Exploratory Research and Hypothesis in Medicine **2022** vol. 000(000) | 000-000 Epub
DOI: 10.14218/ERHM.2022.00003

Original Article

Diagnostics and Management of Dysautonomia in Childhood

Reiner Buchhorn*

MVZ Forchtenberg, Department Pediatric Cardiology and Adults with Congenital Heart Diasease, Forchtenberg, Germany

Received: January 06, 2022 | **Revised:** January 27, 2022 | **Accepted:** February 03, 2022 | **Published:** March 01, 2022

Abstract

Background and Aims: Objective measurements of dysautonomia in children with psychosomatic disease and more recently in SARS-CoV-2-related disorders may clarify current uncertainties by using heart rate analysis for diagnostics and therapy control.

Methods: We analyzed the data of 181 children who had an active standing test, among which 131 had an additional 24-h Holter echocardiogram. The children suffered from dysautonomia due to postural orthostatic tachycardia (n = 48), inappropriate sinus tachycardia (n = 74), or clinical vagovasal syncope (n = 12). We investigated the effect of our treatment on heart rate and heart rate variability, including beta blocker (low dose propranolol 20–20–0 mg, n = 15), ivabradine 5–5–0 mg (n = 11), midodrine 2.5–2.5–0 mg (n = 6), and omega-3-fatty acid supplementation (n = 7).

Results: Lowering increases in heart rate while standing was achieved by low dose propranolol (from 41.7 ± 17.5 to 29.5 ± 17.8 beats per minute) and ivabradine (from 37.5 ± 16.4 to 23.6 ± 8.1 beats per minute). We further found a significant reduction of heart rate while standing after omega-3-fatty acid supplementation (from 44.0 ± 11.9 to 25.6 ± 8.4 beats per minute). Heart rate variability was useful for determining pathophysiology but was not necessary for diagnosis.

Conclusions: Vagus weakness was more common in children with dysautonomia compared to those with inappropriate sinus tachycardia and in the upright position in children with postural orthostatic tachycardia. Dysautonomia was related to autoimmunity in nine cases, including in children following SARS-CoV-2 infection. The current study demonstrates that assessing dysautonomia could be beneficial in the treatment of psychosomatic and SARS-CoV-2-related disorders.

Keywords: Autonomic nervous system; SARS-CoV-2; Anorexia nervosa; Autoimmunity; Omega-3-fatty acids; Beta blocker; Ivabradine.

Abbreviations: BMI, body mass index; COVID-19, corona virus disease 2019; DBP, diastolic blood pressure; DHA, docosahexaenoic acid; ECG, electrocardiogram; ELISA, enzyme-linked immunosorbent assay; EPA, eicosapentaenoic acid; FFA, fast fourier analysis; GPCR, G-protein coupled autoantibody; HF, high frequency power; HR, heart rate; HRV, heart rate variability; IST, inappropriate sinus tachycardia; LF, low frequency power; LF/HF, low to high frequency power ratio; mRNA, messenger ribonucleic acid; O3-FA, omega-3-fatty acids; POTS, postural orthostatic tachycardia; pNN50/pNN20, number of pairs of adjacent NN intervals differing by more than 50/20ms divided by the total number of all NN intervals; rMSSD, square root of the arithmetic mean of the squared deviation of successive normal RR intervals; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBP, systolic blood pressure; SDNN, standard deviation of all normal RR intervals in a time frame; TP, total power; VLF, very low frequency power.

***Correspondence to:** Reiner Buchhorn, Praxis for Pediatrics, Pediatric Cardiology and Adults with Congenital Heart Disease, Am Bahnhof 1, 74670 Forchtenberg, Germany. ORCID: https://orcid.org/0000-0003-3474-8239. Tel: +49-7947919081, Fax: +49-947919091, E-mail: buchrein@gmail.com

How to cite this article: Buchhorn R. Diagnostics and Management of Dysautonomia in Childhood. *Explor Res Hypothesis Med* 2022;00(00):00–00. doi: 10.14218/ERHM.2022.00003.

Introduction

The diagnosis dysautonomia as a clinical entity is questioned in modern medicine, and scientific research on this subject has been neglected.[1] However, dysautonomia may present with a number of frequent seemingly unrelated symptoms, including syncope, dizziness, gastrointestinal dysmotility, headaches, irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, Raynaud's phenomena, and palpitations. There is a close relationship between dysautonomia and emotional diseases and eating disorders likely due to neuronal pathways that connect the limbic system to the autonomic nervous system. Julian Thayer first introduced a model of neurovisceral integration in emotion regulation and dysregulation[2] with a clear historical reference to Claude Bernard.[3] This model is focused on vagal regulation derived from measurement of heart rate variability (HRV)

as a marker of health risks[4] and prognosis related to cardiovascular disease.[5] However, other investigators argue that heart rate alone is sufficient to explain the impact of the autonomic nervous system on life expectancy and the cardiovascular system,[6] explaining the use of therapeutic approaches like beta blocker therapy in heart failure.

We investigated the impact of macro- and micro nutrition on heart rate for a more complete understanding of dysautonomia in children with anorexia nervosa,[7] obesity,[8] and attention deficit disorder[9] to understand heart-brain interactions in children with psychosomatic diseases. Our data clearly indicate a bidirectional interaction between heart rate and emotional regulation as a window of opportunity for new therapeutic approaches. We observed a further increase in cases of dysautonomia in children and adults during the corona virus disease 19 (COVID-19) pandemic that may be related to the impact of SARS-CoV-2 infections on the autonomic nervous system.[10] As such, dysautonomia has been linked to autoimmunity[11] in the context of SARS-CoV-2 infections in adults[12,13] and children.[10] In addition, new diseases such as long COVID are overwhelming our health system.

In the current study, we conducted a retrospective analysis of clinical routine data and found that pharmacotherapy with low dose propranolol or ivabradine and supplementation with omega-3-fatty acids (O3-FA) impacted heart rate in children with dysautonomia. We also present measurable success of our therapeutic approaches in the treatment of dysautonomia within the last 5 years, which could be beneficial for the treatment of COVID-19 patients.

Methods

This work follows the Standards for Reporting Diagnostic accuracy studies (STARD) guidelines (Supplementary File 1). The study protocol was reviewed and approved by the Institutional Review Board of Landesärztekammer Baden Württemberg F-2012-0056. The authors are accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all patients.

Patients

We retrospectively analyzed the data of 181 consecutive children who had an active standing test within the last five years at the pediatric department of Caritas Hospital in Bad Mergentheim and at the author's private practice in Forchtenberg. Of the 181 children, 131 had an additional 24-h Holter echocardiogram (ECG). The children suffered from dysautonomia due to postural orthostatic tachycardia (POTS) and an increased average heart rate of more than 35 beats per minute (bpm) while standing (n = 48), an inappropriate sinus tachycardia (IST) with a mean 24-h heart rate ≥ 95 bpm (n = 74), or vagovasal syncope (VVS) (n = 12). The data were stored in a database generated by a software system (HRV Scanner™, BioSign GmbH; Germany). Children with heart disease (congenital heart defects, arrhythmias, or heart failure) were excluded from the study.

G-protein coupled receptor (GPCR) autoantibody measurements

Whole blood samples from nine subjects were allowed to clot at room temperature and then centrifuged at 2,000 g for 15 m in a refrigerated centrifuge. Serum was purified and stored at −35°C. The anti-alpha and beta adrenergic receptors (α1, α2, β1, β2), anti-muscarinic receptors (M1-M5), anti-endothelin receptor type A, and anti-angiotensin II type 1 receptor autoantibodies were measured in serum samples using a sandwich enzyme linked immunosorbent assay (ELISA) kit (CellTrend GmbH; Luckenwalde, Germany). The microtiter 96-well polystyrene plates were coated with GPCR antibodies. To maintain the conformational epitopes of the receptor, 1 mM calcium chloride was added to all buffers. Duplicate samples of a 1:100 serum dilution were incubated at 4°C for 2 h. After washing, plates were incubated for 60 m with a 1:20,000 dilution of horseradish-peroxidase–labeled goat anti-human IgG used for detection. To obtain a standard curve, plates were incubated with test serum from an anti-GPCR autoantibody positive index patient. The ELISAs were validated according to the Federal Drug Administration's *Guidance for industry: Bioanalytical method validation*.

