Case Report

The Impact of the Autonomic Nervous System on Inflammation Via the Cholinergic Anti-Inflammatory Pathway - Understanding COVID-19 and Autoinflammation in Children

Reiner Buchhorn[1*,2], Christian Willaschek[1,2] and Christoph Baumann[2]

*[*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

Corresponding author: Reiner Buchhorn, Caritas-Krankenhaus Bad Mergentheim, Department of Pediatrics, Uhlandstraße 7, Bad Mergentheim, Germany, Tel: 004917634150774; E-mail: buchrein@gmail.com

Abstract

The autonomic nervous system is involved in the regulation of inflammation. Inflammation is indicated by a heart rate increase and decrease of heart rate variability (HRV). We are investigating heart rate variability (HRV) in an acute COVID-19 infection, an 11-year-old boy with multisystemic inflammation syndrome after COVID-19 (MIS-C) and a 16-year-old girl with Postural Orthostatic Tachycardia Syndrome (POTS) after COVID-19. These data were compared with HRV data from children with periodic fever syndromes and severe heart failure to analyze the impact on prognosis.

Result: In acute COVID-19 infection, after a tachycardia up to the fifth day, the heart rate and HRV drop down, which is unusual for infections. As recently published, this "relative bradycardia" is obviously important on prognosis. The MIS-C is characterized by a maximum suppression of the HRV during the monitoring on the pediatric intensive care unit, which is rapidly reversible with intravenous administration of immunoglobulins. The POTS is characterized by a complete collapse of the vagus activity while standing and may be related to elevated G-protein coupled receptor autoantibodies that are also found in our patient with MIS-C. Data from HRV online monitoring on our pediatric intensive care unit demonstrate the high impact of low HRV on prognosis in children.

Summary: The examination of HRV in patients with COVID-19 improves diagnostics and therapy monitoring. The high impact of COVID-19 on the autonomous nervous system opens the opportunity to better understand the interplay between inflammation and the autonomic nervous system and the impact of current therapeutic approaches by using HRV-monitoring.

Keywords: COVID-19, Multisystemic inflammation syndrome (MIS-C), Postural orthostatic tachycardia syndrome (POTS), Heart rate variability (HRV), Autoantibodies

INTRODUCTION

The autonomic nervous system is involved in the regulation of inflammation. This association probably based on the so-called cholinergic anti-inflammatory pathway, as reviewed in 2011 [1]. It has been proposed that efferent splenic vagus nerve signals regulate cytokine production through the nicotinic acetylcholine receptor subunit alpha 7. A current meta-analysis of 51 studies confirmed negative associations between indices of heart rate variability (HRV) - a noninvasive marker of the autonomic regulation - and inflammatory markers [2]. In detail Interleukins (IL-1α, IL-4, IL-12, TNF-α and E-selectin) were inversely associated with heart rate variability measures, including the whole power spectrum of the Fast Fourier Analysis with both sympathetic and parasympathetic associations [3].

In 2001, we show for the first time the association of the neurohormonal activation in infants with severe heart failure due congenital heart disease with elevated cytokines [4-6]. We try to explain the beneficial effects of the beta blocker propranolol in these infants with its immunomodulatory effects. However, we failed to confirm this therapeutic association in a prospective trial with grown-up with congenital heart disease [7] and later we have to publish a severe immunomodulatory complication in an infant with severe heart failure who received Propranolol [8]. However, this therapeutic approach has been currently discussed to combat SARS-CoV-2 hyperinflammatory syndrome [9].

Based upon these experiences, we introduce HRV-online monitoring on our pediatric intensive care unit with the hope for a better understanding of these interactions between the autonomic nervous system and inflammation and to improve the safety of pharmacotherapy.

The current COVID-19 pandemic and the high mortality due to the so-called cytokines storm has suddenly given the forgotten hypothesis of the cholinergic anti-inflammatory pathway a new popularity, if it may open "new" therapeutic approaches [10,11]. So, it made sense to monitor the COVID-19 disease with the HRV analysis and we are now able to describe the unusual bradycardia effect of this illness [12], the collapse of HRV in a an 11-year-old boy with multisystemic inflammation syndrome after COVID-19 (MIS-C) and a Postural Orthostatic Tachycardia Syndrome (POTS) after COVID-19 in a 16-year-old girl.

