing (Figure 4).

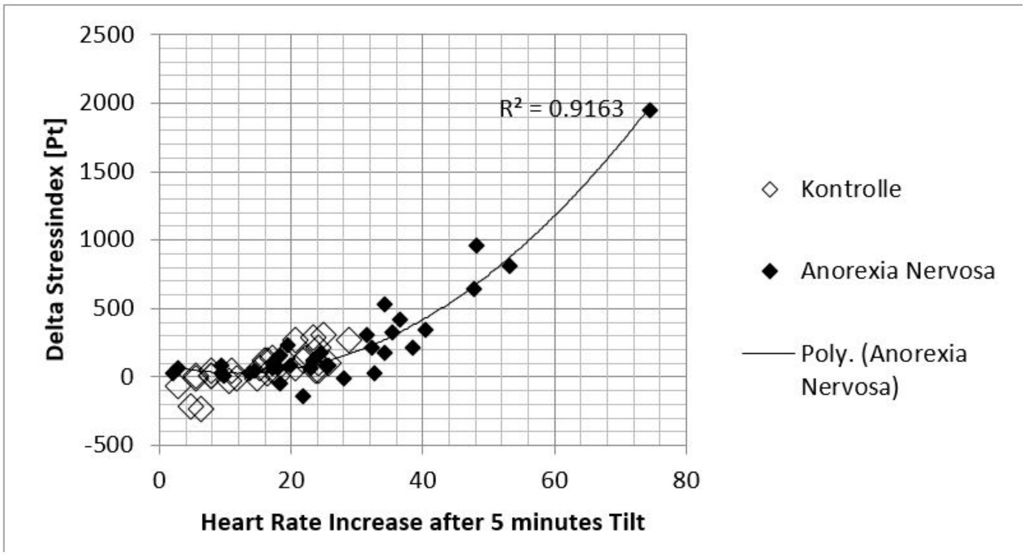


Figure 3: Stress Index during active standing test.

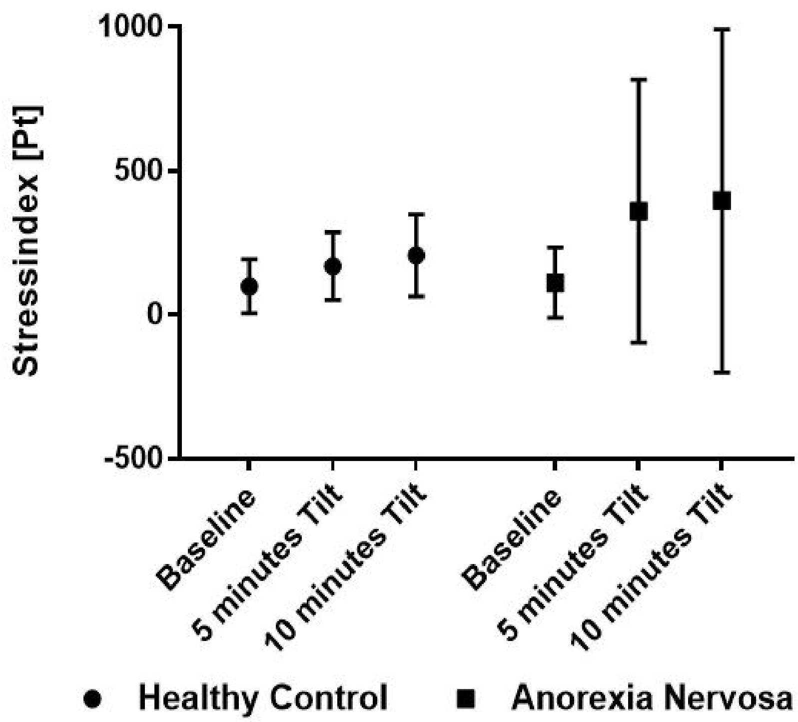


Figure 4: Stress index during active standing test.

Heart rate increments during the first 5 minutes standing are significantly related to the BMI (r=-0.304*), physical activity (r=-0.376**) and orthostatic dizziness (r=0.479**) (Table 4). High heart rate increases and probably the postural orthostatic stress syndrome seems to be related to physical inactivity with less than two hours sports per week most of all in patients with AN (Figure 5).