HRV

For short HRV analysis of two 5 m intervals while lying and standing during the active standing test, we used the HRV Scanner™ (BioSign GmbH; Germany). The method was validated in a large group of children, with a limit value for a normal increase in heart rate (≤ 35 bpm) as recently published.[14] For 24-h HRV analysis, we used a 12-bit digital ECG recorder at 1,024 scans/s (Reynolds Pathfinder II, Spacelabs; Germany). Measurement and interpretation of HRV parameters in the current sample were standardized according to the Task Force Guidelines.[15] The following time domain parameters are included in the analysis: 1) average heart rate [bpm], 2) standard deviation of NN (SDNN [ms]) to reflect global HRV, 3) percent of NN intervals that differ more than 50/20 ms from the prior interval (pNN50, pNN20 [%]), and root mean square of differences between successive NN intervals (rMSSD [ms]). rMSSD, pNN50, and pNN20 reflect the parasympathetic influence. The stress index reacts sensitively to shifts in the vegetative balance between the sympathetic and parasympathetic nerves and is calculated as follows:

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

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.

For frequency domain analysis using the Fourier transformation, the HRV signals were divided into three frequency bands: 1) very low frequency power (VLF = 0,00–0,04 Hz, [ms^2]), 2) low-frequency power (LF = 0,04–0,15 Hz, [ms^2]), and 3) high-frequency power (HF = 0,15–0,4Hz, [ms^2]) that represent respiratory sinus arrhythmia, mediated by alternating levels of parasympathetic tone. Total power (TP) (ms^2) measures the total variance in HRV.

Pharmacotherapy and nutritional supplementation

Many patients received pharmacotherapy (*e.g.*, psychostimulants, antidepressants) with published effects on HRV. For the current analysis, we investigated the effect of a new pharmacotherapy with low dose propranolol, ivabradine, and midodrine in children with POTS in the active standing test: propranolol 10–10–0 up to 20–20–0 mg (n = 15), ivabradine 5–5–0 mg (n = 11), and midodrine 2.5–2.5–0 mg (n = 6). This therapy was based upon a Consensus Statement of the Heart Rhythm Society published in 2015.[16] Patients treated with fludrocortisone (n = 2), mestinon (n = 1), and

Table 1. Anthropometric data of the patient groups

	Healthy control	Postural orthostatic tachycardia	Vagovasal syncope	Inapproriate sinus tachycardia
Patients	47	48	12[#]	74
Age [Years]	14.2 ± 3.8	14.9 ± 2.1	9.9 ± .4.4	13.2 ± 2.2
Height [cm]	160.1 ± 14.2	167.5 ± 10.6**	142.9 ± 30.4	155.0 ± 12.3
Weight [kg]	52.6 ± 14.3	54.0 ± 12.4	44.8 ± 26.1	58.5 ± 24.3
BMI [kg/sqm]	20.1 ± 3.0	19.1 ± 3.5	20.0 ± 6.3	24.0 ± 8.6
SBP [mmHg]	114.5 ± 9.2	117.2 ± 9.3	117.3 ± 19	122.0 ± 16.0
DBP [mmHg]	61.7 ± 11.2	64.9 ± 12.2	58.9 ± 10.5	65.1 ± 11.1

t-test between healthy control and patient groups: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. [#]No statistics of cause lower age.

saline infusions (n = 2) were excluded from statistical analysis.

We further investigated the impact of O3-FA supplementation (n = 7) ± nutritional refeeding in children with anorexia nervosa (n = 6) on heart rate increase in the active standing test.[17] As recently published, we introduced O3-FA supplementation in children with sinus tachycardia after showing a significant reduction of the mean heart rate in 24-h ECG[18] in accordance with a recent metanalysis.[19] Patients usually purchased products based upon 1–2 g fish oil per day from a retail store. The following dose recommendations were provided: children up to 8 years of age should receive at least 400 mg eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as a suspension per day. Children who were able to swallow capsules should receive at least 800 mg EPA and DHA per day.

In the first visit, children with POTS were provided lifestyle advice, including increased fluid and salt intake, low dose exercise, O3-FA supplementation, and avoiding known triggers like prolonged standing. If lifestyle intervention was not successful, we introduced pharmacotherapy with either low dose propranolol, ivabradine, or midodrine.

Statistics

All analyses were performed using IBM SPSS Statistics software, (IBM Corp. IBM SPSS Statistics for Windows, Version 26.0; Armonk, NY, USA). Data are expressed as mean ± standard deviation. The HRV parameters of the 5-m segments in the lying and supine positions during the active standing test in the three groups with dysautonomia were compared to the healthy control group in an unpaired t-test. The treatment data before and after pharmacotherapy and O3-FA supplementation were analyzed with a paired t-test of each patient. The following *p*-values indicated statistical significance: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

Results

Compared to healthy controls anthropometric data showed that children with POTS were significantly taller (Table 1), and children with IST tended to have higher body mass indices (BMIs) consistent with recently published findings.[18] Children with VVS were younger compared to the other groups, and we did not analyze the anthropometric data in this group. Blood pressures were in the normal range in all groups.

Based on the definition, 24-h heart rates were significantly elevated in children with IST (99.9 ± 5.0 bpm) compared to healthy controls (80.8 ± 13.5 bpm) but not in the other two groups with dysautonomia. Based on the second definition, heart rate increases in the active standing test were significantly enhanced in children with POTS (43.5 ± 8.6 bpm) compared to healthy controls (16.2 ± 7.1) but not in the other two groups with dysautonomia. In children with POTS heart rate and HRV in the lying position were normal, but HRV suddenly decreased and heart rate increased while standing. These data indicated that a sudden postural collapse of vagus activity was induced by the significant decrease of rMSSD (from 67.1 ± 42.6 ms to 15.7 ± 8.1 ms***), pNN50 (from 38.7 ± 24.7 to 2.8 ± 7.1%***), and HF (from 2,229 ± 4,238 to 111 ± 115 ms^2***), which represents the vagal tone. When LF showed no significant changes, the LF to HF ratio, which represents the sympatho-vagal balance, significantly increased to 7.4 ± 8.4 compared to 2.5 ± 1.9 in healthy children. In contrast, we found a global decrease in HRV and increase in heart rate in the lying and standing position in children with IST that may explain global dysautonomia in the 24-h Holter ECG (Table 2). The small group of 12 children with VVS did not show a clear pattern of dysautonomia and most values ranged between the two other groups.

Figure 1 demonstrates the effect of pharmacotherapy, O3-FA supplementation, and refeeding in children with POTS. We found significant effects on postural heart rate increases after pharmacotherapy with beta blockers and ivabradine but also after O3-FA supplementation and nutritional refeeding in six patients with anorexia nervosa. In contrast to ivabradine, we found a significant increase in the decreased vagus parameter RMSSD (from 11.9 ± 2.7 ms to 35.1 ± 9.7 ms*) in the standing position that was accompanied by a significant decrease in elevated stress index (from 947 ± 171 to 443 ± 103**) in patients who received a low dose beta blocker (propranolol 10–10–0 or 20–20–0 mg) (Table 3). Low dose propranolol reduced heart rates while lying and standing compared to ivabradine and O3-FA supplementation that reduced heart rate only in the standing position (Table 3). Nutritional refeeding together with O3-FA supplementation in patients with anorexia nervosa increased heart rate while lying and decreased postural heart rate while standing, explaining the significant effect on the postural heart rate increase (from 50.0 ± 13.9 to 33.0 ± 9.9**). We did not find significant effects in the small group of patients who were treated with Midodrine.