METHODS

Fundamentals of every HRV data analysis are a group of successive normal RR intervals in sinus rhythm (so-called NN intervals) in a defined period of time of minutes (so called short-term HRV) or 24 h (so-called long-term HRV) (Guidelines 1996). The Time Domain Analysis is done by the processing of the data with simple statistical methods. For frequency domain measures, beat-to-beat fluctuations were transformed to the frequency domain using the fast Fourier transformation algorithm. Spectral power was determined over frequency regions of interest **(Table 1)**.

Table 1. Definitions of Variables of Heart Rate Variability.

Variable	Unit	Description
		Time domain measures
Mean NN	ms	Mean value of all normal RR intervals during 24 h
SDNN	ms	Standard deviation of all NN intervals
SDANN	ms	Standard deviation of the averages of NN intervals in all 5-minute segments
pNN50	%	Number of pairs of adjacent NN intervals differing by more than 50ms divided by the total number of all NN intervals
RMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals, indicates Vagus activity
		Frequency domain measures
Total Power	ms^2	Heart rate power spectrum between 0,003 and 0,4 Hz
VLF	ms^2	Very low frequency power spectrum between 0,003 and 0,04 Hz
LF	ms^2	Low frequency power spectrum between 0,04 and 0,15 Hz
HF	ms^2	High frequency power spectrum between 0,15 and 0,4 Hz, indicates Vagus activity
LF/HF ratio		Ratio of low to high frequency power

The children are routinely monitored on the pediatric care unit with Dräger Infinity Monitors™ (Dräger; Germany). For analysis of heart rate variability, we daily export the monitor data to the Pathfinder ™ ECG Software using a network connection. All Holter recordings were reviewed by an experienced cardiologist and were edited to validate the system's QRS labeling to exclude artifacts. Measures of HRV were calculated employing only normal to normal intervals. The Holter ECGs were analyzed as average values from the entire 24 h of analyzable data. In infants, we use frequency domain measures if the time domain measures have very low values and cannot differentiate the changes of the autonomic nervous system.

Trend of heart rate variability in the human life cycle (Figure 1)

The standard values for children have been published 1997 by Massin [13] and our own group in 2012 [14]. Standard values for adults have been published 2010 for the United States [15], for Germany in 2005 [16] and 2016 [17]. During lifetime, these standard values show most importantly trends:

- Global HRV is low in infancy and at the end of life, most of all indicated by the parameter Total Power and to a lesser degree by SDNN. There is a peak of global HRV at the age of 11 years.
- Vagus activity indicated by RMSSD and High Frequency power is low in infancy, has a peak in puberty and slowly decrease until the end of life.
- Heart rate decrease with vagus maturation until puberty and remains stable up to the end of life. Interestingly heart rate doesn't correlate with the LF to HF ratio, often interpret as sympathy-vagal balance.
- The linear relationship between the heart rate and bodyweight/body ratio is highly correlated in biology. The steep increase of Total power in childhood is mostly influenced by the parameter VLF -power that probably represent energy metabolism and thermogenesis due to the heat loss that depends on the ratio of body weight and body surface.
- At the end of adolescence, the VLF Power becomes low and HRV is dominated by the Low - and High - frequency power. The LF to HF ratio increase from 2 to 3.5 during adult life but the mean 24 h heart rate remains stable at 75 bpm on average. The current understanding of the loss of HRV by aging in adults as a loss of vagus activity is questionable, if the heart rate remains unchanged the same time.
- We previously describe a time trend to lower RMSSD values in children of today and anticipate a loss of vagus activity probably induced the current nutrition with low omega-3-fatty acids [14].