Clinical Symptomes	Heart Rate Increase after		HRV-Parameters after 5 minutes Tilt Test										
	5 min	10 min	Heart Rate	SDNN	PNN50	RMSSD	Stress-index	HF-Power	LF- Power	VLF-Power	Power Total	LF/HF Ratio	Rhyt. Grad
Body Mass Index [kg/m²]	-.309*	-.345**	-0.114	0.109	0.103	0.094	-0.213	0.046	0.098	0.046	0.069	-0.117	0.187
Sports [Hours/week]	-.376**	-.301*	-.377**	0.102	.304*	.318**	-.315*	0.172	0.182	-0.054	0.072	-0.108	0.153
Nausea [scale]	0.259	0.149	0.096	-0.204	-0.257	-0.214	0.201	-0.228	-.388**	-0.136	-0.246	-0.137	-.389**
Dizziness [scale]	.295*	0.253	0.262	-.361**	-.346*	-.301*	.289*	-.284*	-.367**	-.330*	-.376**	-0.071	-.300*
Tilt Dizziness [scale]	.479**	.387**	.494**	-.327*	-.372**	-.373**	.491**	-0.222	-0.238	-0.199	-0.244	-0.05	-.326*
Concentration Problems	0.131	0.01	-0.023	0.037	0.034	-0.026	0.028	-0.006	-0.037	0.113	0.059	-0.259	-0.099
**Pearson correlation $p < 0.01$; *Pearson correlation $p < 0.05$													

Table 4: Pearson correlation coefficients between heart rate increment/HRV analysis after 5 minutes with clinical symptoms.

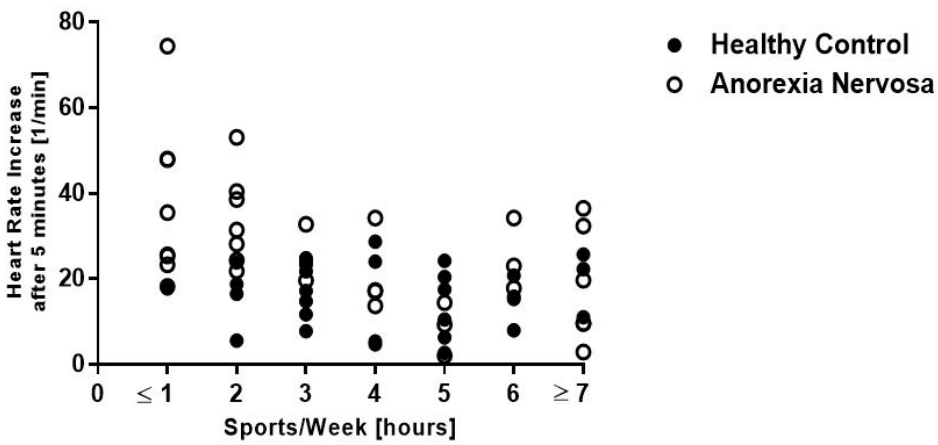


Figure 5: Heart Rate Increase during the active standing test and sports activities.

Thirteen patients with AN of the Caritas Hospital Bad Mergentheim had a second active standing test after one-month refeeding with a weight gain of 4.4±2.9 kg on average (Table 5). We found significantly higher heart rates in the supine position (73.8±12.9 versus 61.8±16* bpm, p=0.0238) but lower heart rate increases (20.9±9.4 versus 35.7±16.3***, p<0.001) while standing.

N=13	Baseline	Refeeding	P-value
Bodyweight [kg]	40.4±6.5	44.7±7.6***	< 0.001
Heart Rate [bpm]	61.8±16	73.8±12.9*	0.0238
Heart Rate 5 Min Tilt [bpm]	97.5±28.8	94.7±17.5	ns
Heart Rate Increase [bpm]	35.7±16.3	20.9±9.4***	< 0.001

Table 5: Heart Rate Changes during active standing test after 4 weeks nutritional refeeding and a weight gain of 4.4±2.9 kg.