Analysis of GPCR autoantibodies in nine patients with POTS showed many elevated values (Table 4). There was no clear pattern of autoimmunity except in one female patient with anorexia nervosa, and most patients showed elevated autoantibodies against vasoconstrictive receptors (anti-angiotensin 1 receptor, anti-endothelin receptor, anti-α_1 adrenergic receptor) that may explain postural hypotension as well as the compensatory heart rate increase to maintain blood pressure. Some anti-mucarinergic autoantibodies may explain postural tachycardia and the collapse of the vagal tone in

Table 2. Heart rate and HRV during active standing test and 24-h Holter ECG

	Healthy control	Postural orthostatic tachycardia	Vasovagal syncope	Inappropriate sinus tachycardia
Patients	47	48	12	74
24-hours Holter ECG				
24h mean HR	80.8 ± 13.5	78.5 ± 9.9	84.2 ± 11.1	99.9 ± 5.0***
Night HR	64.8 ± 11.4	60.0 ± 6.9	70.3 ± 8.2	87.2 ± 10.3***
Min HR	51.7 ± 8.8	50.9 ± 7.1	58.0 ± 7.1	69.2 ± 8.7***
Day HR	84.5 ± 13.7	86.5 ± 11.0	98.7 ± 19.3	107.8 ± 7.0***
Max HR	158.4 ± 29.3	164.4 ± 21.0	151.2 ± 29.8	167.6 ± 20.6**
SDNN	164.7 ± 45.4	184.5 ± 42.2	138.3 ± 34.4	105.4 ± 31.0***
rMSSD	48.8 ± 15.8	47.2 ± 19.7	38.4 ± 8.5	22.5 ± 7.4***
Active standing test				
HR Increase	16.2 ± 7.1	43.5 ± 8.6***	17.7 ± 15.1	15.3 ± 6.9
Lying HR	73.6 ± 12.5	72.0 ± 11.1	78.8 ± 10.4	96.0 ± 5.3***
Standing HR	89.8 ± 13.2	115.3 ± 15.4***	96.5 ± 16.3	110.8 ± 7.4***
rMSSD Lying	85.1 ± 56.2	67.1 ± 42.6	39.6 ± 19.7**	40.4 ± 22.7***
rMSSD Standing	40.4 ± 22.7	15.7 ± 8.1***	36.6 ± 43.8	33.6 ± 33.5
pNN50 Lying	43.3 ± 22.8	38.7 ± 24.7	20.0 ± 17.2***	7.2 ± 9.6***
pNN50 Standing	15.7 ± 14.3	2.8 ± 7.1***	10.9 ± 15.2	5.3 ± 6.1
Stress Index Lying	97.8 ± 85.1	113.3 ± 106.8	177.3 ± 137.6	288.2 ± 162.3***
Stress Index Standing	168.5 ± 116.5	568.0 ± 438.2***	214.4 ± 171.7	358.5 ± 177.1***
HF Power Lying	2,920 ± 4,403	2,229 ± 4,238	794 ± 1,017	470 ± 735*
HF Power Standing	949 ± 1,222	111 ± 115***	850 ± 2,080	394 ± 469*
LF Power Lying	1,518 ± 2,795	1,381 ± 1,705	757 ± 566	471 ± 329
LF Power Standing	1,331 ± 1,115	558 ± 628***	1,637 ± 2,148	970 ± 1,091
VLF Power Lying	1,553 ± 2,182	1,123 ± 1,820	689 ± 443	559 ± 565*
VLF Power Standing	1,299 ± 1,506	451 ± 432***	4,355 ± 6,570**	606 ± 554*
Total Power Lying	5,819 ± 6,203	4,718 ± 6,273	2,240 ± 1,749*	1,501 ± 1,475**
Total Power Standing	3,579 ± 3,012	1,116 ± 967***	6,842 ± 9,660*	1,970 ± 1,866*
LF/HF Lying	0.97 ± 1.10	1.65 ± 3.68	1.82 ± 1.48*	1.93 ± 1.46**
LF/HF Standing	2.54 ± 1.95	7.40 ± 8.42***	4.18 ± 2.53*	3.84 ± 2.70*

HR, heart hate; SDNN, standard deviation of all NN intervals; RMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; pNN50, percent of NN intervals that differ by more than 50 ms from the prior interval; TP, total power; VLF, very low frequency power; LF, Low frequency power; HF, High frequency power; HF/LF, HF to LF ratio. *t*-test between healthy control and patient groups: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

the standing position (Table 4).

Case 1: Dysautonomia after COVID-19 infection (long COVID)

After a mild COVID-19 infection in April 2020, a 16-year-old girl presented clinical symptoms of long COVID with palpitations, headache, and low physical performance for more than a year. In-hospital diagnostics did not lead to a therapeutic approach. We diagnosed the patient with IST and the 24-h Holter ECG showed a significant decrease in mean heart rate from 104 bpm to 85 bpm after low dose propranolol (Fig. 2). The patient did not tolerate ivabradine to treat headache and showed little clinical improvement with propranolol to induce overshooting vagus activity indicated by RMSSD and pNN20 (Fig. 3). The patient was dissatisfied with performance at 16 months after COVID-19 infection, which may be related to Hashimoto thyroiditis (additional elevated antithyroid peroxidase antibodies and thyrotropin receptor antibodies). Angiotensin 1 receptor, endothelin receptor, α1 adrenergic receptor, muscarinic cholinergic receptor-2, and muscarinic cholinergic receptor-3 autoantibodies were elevated.

Case 2: Dysautonomia after SARS-CoV-2 mRNA vaccination

A 16-year-old girl suffered from palpitation, dizziness, and deterio-

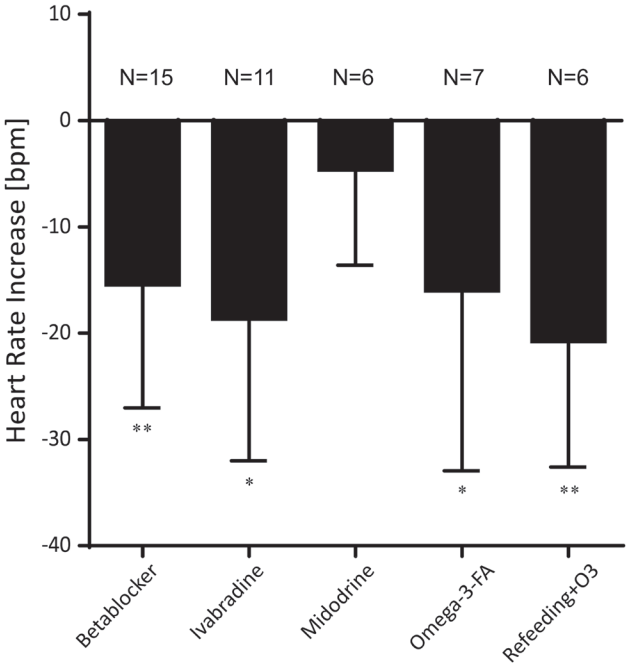

Fig. 1. The effect of pharmacotherapy, Omega-3-Fatty acid supplementation and refeeding in 6 patients with anorexia nervosa and postural orthostatic tachycardia.

ration in performance after a second SARS-CoV-2 mRNA vaccination. She could not attend school and in-hospital diagnostics did not lead to a therapeutic approach. We diagnosed the patient with POTS and started ivabradine therapy one month after vaccination. At baseline, the mean 24-h heart rate was elevated to 96 bpm with normal blood pressure during the day and night. After ivabradine treatment, heart rate decreased to 77 bpm and blood pressure remained unchanged (Fig. 4). As shown in Figure 3, HRV during the active standing test progressively improved within the next 10 weeks; due to the clinical improvement, the patient was able to return to school. However, stopping ivabradine treatment after 3 months was not successful. Angiotensin 1 receptor, endothelin receptor, α1 adrenergic receptor, β1 adrenergic receptor, β2 adrenergic receptor, and muscarinic cholinergic receptor-2 autoantibodies were elevated.

Case 3: Dysautonomia in post-traumatic stress disorder in a Syrian refugee

Data of a 16-year-old girl with post-traumatic stress disorder after escaping the Syrian civil war to Germany are shown in Figure 3. Therapy with low dose propranolol[20] was not well tolerated, but the patient completely recovered after ivabradine treatment, which has not been used in this setting. HRV data (Fig. 3) showed an overshooting vagus activity (pNN50/RMSSD) after low dose propranolol that may explain the discomfort of this therapy and why the change to ivabradine had a slightly better effect on the heart rate increase in the active standing test.