Vagus Activity in the Human Life Cycle

Based on thousands of 24-h HRV analysis in children and the adult from literature, we try to interpret these data with respect to the vagus parameter RMSSD **(Figure 2)**. The steep increase of RMSSD within infancy and puberty appears to be a vulnerable phase in the development of the autonomic nervous system (we use the term autonomic imprinting) [18].
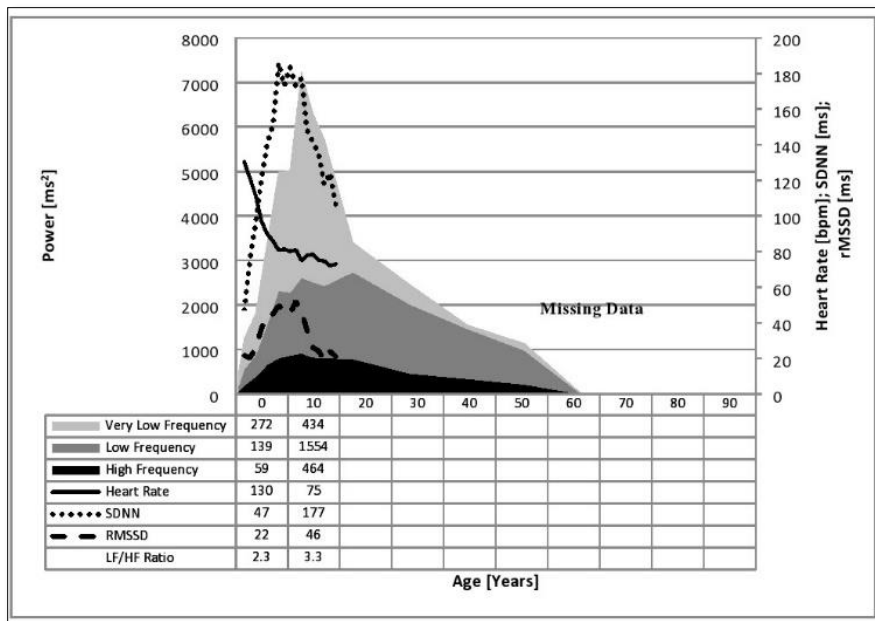
Figure 1. Trend of Heart Rate Variability in the human life cycle.

and offers a potential window of opportunity for therapeutic interventions. Beside this well-known trends of vagus activity during human life cycle, we found significant differences with lower and higher values that depends on the nutritional state (Anorexia Nervosa with high RMSSD, Obesity with low RMSSD), physical activity (competition sports high RMSSD, Inactivity low RMSSD) and emotional state (Attention deficit hyperactivity disorder/depression/chronic fatigue/posttraumatic stress disorder low RMSSD, the dreaming variant of attention deficit disorder with high RMSSD?)
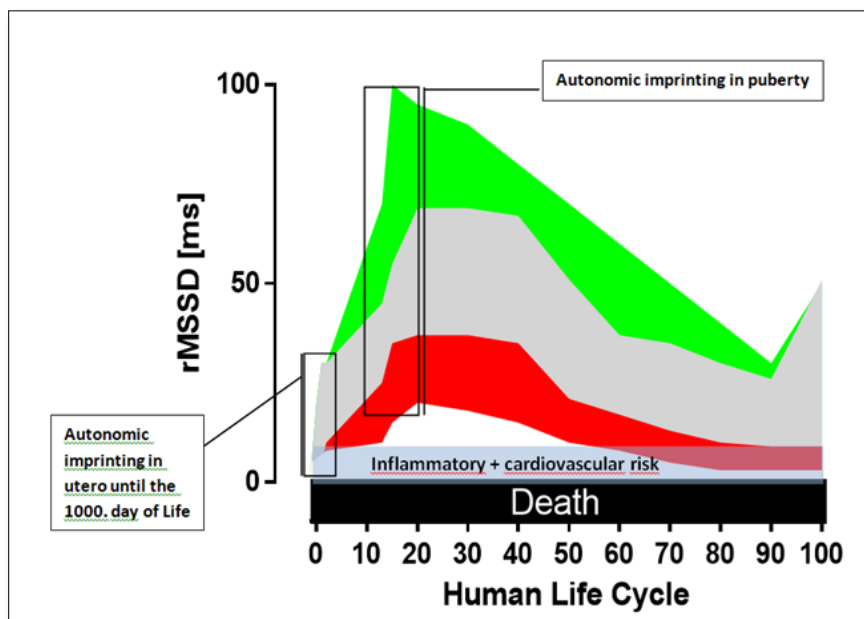

Figure 2. Vagus activity in the human life cycle.