Discussion

It is one sixteen-year-old boy who suffer from anorexia nervosa with an orthostatic heart rate increment of 75 bpm after 5 minutes active standing test - as show in Figure 3- who open our eyes to the problem of an Postural Orthostatic Tachycardia Syndrome (POTS) in patients with anorexia nervosa in august 2018. He became bedridden during nutritional refeeding and gains more than 20kg bodyweight after the successful POTS treatment with metoprolol and midodrine. Since that time, we include the active standing test in our clinical routine and found a lot of adolescents who suffer from POTS. Recently an online, community-based, cross-sectional survey in partnership between academic institutions and "Dysautonomia International", a patient advocacy organization, had shown lengthy delays (24 months; 6-72 months) and misdiagnosis of POTS [15]. In this survey patients present with a myriad of symptoms most commonly including lightheadedness (99%), tachycardia (97%), presyncope (94%), headache (94%) and difficulty concentrating (94%). Others report about gastrointestinal symptoms like nausea (90%), stomach pains (83%), bloating (79%), constipation (71%) or diarrhea (69%). However, W Singer, et al. report about methodological insecurities in the definition of postural orthostatic tachycardia syndrome based upon the orthostatic heart increment of at least 30 bpm of active standing in adults or 40 bpm in adolescents [9]. That is the reason because we decide for a continuous heart rate measurement during a 15 minutes active standing test (5 minutes supine position, 10 minutes active standing) together with a short time HRV analysis.

Based upon this sophisticated method, we really found significantly higher orthostatic heart rate increments during standing in patients with AN (Figure 1, Table 2). The higher heart rate increments in patients with AN is mostly related a trend to lower heart rates in the supine position – a well-known phenomenon from our 24 hours HRV analysis [5]. However, we cannot reproduce the significant differences in 24 hours HRV in patients with AN with the current 5-minute HRV analysis in the supine position. This may explain contradicting results of HRV data in AN reviewed by Mazurak, et al. [4].

In contrast, we found significant lower HRV in patients with AN while standing (Table 2) that is related to global heart rate variability indicated by SDNN and Total Power. The Pearson correlation coefficients of the heart rate increments after 5 and 10 minutes are not related to the HRV parameters in the supine position (Table 3) but to many of the HRV parameters during the first and second 5-minute segment while standing. These data open a methodological dilemma of HRV analysis, if these changes are not clearly attributable to the sympathetic or parasympathetic branch of the autonomic nervous system (Table 3). We observe significant correlations with the classic vagus parameters like pNN50 and RMSSD, but frequency domain analysis shows no consistent correlation of heart rate increments to the high frequency power that indicates the vagus. We recently published a paper to this methodological dilemma: Our 24 hours HRV data indicate a third regulatory system that is important in HRV analysis in addition to the current doctrine of a dual regulation by the vagus and sympathicus. This system is related to age-dependent changes in body surface area, height, and weight. This dominant system regulates intrinsic heart rate, SDNN and Total Power of spectral analysis and depends on nutrition and energy demands and is probably regulated by the HCN4 gene.

However, the most consistent correlations of heart increments while standing in the current study are related to the stress index (Figure 3, Table 3), that is not measured in our former 24 hours HRV analysis. The stress index is significantly related to the orthostatic heart rate increments after 5 and 10 minutes as well to clinical symptoms like dizziness. Prof. Baevsky had developed and validated the stress index in the context of Russian space medicine to estimate the clinical symptoms of astronauts by gravitational forces. Interestingly, some patients achieve levels of astronauts during the start of a shuttle (up to 3500 Pt.). However, the stress index shows an exponential increase (Figure 3) and a very high standard deviation (Figure 4) if not all patients with anorexia nervosa develop a POTS. We conclude that POTS have a high impact on clinical symptoms in patients with AN and should be treated.

First, we analyze the impact of physical activity on heart rate increase in our patients and found the highest values in patients who perform less than 2 hours sports per week (Figure 5). Our data confirms a variety of studies that assess the POTS as a result of physical inactivity [16]. We had already removed the frequently practiced ban on sports from our treatment protocol at an early stage [17-19]. However, more than 5 hours sports week did not further improve the heart rate increases but may have a negative impact on weight gain [20].

Moreover, in 3 of our patients we decide for a pharmacotherapy of POTS to improve clinical symptoms (metoprolol+midodrine or ivabradine in two patients). All our patients routinely receive 2g omega-3-fatty acids supplementation to limit heart rate increases during refeeding as recently published [6,21]. Based upon these therapeutic approaches to improve autonomic dysfunction in adolescents with AN we are now able to show a significant improvement of the orthostatic heart rate increments (20.9±9.4 versus 35.7±16.3 bpm***; $p < 0.001$) in our last 13 patients (Table 5).

Conflict of Interest

This study was carried out independently. The authors had no conflict of interest and did not receive any funding for the conduction of the study.