Case 4: Dysautonomia in boy with anorexia nervosa

Figure 5 shows the clinical course of a 15-year-old boy with severe anorexia nervosa who became bedridden under nasogastric tube feed-

Table 3. The effect of treatment of postural orthostatic tachycardia on heart rate and heart rate variability in the active standing test

	Betablocker (N=15)		Ivabradine (N=11)		Midodrine (N=6)		Omega-3-FA(N=7)		Refeeding +O3-FA (N=6)	
HR Increase	41.7 ± 17.5	29.5 ± 17.8**	37.5 ± 16.4	23.6 ± 8.12*	31.9 ± 8.4	27.4 ± 10.5	44.0 ± 11.9	25.6 ± 8.4*	50.0 ± 13.9	33.0 ± 9.9**
HR Lying	88.4 ± 20.5	75.9 ± 12.3*	80.6 ± 17.9	77.9 ± 14.5	65.1 ± 6.7	67.5 ± 13.7	82.2 ± 17.6	84.3 ± 13.9	71.3 ± 13.4	81.6 ± 16.6
HR Standing	130.1 ± 17.1	104.1 ± 20.8**	118.2 ± 15.0	101.4 ± 16.9**	97.1 ± 12.0	94.9 ± 16.0	126.2 ± 11.4	109.9 ± 16.9*	121.4 ± 26.7	114.6 ± 17.1
RMSSD Lying	38.3 ± 6.8	70.4 ± 16.5	52.0 ± 17.0	44.0 ± 6.0	91.9 ± 68	90.1 ± 45.3	87.6 ± 35.0	54.6 ± 12.4	51.6 ± 14.2	42.0 ± 41.7
RMSSD Standing	11.9 ± 2.7	35.1 ± 9.7*	17.5 ± 3.8	24.5 ± 9.5	24.1 ± 14.2	44.9 ± 38.0	11.8 ± 3.2	27.2 ± 12.6	17.4 ± 6.2	18.0 ± 8.0
Stressindex Lying	354 ± 145	115 ± 106	232 ± 73	185 ± 38	63.7 ± 36.2	90.4 ± 84.4	192 ± 182	146 ± 111	206 ± 77	216 ± 59
Stressindex Stand	947 ± 171	443 ± 103**	609 ± 123	548 ± 197	239 ± 178	238 ± 222	855 ± 160	561 ± 217	959 ± 334	944 ± 283

HR, heart rate; RMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; FA, fatty acids. Paired *t*-test between baseline and therapy: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

Table 4. Autoantibodies in children with postural orthostatic tachycardia

Patient	Anti AT1R	Anti ETAR	Anti α_1 adrenerg	Anti α_2 adrenerg	Anti β_1 adrenerg	Anti β_2 adrenerg	Anti MC R_1	Anti MC R_2	Anti MC R_3	Anti MC R_4	Anti MC R_5
Reference [U/mL]	<10	<10	<7	<15	<15	<8	<9	<9	<6	<10,7	<14,2
POTS (Post Lyme Disease)	9.3	9.2	29	21	9.8	8.8	4.1	3.8	12.0	8.7	11.5
POTS (Emery Dreifuss myopathy)	21.2	20.6	14.2	22.6	21.5	19.3	9.0	7.5	12.0	9.0	9.0
POTS (Chronic Fatigue Syndrome)	6.6	6.5	18.3	10.6	8.2	6.5	2.7	1.6	7.8	3.5	7.3
POTS (Dizziness)	10,8	8,2	13,5	12,4	5,1	3,3	1,3	2,5	3,5	4,1	4,6
POTS (Anorexia Nervosa)	10,3	8,2	3,9	9,8	5,6	13,0	4,2	1,6	6,4	15,3	12,4
Long COVID after SARS-CoV-2 infection											
POTS	13.0	11.8	7.8	8.8	8.8	6.4	9.9	12.8	5.4	4.7	11.4
POTS	14,7	14,4	13,9	8,6	11,9	21,7	3,6	3,6	12,3	10,4	3,6
POTS	24,8	43,7	28,5	5	42,8	41,7	4,2	7,7	38,4	24,1	7,4
SARS-CoV-2 Vaccination (Cominaty™)											
POTS post Vaccination	20,7	18,1	10,7	8,4	25,7	27,5	6,1	6,6	8,7	10,6	11,0

Anti AT1R, anti-angiotensin 1 receptor autoantibody; Anti ETAR, anti-endothelin receptor autoantibody; Anti α_1 adrenerg, anti-α_1 adrenergic receptor autoantibody; Anti α_2 adrenerg, anti-α_2 adrenergic receptor autoantibody; Anti β_1 adrenerg, anti-β_1 adrenergic receptor autoantibody; Anti β_2 adrenerg, anti-β_2 adrenergic receptor autoantibody; Anti MC R_1, anti-muscarinic cholinergic receptor-1 autoantibody; Anti MC R_2, anti-muscarinic cholinergic receptor-2 autoantibody; Anti MC R_3, anti-muscarinic cholinergic receptor-3 autoantibody; Anti MC R_4, anti-muscarinic cholinergic receptor-4 autoantibody; Anti MC R_5, anti-muscarinic cholinergic receptor-5 autoantibody.

ing and showed clinical symptoms of severe depression despite psychopharmacological therapy. After diagnosis and treatment of severe POTS with metoprolol and midodrine, the patient recovered immediately and showed an above-average weight gain following discharge.

Discussion

The current study demonstrates that dysautonomia could be used in diagnosis to improve treatment of psychosomatic diseases and COVID-19-related disorders children. Our data show that an objective diagnosis is possible in children with dysautonomia using the 24-h Holter ECG and the active standing test. We propose a mean heart rate ≥ 95 bpm in the Holter ECG[18] to diagnosis an IST and an increase in the average of the heart rate after 5 m lying to 5 m standing of ≥ 35 bpm[14] to diagnosis POTS. Lowering heart rate in the active standing test was achieved using pharmacotherapy with low dose propranolol (from 41.7 ± 17.5 to 29.5 ± 17.8 bpm

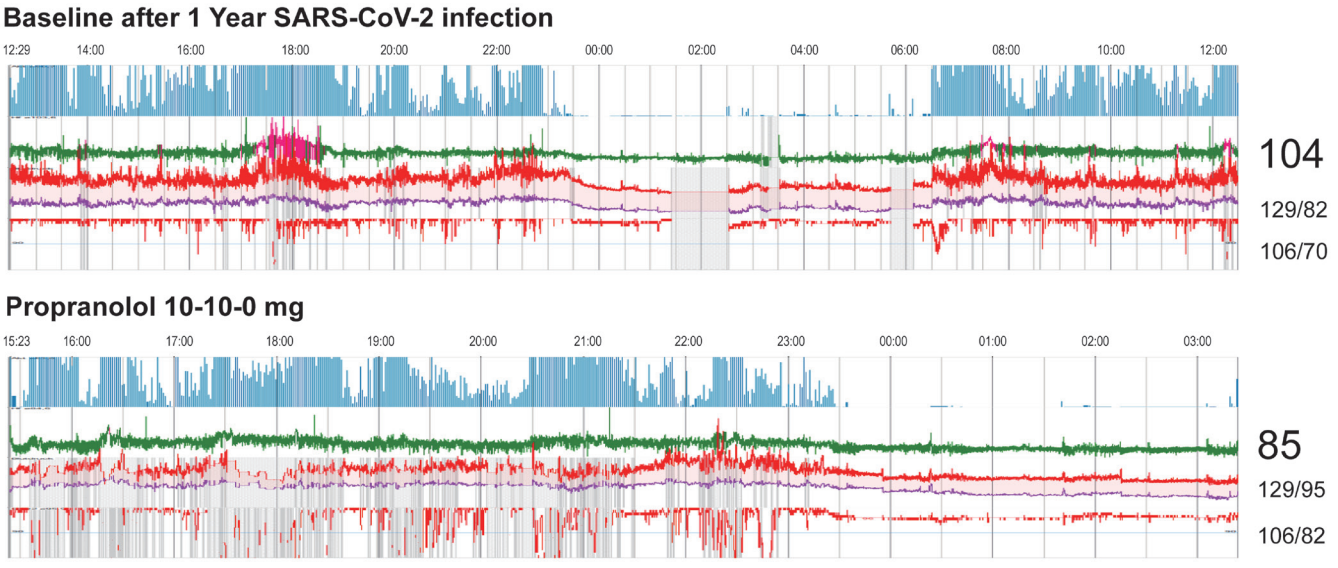

Fig. 2. Heart rate (green), blood Pressure (red), and physical activity (blue) monitoring using SOMNOtouch™ NIBP in a 16-years old girl withlLong COVID. At baseline the girl suffered from IST with a mean 24-h heart rate of 104 bpm with normal blood pressure during the day and night. After low dose propranolol the heart rate decreased to 85 bpm and the blood pressure remain unchanged. Physical activity was high at day in both conditions, but the patient was still dissatisfied with her performance for more than a year after COVID-19 infection, that may be related to Hashimoto thyroiditis. Antithyroid peroxidase antibodies (TPO), thyrotropin receptor antibodies (TRAK), anti-angiotensin 1 receptor autoantibody, anti endothelin receptor autoantibody, anti-α1 adrenergic receptor autoantibody, anti-muscarinic cholinergic receptor-2 autoantibody, and anti-muscarinic cholinergic receptor-3 autoantibody were elevated.