Gray: Normal Range of Vagus Activity; Green: High vagus activity: Vagus "Junkees" induced by sports and caloric restriction, dreaming variant of attention deficit disorder; Red: Low Vagus activity: Vagus deficiency induced by hyper alimentation, attention deficit hyperactivity disorder, emotional disease, severe somatic disease. e.g., heart failure ± inflammation

HRV-MONITORING IN COVID-19

HRV-Monitoring During Acute COVID-19 Infection

Based upon our experience with HRV-analysis, we are able to demonstrate that inflammation in acute COVID-19 in 58-year-old men is associated with unusual lower heart rates and low HRV [11] in contrast to other inflammatory diseases. This observation was confirmed by many other groups [19-22] and seems to be a specific complication in COVID-19 with a high impact on mortality [23,24]. In contrast to these groups who speculate about specific effects of SARS-COV-2 on the sinoatrial node, we anticipate a shared pathophysiology of a brainstem network disruption as shown in other disease like sudden unexplained death in epilepsy [25,26].

Our concept opens new opportunities for risk stratification in the current COVID-19 pandemic in the era of using health technologies in millions of smart watches. Prospectively user-friendly smart watches, mobile ECG devices or chest straps may represent an elegant option in an ambulatory setting to monitor the health risks. Thus, the development of algorithms and advances in machine learning techniques to recognize severe disease like COVID-19 are necessary. A recently published paper used data on 2745 active Fitbit™ users in the USA and Canada who were diagnosed with COVID-19 (active infection, PCR test) [27]. **Figure 3** from this publication show the assessment of the physiological measurements with this fitness tracker: Resp Rate=Respiratory Rate, HR=Heart Rate, RMSSD=Heart Rate Variability Parameter that indicate Vagus activity, Entropy=indicating global HRV. There is the expected increase of heart rate, respiratory rate and decrease of HRV within the first two days of COVID-19. In contrast to other infection heart rate drop down within the next 14 days while HRV remained low up to the tenth day. During this time, the life-threatening complication of COVID-19 occur, while the physiological measurements completely recover in most patients who survive.
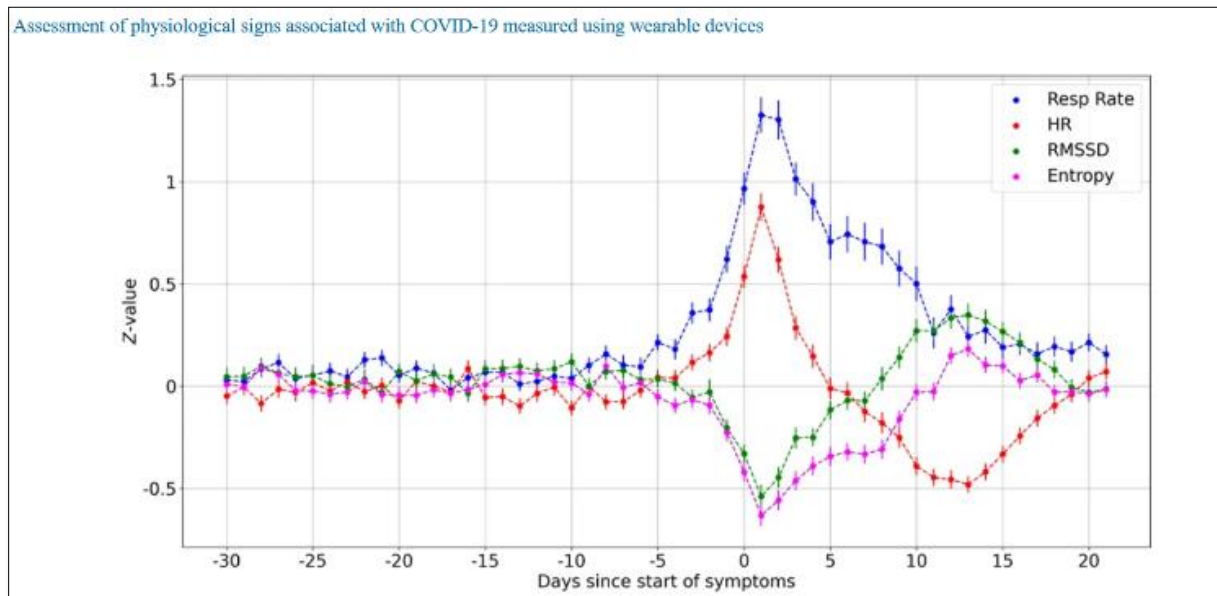
Figure 3. Assessment of physiological measurement from a fitness tracker in patients with COVID-19 taken from publication [27].