References

1. Keski-Rahkonen A, Mustelin L (2016) Epidemiology of eating disorders in Europe: prevalence, incidence, comorbidity, course, consequences, and risk factors. Curr Opin Psychiatry 29: 340-345.
2. Brown C, Mehler PS (2015) Medical complications of anorexia nervosa and their treatments: an update on some critical aspects. Eat Weight Disord 20: 419-425.
3. Galetta F, Franzoni F, Prattichizzo F, Rolla M, Santoro G, et al. (2003) Heart rate variability and left ventricular diastolic function in anorexia nervosa. J Adolesc Health 32: 416-421.
4. Mazurak N, Enck P, Muth E, Teufel M, Zipfel S (2011) Heart rate variability as a measure of cardiac autonomic function in anorexia nervosa: a review of the literature. Eur Eat Disord Rev 19: 87-99.
5. Dippacher S, Willaschek C, Buchhorn R (2014) Different nutritional states and autonomic imbalance in childhood. Eur J Clin Nutr 68: 1271-1273.
6. Baumann C, Willaschek C, Kertess-Szlaninka T, Lang J, Buchhorn R (2017) Implementing high energy liquid nutrition, omega-3 fatty acids and nutritional supplements for the treatment of anorexia nervosa Journal of Pediatric Health And Nutrition 1: 1-12.
7. Takimoto Y, Yoshiuchi K, Ishizawa T, Yamamoto Y, Akabayashi A (2014) Autonomic dysfunction responses to head-up tilt in anorexia nervosa. Clin Auton Res 24: 175-181.
8. Mehr SE, Barbul A, Shibao CA (2018) Gastrointestinal symptoms in postural tachycardia syndrome: a systematic review. Clin Auton Res 28: 411-421.
9. Singer W, Sletten DM, Opfer-Gehrking TL, Brands CK, Fischer PR, et al. (2012) Postural tachycardia in children and adolescents: what is abnormal? J Pediatr 160: 222-226.
10. Kirbis M, Grad A, Meglic B, Bajrovic FF (2013) Comparison of active standing test, head-up tilt test and 24-h ambulatory heart rate and blood pressure monitoring in diagnosing postural tachycardia. Funct Neurol 28: 39-45.
11. (1996) Heart Rate Variability: Standards of Measurement, Physiological Interpretation and Clinical Use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 93: 1043-1065.
12. Millis RM, Austin RE, Hatcher MD, Bond V, Goring KL (2011) Metabolic Energy Correlates of Heart Rate Variability Spectral Power Associated with a 900-Calorie Challenge. J Nutr Metab 2011: 715361.
13. Fujibayashi M, Hamada T, Matsumoto T, Kiyohara N, Tanaka S, et al. (2009) Thermoregulatory sympathetic nervous system activity and diet-induced waist-circumference reduction in obese Japanese women. Am J Hum Biol 21: 828-835.
14. Nakai Y, Fujita M, Nin K, Noma Si, Teramukai S (2015) Relationship between duration of illness and cardiac autonomic nervous activity in anorexia nervosa. Biopsychosoc Med 9: 12.
15. Shaw BH, Stiles LE, Bourne K, Green EA, Shibao CA, et al. (2019) The face of postural tachycardia syndrome - insights from a large cross-sectional online community-based survey. J Intern Med 286: 438-448.
16. Parsaik A, Allison TG, Singer W, Sletten DM, Joyner MJ, et al. (2012) Deconditioning in patients with orthostatic intolerance. Neurology 79: 1435-1439.
17. Nagata JM, Carlson JL, Golden NH, Murray SB, Long J, et al. (2019) Associations between exercise, bone mineral density, and body composition in adolescents with anorexia nervosa. Eat Weight Disord 24: 939-945.
18. Kolnes LJ (2017) Exercise and physical therapy help restore body and self in clients with severe anorexia nervosa. J Bodyw Mov Ther 21: 481-494.
19. Schlegel S, Hartmann A, Fuchs R, Zeeck A (2015) The Freiburg sport therapy program for eating disordered outpatients: a pilot study. Eat Weight Disord 20: 319-327.
20. Gianini LM, Klein DA, Call C, Walsh BT, Wang Y, et al. (2016) Physical activity and post-treatment weight trajectory in anorexia nervosa. Int J Eat Disord 49: 482-489.
21. Buchhorn R, Baumann C, Willaschek C (2019) Alleviation of arrhythmia burden in children with frequent idiopathic premature ventricular contractions by omega-3-fatty acid supplementation. Int J Cardiol 291: 52-56.