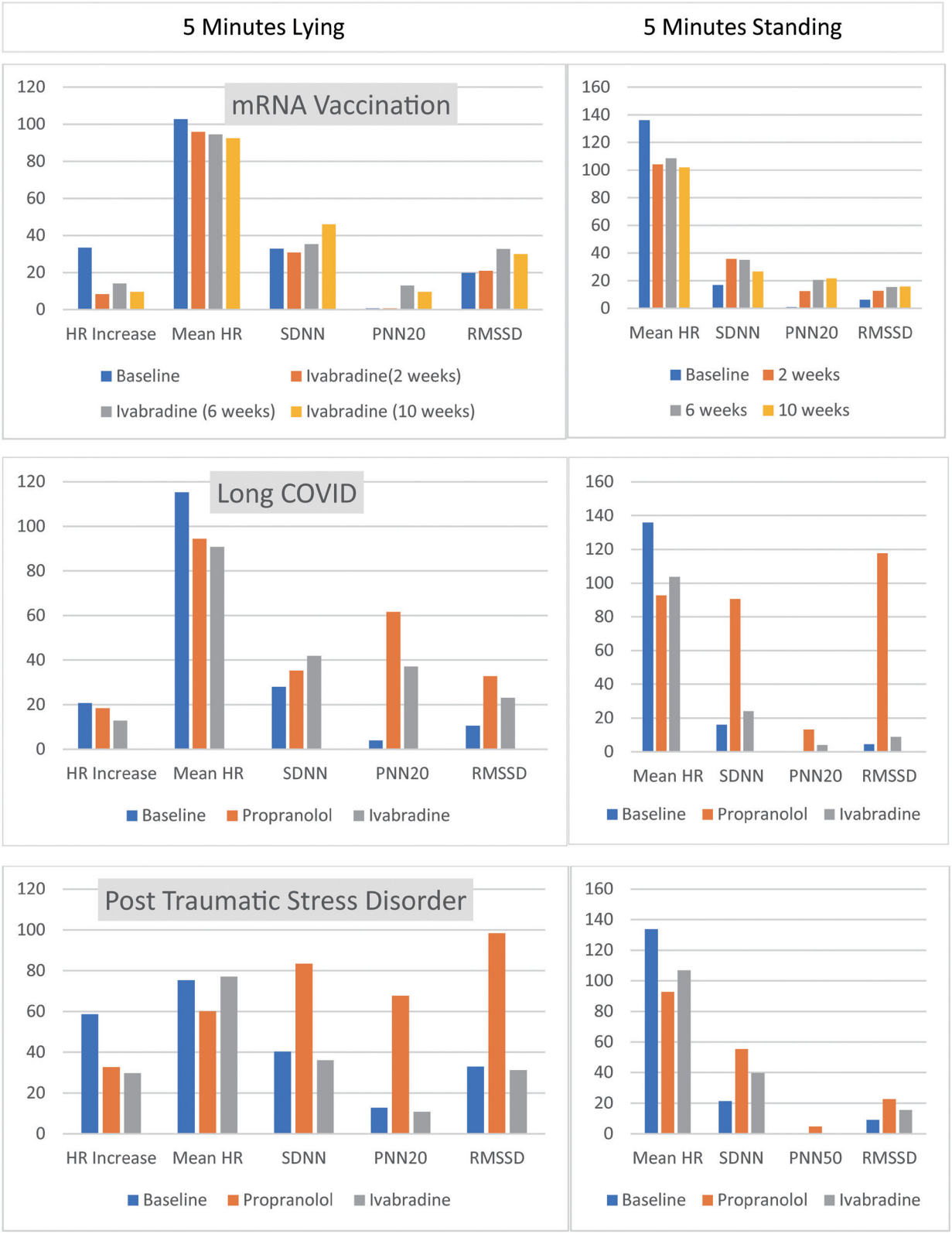

Fig. 3. Response of heart rate variability after pharmacotherapy in three 16-year old girls with dysautonomia due to SARS-CoV-2 mRNA vaccination, long COVID, and post-traumatic stress disorder. HR, hear rate; SDNN, standard deviation of all NN intervals; RMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; pNN20, percent of NN intervals that differ more than 20 ms from the prior interval.

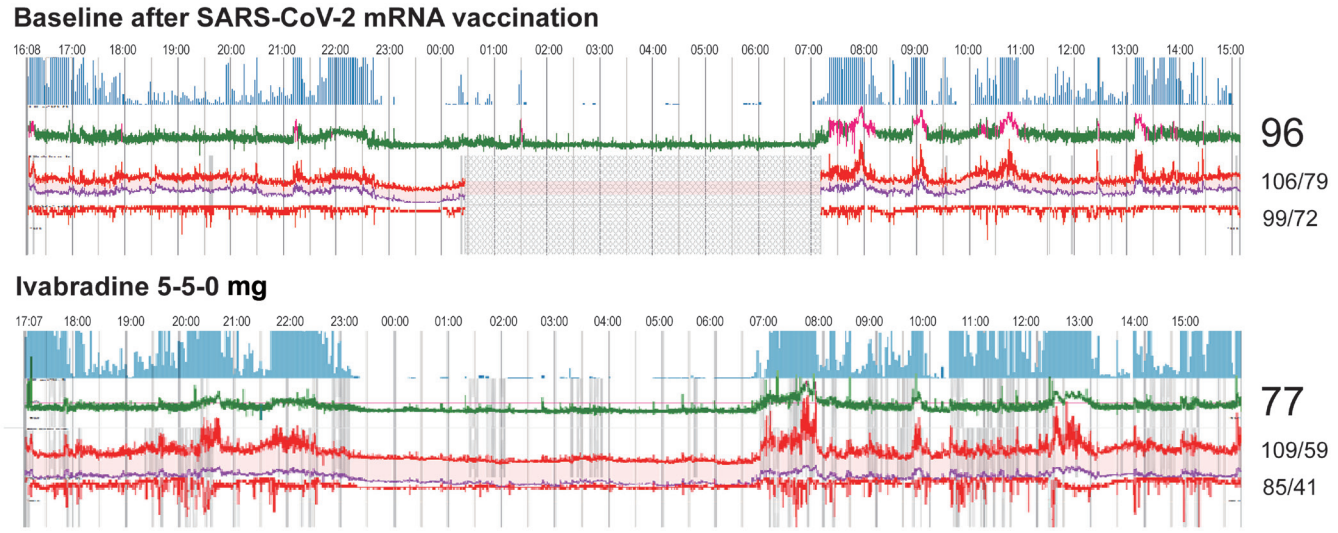

Fig. 4. Heart rate (green), blood pressure (red), and physical activity (blue) monitoring using SOMNOtouch™ in a 16-years old girl withlLong COVID=like symptoms afterSARS-CoV-2 mRNA vaccination. At baseline, the girl suffered from PITS with a mean 24-h heart rate of 96 bpm and normal blood pressure during day and night. After ivabradine treatment, the heart rate decreased to 77 bpm and the blood pressure remained unchanged. Physical activity was low and was stopped immediately due to sinus tachycardia at baseline and improved with therapy. Anti-angiotensin 1 receptor autoantibody, anti-endothelin receptor autoantibody, anti-α1 adrenergic receptor autoantibody, anti-β1 adrenergic receptor autoantibody, anti-β2 adrenergic receptor autoantibody, and anti-muscarinic cholinergic receptor-2 autoantibody were elevated.