Resp Rate: Respiratory Rate; HR: Heart Rate; RMSSD: Heart Rate Variability Parameter that indicate Vagus activity; Entropy: indicating global HRV

We recently develop an algorithm to predict life-threatening complications using heart rate variability and the circadian heart rate difference with a special interest on COVID-19, sudden death in epilepsy, children with congenital heart disease and obesity [28]. The algorithm must be proofed in a prospective study to be able to answer the urgent questions of the patients and their parents based on objective data. Otherwise, we must advise all the patients with preexisting chronic disease that they are probably on a higher risk for COVID-19 complications based on single reported cases.

HRV-Monitoring in an 11-Year-Old Boy with Multisystemic Inflammation Syndrome After COVID-19 (MIS-C)

Healthy children who are obviously not at risk from the acute infection can develop the multisystem inflammatory syndrome (MIS-C), who needs pediatric intensive care in 80% of cases with a mortality of 2% [29]. Therapeutical guidelines who based on the experience with the Kawasaki Disease are currently developed [30] and are successful in our current case: It's a 11-year-old boy whose asymptomatic SARS-COV-2 infection was discovered by chance during a test of contact persons 4 weeks earlier. He developed persistent fever for one week, conjunctivitis and

gastrointestinal symptoms. His C-reactive protein (9,4 mg/dl, reference <0,5) and NT-Pro-BNP value (8137 pg/ml, Normwert <85) are highly elevated and decrease after intravenous immunoglobulin therapy (CRP =1,57 mg/dl and NT-Pro-BNP=1108 pg/ml). He completely recovered after a one-week hospital stay. As shown in **Figure 4**, his heart rate

variability indicated by the power spectrum of HRV analysis completely collapsed during the multisystem inflammatory syndrome (MIS-C) and increase to normal values after intravenous immunoglobulin therapy. His coronary arteries are completely normal in the echocardiography.
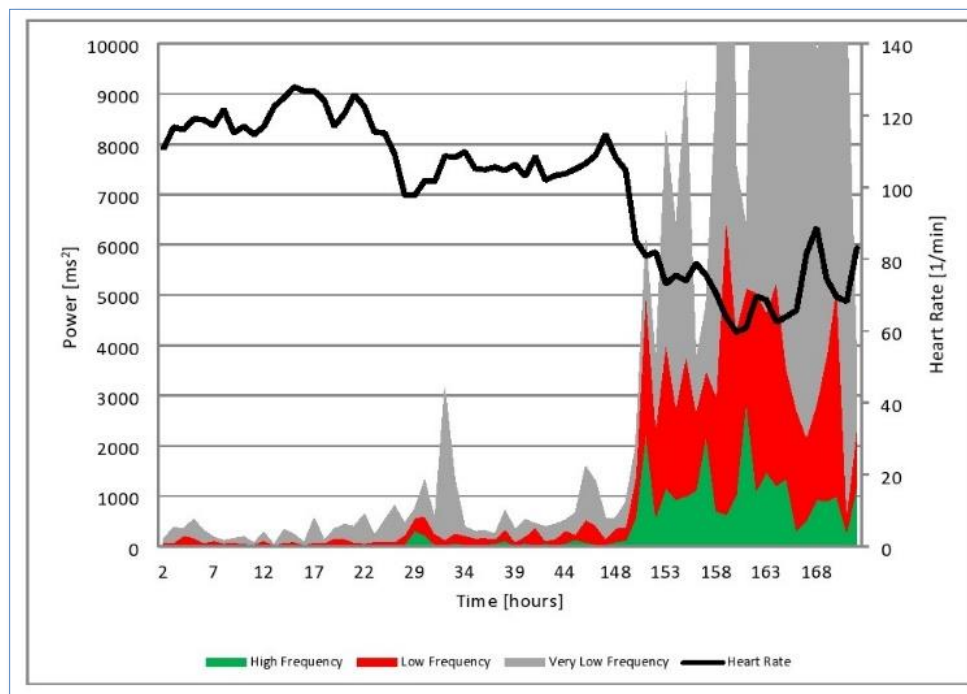
Figure 4. HRV-monitoring in an 11-year-old boy with multisystemic inflammation syndrome after COVID-19 (MIS-C).
iv-IgG: Intravenous immunoglobulin therapy

16-Year-Old Girl with Postural Orthostatic Tachycardia Syndrome (POTS) After COVID-19

The 16-years-old girl developed dizziness and syncope two weeks after a mild SAR-COV-2 infection proofed by a positive PCR test. The active standing test as shown in **Figure 5** show a more than 40 bpm increase of heart rate and the girl had to interrupt the test after one minute. We used the standard therapy for Postural Orthostatic Tachycardia Syndrome (POTS) with low dose propranolol (10mg at 7:00 and 12:00) [31] and the symptoms disappear. However, the girl had severe vasovagal syncope in the control active standing test with sinus arrest > 5 seconds **(Figure 6)**. We must stop propranolol and start midodrine therapy.

This is the first published case of POTS after COVID-19 in a child after some published cases in adults [32]. We are not surprised to anticipate POTS as one correlate of the so called post-acute COVID-19 syndrome if we recently published similar cases of children with POTS after infectious mononucleosis and chronic borreliosis[33]. In all these children with autonomic dysfunction, we found elevated G-protein coupled receptor autoantibodies as show in **Table 2**. The current discussion focusing on the role of angiotensin

converting enzyme receptors 2 in allowing the viral entry into cells shows, that such receptor networks are important to understand COVID-19.

HRV IN THREE CHILDREN WITH PERIODIC FEVER SYNDROME

Neonatal Onset Multisystem Inflammatory Disease (Figure 7)