) and ivabradine (from 37.5 ± 16.4 to 23.6 ± 8.12 bpm*), as shown in Table 3. However, as recently shown in children with IST,[18] our data clearly showed a significant reduction in heart rate while standing after O3-FA supplementation (from 44.0 ± 11.9 to 25.6 ± 8.4 bpm*) and additional nutritional refeeding in patients with anorexia nervosa (from 50.0 ± 13.9 to 33.0 ± 9.9 bpm). There was no significant effect on heart rate increase in the active standing test after midodrine treatment (Fig. 1). In accordance with Lin J *et al*,[21] we observed POTS more often in tall adolescents (Table 1) and patients with anorexia nervosa[17] but less in those with IST who were obese, had small stature, and attention deficit disorder.[18] If heart rate in patients with anorexia nervosa is low, we propose O3-FA supplementation during nutritional refeeding to prevent an overshooting heart rate increase that is not well tolerated by the patient.[8]

Analysis of HRV as shown in Tables 2 and 3 may help to un-

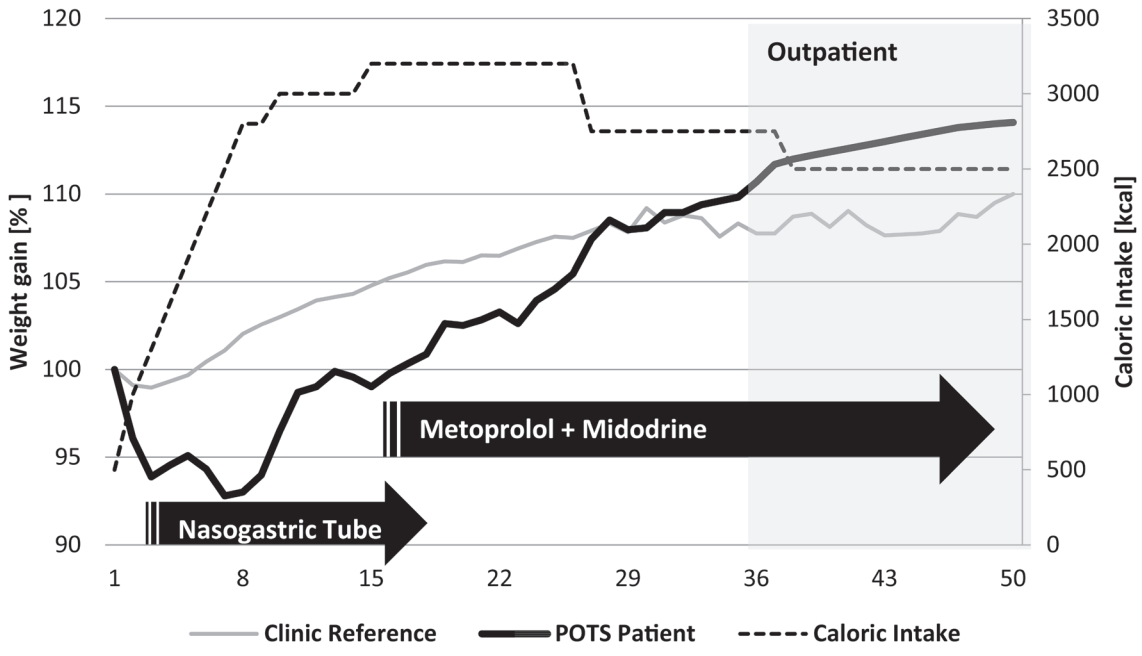

Fig. 5. Treatment of postural orthostatic tachycardia in a boy with severe anorexia nervosa. The clinic reference is the average of the weight gain during in hospital refeeding in children with anorexia nervosa with the current standard protocol (n = 35) starting with the weight at the first day (= 100%)

Table 5. The effect of the pharmacotherapy and Supplements on heart rate and heart rate variability in 24-hours Holter-ECG

	Children with somato-form Disorder (N=10)		Adults with Cardio-myopathy (N=48)[24]		Children with somatoform Disorders (N=19)		Children with Ano-rexia Nervosa (N=10)		Adults with vitamin D deficiency (N=52)[25]	
	Baseline	Beta-blocker	Base-line	Ivabradine	Baseline	Omega-3-FA	Baseline	Refeeding +O-3-FA	Baseline	Vitamine D
24h HR [bpm]	81 ± 10	74 ± 12***	83.6 ± 6.0	64.6 ± 5.8***	96 ± 11	85 ± 10***	59 ± 8	70 ± 8***	77.4 ± 6.6	78.08 ± 6.1
HR Day [bpm]	90 ± 10	80 ± 13***	89.2 ± 8.9	68.6 ± 7.5***	102 ± 13	95 ± 12*	69 ± 10	80 ± 10**		
HR Night [bpm]	69 ± 9	65 ± 11*	79.7 ± 7.7	61.4 ± 5.5***	85 ± 16	71 ± 9***	44 ± 6	54 ± 9**		
SDNN [ms]	154 ± 36	161 ± 57	56.2 ± 15.7	87.9 ± 19.4***	127 ± 49	148 ± 32**	289 ± 66	225 ± 86**	68.6 ± 13.5	119.9 ± 28.3***
RMSSD [ms]	43 ± 22	50 ± 25*	13.5 ± 4.6	17.8 ± 5.4***	27 ± 16	38 ± 11***	73 ± 13	55 ± 14**	23(12/3)	58(46/92)***
TP 24h	5,736 ± 3,570	7,726 ± 5,879			3,201 ± 2,246	4,608 ± 1,883***	9,132 ± 3,036	7,412 ± 4,357		
VLF 24h	3,618 ± 2,488	5,206 ± 4,464			1,926 ± 1,462	2,634 ± 1,410**	5,533 ± 2,795	4,636 ± 370		
LF 24h	1,367 ± 712	1,675 ± 1,089			836 ± 614	1,224 ± 577**	2,114 ± 492	1,566 ± 838	62.9 ± 15.6 (normalized)	59.4 ± 13.9 (normalized)
HF 24h	689 ± 450	779 ± 467			396 ± 288	688 ± 312****	1,442 ± 450	1,148 ± 483*	19.6 ± 10.2 (normalized)	39.4 ± 11.7*** (normalized)
HF/LF 24h	0.48 ± 0.13	0.48 ± 0.13			0.5 ± 0.26	0.61 ± 0.26*	0.73 ± 0.34	0.88 ± 0.55		

HR, Heart Rate; SDNN, Standard deviation of all NN intervals; RMSSD, The square root of the mean of the sum of the squares of differences between adjacent NN intervals; pNN50, Percent of NN intervals which differ more than 50 ms from the prior interval; TP, Total Power; VLF, Very low frequency power; LF, Low frequency power; HF, High frequency power; HF/LF, Ratio HF to LF. Paired *t*-test between baseline and therapy: * *p*-value < 0.05; ** *p*-value < 0.01; *** *p*-value < 0.001. Ivabradine[24] and Vitamin D[25] data are cited from literature.

derstand the underlying pathophysiology but is not necessary for diagnosis. In contrast to IST with a global decrease in HRV, children with POTS have normal HRV in the 24-h Holter ECG (Table 2) and in the lying position (Table 3). In accordance with a previously published meta-analysis,[22] we found a postural collapse of HRV as causal for an overshooting heart rate increase while standing in children with POTS. However, this collapse involves both the time domain and the frequency domain analysis with a clear emphasis on the vagus parameters RMSSD, pNN50, HF, and LF/HF. In summary, a vagus weakness seems to be common in children with dysautonomia and IST and only in upright position in children with POTS.

In our analysis, children with postural VSS had normal 24-h mean heart rates and a normal heart rate increase in the active standing test. However, Medow *et al*[23] reported a heart rate increase in patients with VSS of 39.8 ± 2.1 bpm that was significantly greater ($p < 0.001$) than in the healthy controls. In this study, an increase in heart rate ≥ 40 bpm by 5 m and 10 m or before fainting with a head-up tilt, occurred in 26% and 44% of patients with VSS, respectively, but not in controls. This difference could be attributed to the following. We regularly observed an increase in heart rate before a sudden drop of heart rate caused by the vagus reflex before we had to stop the test in children with VSS. If we were able to completely analyze the standing test, we calculated a normal mean heart rate on average. However, the vagus is at the center of the pathophysiology in children with postural VSS and may be recognized by low rMSSD and pNN50 values in the lying position, as shown in Table 2. Furthermore, there are some children whose clinical presentation in the active standing test changed between POTS, IST, and VSS. However, a sick vagus remains the focus of therapy.

Based on the literature, we found a significant effect on postural heart rate increases after pharmacotherapy with beta blockers and ivabradine but also after O3-FA supplementation and nutritional refeeding in six patients with anorexia nervosa (Fig. 1, Table 3). However, we did not find significant effects in a small group of patients who were treated with midodrine, which is in contrast to Chen *et al*., who found a significant decrease in the heart rate increase in the standing test from 36 ± 1.3 bpm to 25 ± 1.9 bpm** in 19 children using a standardized protocol.[24]

There is important additional information to be gained from understanding the effects of therapy on HRV using our data in Table 3 and our additional published data from 24-h Holter ECG, as shown in Table 5.[24,25] First, beta blockers reduce heart rate while lying and standing, together with a significant increase of the vagus parameter RMSSD and a significant reduction in the stress index, which could be due to the fact that heart rate decreases during day and to a lesser degree at night. Secondly, there were nearly no significant effects on HRV in the 24-h Holter ECG (Table 5). In contrast, O3-FA supplementation exclusively reduced heart rate while standing with no significant effects on HRV in the active standing test. However, there were significant effects of O3-FA supplemen-

tation on heart rate during the day and night, as well the global HRV in the 24-h Holter ECG (Table 5). This effect was completely reversed by nutritional refeeding in 10 children with anorexia nervosa, who had significant heart rate increases during the day and night, as well as a significant decrease in elevated HRV in the 24-h Holter ECG (Table 5). However, increasing heart rate in the lying position and decreasing heart rate while standing combined with nutritional refeeding and O3-FA supplementation induced a significantly lower postural heart rate increase in children with anorexia nervosa in the active standing test (from 50.0 ± 13.9 to 33.0 ± 9.9 bpm**). Ivabradine (n = 11), midodrine (n = 6), O3-FA (n = 7), and refeeding + O3-FA (n = 6) had no significant effect on the stress index in the active standing test.

If the effect of ivabradine on HRV in the 24-h Holter ECG was not well documented, we had to use the data from adults with nonischaemic dilated cardiomyopathies (Table 5).[25] In those patients, ivabradine significantly reduced heart rate during the day and night and significantly improved the reduced HRV.

With respect to our sick vagus theory in children with dysautonomia, we concluded that O3-FA supplementation improves parameters of HRV, indicating vagus activity as determined by 24-h RMSSD (from 27 ± 16 to 38 ± 11 ms***) and 24-h HF (from 396 ± 288 to 688 ± 312 ms^2***). Beta blockers improved RMSSD while standing (from 11.9 ± 2.7 to 35.1 ± 9.7 ms*) and in the 24-h Holter ECG (from 43 ± 22 to 50 ± 25 ms*) but had no significant effect on frequency domain analysis. Thus, ivabradine may improve vagus activity as shown in adults with cardiomyopathies[25] (RMSSD from 13.5 ± 4.6 to 17.8 ± 5.4 ms***), but these data are missing in children with dysautonomia. Nutritional refeeding in children with anorexia nervosa reduced highly elevated HRV with an overshooting increase of low heart rates that was not well tolerated from patients but should be treated. However, prospective trials are needed to clarify if O3-FA supplementation and/or ivabradine/beta blockers can improve the success of nutritional refeeding in children with anorexia nervosa (as presented in Case 4).

Management of dysautonomia in the COVID-19 pandemic

Modern medicine is characterized by major pathophysiological concepts, such as the neurovisceral integration concept from Claude Bernard,[3] which have been abandoned as current medicine becomes more detailed. However, since medicine is becoming increasingly expensive and more people are being excluded from its benefits, this policy is being revisited during the pandemic to provide patients with effective, cheap therapies. This explains the re-emergence of vitamin D[26] and O3-FA in the ongoing COVID-19 pandemic, specifically in countries with a low budget for health care. As shown in Table 5, these therapies have significant effects on objective measured parameters that represent vagus activity that likely play key roles in the pathophysiology of COVID-19-related disease (*e.g.*, elevated heart rates, reduced rMSSD, and SDNN).[10]

There is growing evidence that post-acute complications after SARS-CoV-2 infections are related to dysautonomia.[27] In children with dysautonomia after SARS-CoV-2 infections/vaccination, we found elevated functional autoantibodies against G-protein coupled receptors (Table 4, Figs. 2 and 4). Our data are in accordance with Wallukat *et al*., who found these autoantibodies in adults with persistent long COVID-19 symptoms.[13] In summary dysautonomia may be one of multiple autoimmune diseases triggered by the spike protein of the SARS-CoV-2 virus or more precise with immune responses to SARS-CoV-2 proteins.[12] These autoantibodies have been found in other patients with POTS[11] and myalgiac encephalomyelitis/chronic fatigue syndrome[28] and may be treated with immunoabsorption.[29] However, since immunoabsorption is an expensive therapy that is not an option for many patients during the pandemic, we propose well-known pharmacotherapies such as low dose propranolol, ivabradine, and O3-FA supplementation that are effective in adolescents with IST due to long COVID (Fig. 2) or POTS after SARS-CoV-2 mRNA vaccination (Fig. 4).

Improvement in physical performance is the most important therapeutic goal in patients with POTS in the context of chronic fatigue syndrome caused by long COVID and/or dysautonomia. There is evidence from prospective randomized trials that low dose propranolol[30] as well as ivabradine[31] improve performance in patients with POTS.

Limitations

This retrospective study included data from clinical routine exams. All included children suffered from dysautonomia caused by different diseases such as nutritional disorders, post-traumatic stress disorder, or more recently COVID-19-related disorders. All children received the established standard therapies, which often did not lead to clinical improvement. These therapies were not considered in this analysis. The evidence and symptoms associated with COVID-19 are still very new and we need to determine if the long-term problems of this disease are actually an expression of dysautonomia.

Future directions

Based upon clinical routine data, the current study demonstrates that dysautonomia could be a diagnostic tool to improve therapy for many psychosomatic disease and COVID-19 related disorders in childhood and adults. Based upon the bidirectional interaction between heart rate and emotions, we can more objectively diagnose and treat poorly defined psychosomatic diseases like long COVID. These methods should increasingly be used by physicians in clinical practice. However, where clinicians are still hesitant to use this diagnostic tool, patients can use the widely available wearables to measure parameters themselves. We demonstrated significant effects of cheap and widely available cardiovascular drugs including propranolol, ivabradine, and O3-FA supplementation. However, these novel therapeutic approaches to psychosomatic diseases have to be further tested in prospective randomized trials, as it should be noted that some patients did not respond to this therapy. Future research is needed to clarify the impact of autoimmunity on dysautonomia to improve ongoing symptoms that do not improve with cardiovascular medication.

Conclusions

Our data show that an objective diagnosis is possible in children with dysautonomia using the 24-h heart rate and Holter ECG and the heart rate increase in the active standing test. Based upon HRV analysis, a vagus weakness is common among children with dysautonomia compared to those with IST and those with POTS only in upright position. In some children, dysautonomia may be related to G-protein coupled receptor autoantibodies against receptors of the autonomous nervous system.

Lowering heart rate increases in the active standing test is possible with the use of low dose propranolol (from 41.7 ± 17.5 to

29.5 ± 17.8 bpm**) and ivabradine (from 37.5 ± 16.4 to 23.6 ± 8.12 bpm*). Furthermore, O3-FA supplementation significantly reduced the heart rate increase while standing (from 44.0 ± 11.9 to 25.6 ± 8.4 bpm*). Beta blockers reduced heart rate while lying and standing together with a significant increase in the vagus parameter RMSSD. O3-FA supplementation exclusively reduced heart rate while standing with highly significant effects on heart rates during the day and night, as well global HRV in the 24-h Holter ECG. We presented four case studies showing clinical improvements with treatment of dysautonomia in adolescents with the following diagnoses: 1) long COVID syndrome, 2) long COVID-like symptoms after SARS-CoV-2 mRNA vaccination, 3) POTS in a Syrian refugee, and 4) anorexia nervosa.

Based on a bidirectional pathway between heart rate and emotions via the autonomic nervous system, it is possible to modulate emotions with therapies that improve vagus activity.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/ERHM.2022.00003.

Supplementary File 1. STARD checklist.

Acknowledgments

The author thanks Dr. Harald Heidecke (CellTrend GmbH Luckenwalde, Germany) rfor measure G-coupled receptor antibodies in the 9 patients (Table 4) when these measurements were not covered by the patient's health insurance.

Funding

None.

Conflict of interest

The author has no conflicts of interest related to this publication.

Author contributions

RB was the sole author.

Ethical statement

The study was reviewed and approved by the Institutional Review Board of Landesärztekammer Baden Württemberg F-2012-0056. The authors are accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all patients.

Data sharing statement

The data used to support the findings of this study are available from the corresponding author.

References

[1] Rees CA. Lost among the trees? The autonomic nervous system and paediatrics. Arch Dis Child 2014;99(6):552–562. doi:10.1136/archdischild-2012-301863, PMID:24573884.
[2] Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord 2000;61(3):201–216. doi:10.1016/s0165-0327(00)00338-4, PMID:11163422.
[3] Thayer JF, Lane RD. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev 2009;33(2):81–88. doi:10.1016/j.neubiorev.2008.08.004, PMID:18771686.
[4] Jarczok MN, Koenig J, Wittling A, Fischer JE, Thayer JF. First Evaluation of an Index of Low Vagally-Mediated Heart Rate Variability as a Marker of Health Risks in Human Adults: Proof of Concept. J Clin Med 2019;8(11):1940. doi:10.3390/jcm8111940, PMID:31717972.
[5] Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol 2007;74(2):224–242. doi:10.1016/j.biopsycho.2005.11.013, PMID:17182165.
[6] Boudoulas KD, Borer JS, Boudoulas H. Heart Rate, Life Expectancy and the Cardiovascular System: Therapeutic Considerations. Cardiology 2015;132(4):199–212. doi:10.1159/000435947, PMID:26305771.
[7] Buchhorn R, Baumann C, Willaschek C. Pathophysiological mechanisms of bradycardia in patients with anorexia nervosa. Health Sci Rep 2021;4(3):e331. doi:10.1002/hsr2.331, PMID:34322602.
[8] Buchhorn R, Hauk F, Meint S, Willaschek C. The Impact of Nutrition on the Autonomic Nervous System. Int J Food Nutr Sci 2016;3(3):1–16. doi:10.15436/2377-0619.16.942.
[9] Buchhorn R, Conzelmann A, Willaschek C, Störk D, Taurines R, Renner TJ. Heart rate variability and methylphenidate in children with ADHD. Atten Defic Hyperact Disord 2012;4(2):85–91. doi:10.1007/s12402-012-0072-8, PMID:22328340.
[10] Buchhorn R, Willaschek C, Baumann C. SARS-CoV-2 Infektionen und das autonome Nervensystem [SARS-CoV-2 infections and the autonomic nervous system]. Monatsschr Kinderheilkd 2021;169:645–648. doi:10.1007/s00112-021-01197-7, PMID:33935300.
[11] Gunning WT 3rd, Kvale H, Kramer PM, Karabin BL, Grubb BP. Postural Orthostatic Tachycardia Syndrome Is Associated With Elevated G-Protein Coupled Receptor Autoantibodies. J Am Heart Assoc 2019;8(18):e013602. doi:10.1161/JAHA.119.013602, PMID:31495251.
[12] Chang SE, Feng A, Meng W, Apostolidis SA, Mack E, Artandi M, *et al*. New-onset IgG autoantibodies in hospitalized patients with COVID-19. Nat Commun 2021;12(1):5417. doi:10.1038/s41467-021-25509-3, PMID:34521836.
[13] Wallukat G, Hohberger B, Wenzel K, Fürst J, Schulze-Rothe S, Wallukat A, *et al*. Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. J Transl Autoimmun 2021;4:100100. doi:10.1016/j.jtauto.2021.100100, PMID:33880442.
[14] Buchhorn J, Buchhorn R. The postural orthostatic stress syndrome in childhood: HRV analysis and the active standing test. Prev Med Community Health 2020;3:1–7. doi:10.15761/PMCH.1000148.
[15] Electrophysiology,Task Force of the European Society of Cardiology the North American Society of Pacing. 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 1996;93(5):1043–1065. PMID:8598068.
[16] Sheldon RS, Grubb BP 2nd, Olshansky B, Shen WK, Calkins H, Brignole M, *et al*. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm 2015;12(6):e41–63. doi:10.1016/j.hrthm.2015.03.029, PMID:25980

576.
[17] Buchhorn R, Buchhorn J. 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 2020;4:149. doi:10.29011/2688-7460.100049.
[18] Buchhorn R, Baumann C, Gündogdu S, Rakowski U, Willaschek C. Diagnosis and management of an inappropriate sinus tachycardia in adolescence based upon a Holter ECG: A retrospective analysis of 479 patients. PLoS One 2020;15(8):e0238139. doi:10.1371/journal.pone.0238139, PMID:32845894.
[19] Hidayat K, Yang J, Zhang Z, Chen GC, Qin LQ, Eggersdorfer M, *et al*. Effect of omega-3 long-chain polyunsaturated fatty acid supplementation on heart rate: a meta-analysis of randomized controlled trials. Eur J Clin Nutr 2018;72(6):805–817. doi:10.1038/s41430-017-0052-3, PMID:29284786.
[20] Thierrée S, Richa S, Brunet A, Egreteau L, Roig Q, Clarys D, *et al*. Trauma reactivation under propranolol among traumatized Syrian refugee children: preliminary evidence regarding efficacy. Eur J Psychotraumatol 2020;11(1):1733248. doi:10.1080/20008198.2020.1733248, PMID:32194925.
[21] Lin J, Zhao H, Ma L, Jiao F. Body mass index is decreased in children and adolescents with postural tachycardia syndrome. Turk J Pediatr 2019;61(1):52–58. doi:10.24953/turkjped.2019.01.009, PMID:31559722.
[22] Swai J, Hu Z, Zhao X, Rugambwa T, Ming G. Heart rate and heart rate variability comparison between postural orthostatic tachycardia syndrome versus healthy participants; a systematic review and meta-analysis. BMC Cardiovasc Disord 2019;19(1):320. doi:10.1186/s12872-019-01298-y, PMID:31888497.
[23] Medow MS, Merchant S, Suggs M, Terilli C, O'Donnell-Smith B, Stewart JM. Postural Heart Rate Changes in Young Patients With Vasovagal Syncope. Pediatrics 2017;139(4):e20163189. doi:10.1542/peds.2016-3189, PMID:28351846.
[24] Chen L, Wang L, Sun J, Qin J, Tang C, Jin H, *et al*. Midodrine hydrochloride is effective in the treatment of children with postural orthostatic tachycardia syndrome. Circ J 2011;75(4):927–931. doi:10.1253/circj.cj-10-0514, PMID:21301135.
[25] Kurtoglu E, Balta S, Karakus Y, Yasar E, Cuglan B, Kaplan O, *et al*. Ivabradine improves heart rate variability in patients with nonischemic dilated cardiomyopathy. Arq Bras Cardiol 2014;103(4):308–314. doi:10.5935/abc.20140109, PMID:25119894.
[26] Dogdus M, Burhan S, Bozgun Z, Cinier G, Koyuncu I, Yucel Karabay C, Zoghi M. Cardiac autonomic dysfunctions are recovered with vitamin D replacement in apparently healthy individuals with vitamin D deficiency. Ann Noninvasive Electrocardiol 2019;24(6):e12677. doi:10.1111/anec.12677, PMID:31339201.
[27] Ståhlberg M, Reistam U, Fedorowski A, Villacorta H, Horiuchi Y, Bax J, *et al*. Post-COVID-19 Tachycardia Syndrome: A Distinct Phenotype of Post-Acute COVID-19 Syndrome. Am J Med 2021;134(12):1451–1456. doi:10.1016/j.amjmed.2021.07.004, PMID:34390682.
[28] Freitag H, Szklarski M, Lorenz S, Sotzny F, Bauer S, Philippe A, *et al*. Autoantibodies to Vasoregulative G-Protein-Coupled Receptors Correlate with Symptom Severity, Autonomic Dysfunction and Disability in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. J Clin Med 2021;10(16):3675. doi:10.3390/jcm10163675, PMID:34441971.
[29] Tölle M, Freitag H, Antelmann M, Hartwig J, Schuchardt M, van der Giet M, *et al*. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Efficacy of Repeat Immunoadsorption. J Clin Med 2020;9(8):2443. doi:10.3390/jcm9082443, PMID:32751659.
[30] Arnold AC, Okamoto LE, Diedrich A, Paranjape SY, Raj SR, Biaggioni I, *et al*. Low-dose propranolol and exercise capacity in postural tachycardia syndrome: a randomized study. Neurology 2013;80(21):1927–1933. doi:10.1212/WNL.0b013e318293e310, PMID:23616163.
[31] Cappato R, Castelvecchio S, Ricci C, Bianco E, Vitali-Serdoz L, Gnecchi-Ruscone T, *et al*. Clinical efficacy of ivabradine in patients with inappropriate sinus tachycardia: a prospective, randomized, placebo-controlled, double-blind, crossover evaluation. J Am Coll Cardiol 2012;60(15):1323–1329. doi:10.1016/j.jacc.2012.06.031, PMID:22981555.