The infant developed a severe inflammatory disease after premature birth called Neonatal Onset Multisystem Inflammatory Disease (NOMID). Our suspected diagnosis was confirmed late by the specialists and we start a specific therapy with the IL-1 antagonist Anakinra at the 215 day of life with a significant improvement of clinical symptoms and autonomic dysfunction. **Figure 7** clearly show that low HRV in this infant due to inflammation that was accompanied by very high NT-Pro BNP values, indicating heart failure despite a primary healthy heart. Pro-inflammatory cytokines like Interleukin-1β (8.28 pg/ml), Interleukin-6 (34.6 pg/ml), Interleukin 8 (1500 pg/ml), TNF-α (33 pg/ml) and soluble CD25 (1486U/ml) are significantly elevated. However, after a long in hospital treatment the baby died with one year of age during this therapy in the context of a foudroyant pneumonia.
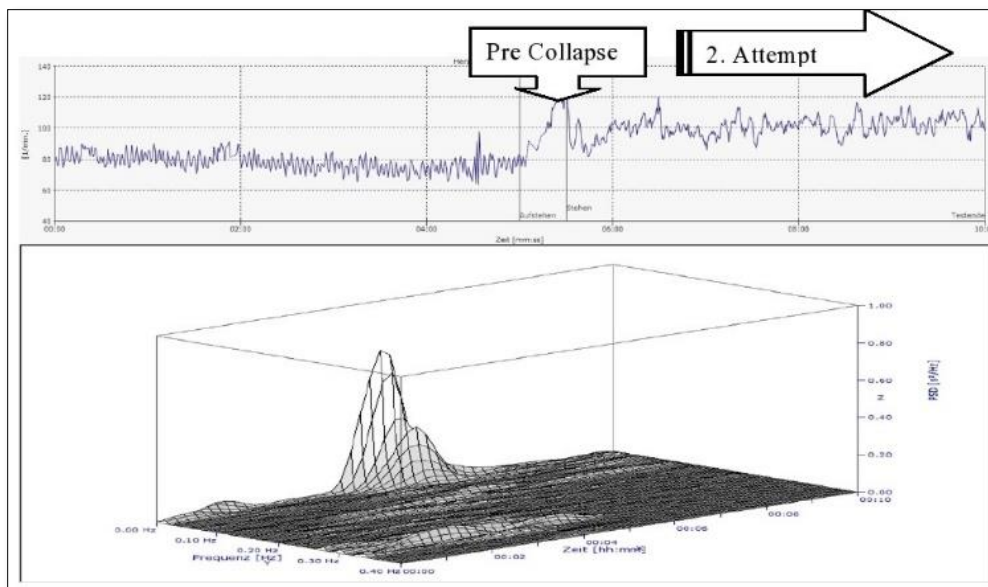
Figure 5. 10 minutes active standing test monitors with the HRV Scanner™ (BiosignGmbH) after COVID-19: heart rate and the power spectrum of heart rate variability.
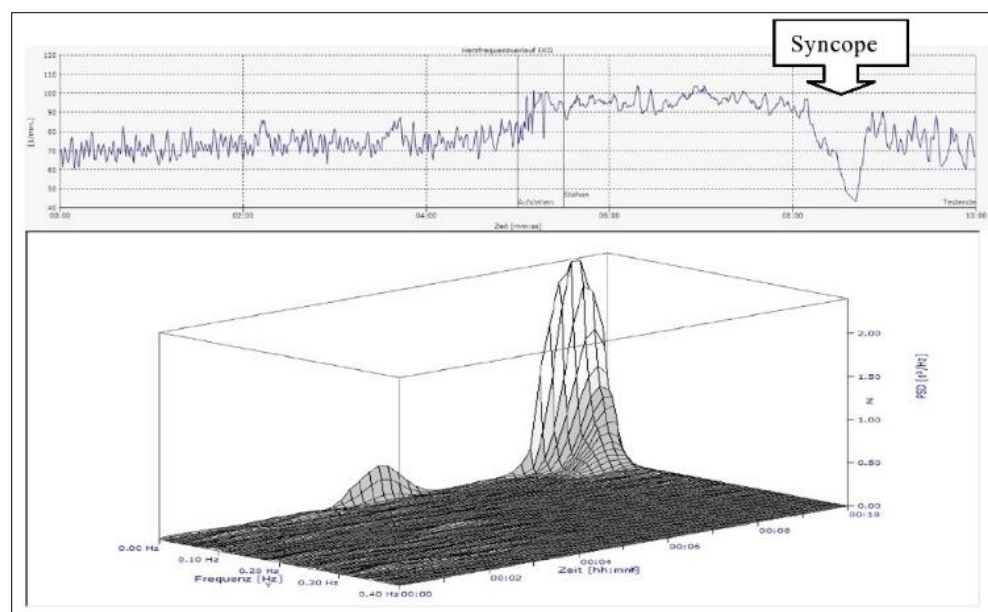

Figure 6. 10 minutes active standing test monitored with the HRV Scanner™ (Biosign GmbH) after 10 mg propranolol: heart rate and the power spectrum of heart rate variability.

Table 2. Autoantibodies in children with autonomic dysfunction.

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	13.5	14.2	13.4	9.2	10.0	20.5	4.3	3.3	9.7	6.5	6.1
POTS	10.8	8.2	13.5	12.4	5.1	3.3	1.3	2.5	3.5	4.1	4.6
Chronic Borreliosis	9.3	9.2	29.0	21.0	9.8	8.8	4.1	3.8	12.0	8.7	11.5

Emery Dreyfuss Myopathy	21.2	20.6	14.2	22.6	21.5	19.3	9.0	7.5	12.0	9.0	9.0
Chronic Fatigue	6.6	6.5	18.3	10.6	8.2	6.5	2.7	1.6	7.8	3.5	7.3
Anorexia Nervosa	10.3	8.2	3.9	9.8	5.6	13.0	4.2	1.6	6.4	15.3	12.4
MIS-C	14.6	16.0	13.3	18.2	7.8	13.5	6.4	5.6	14.7	15.5	15.7

POTS: Postural orthostatic tachycardia syndrome; 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
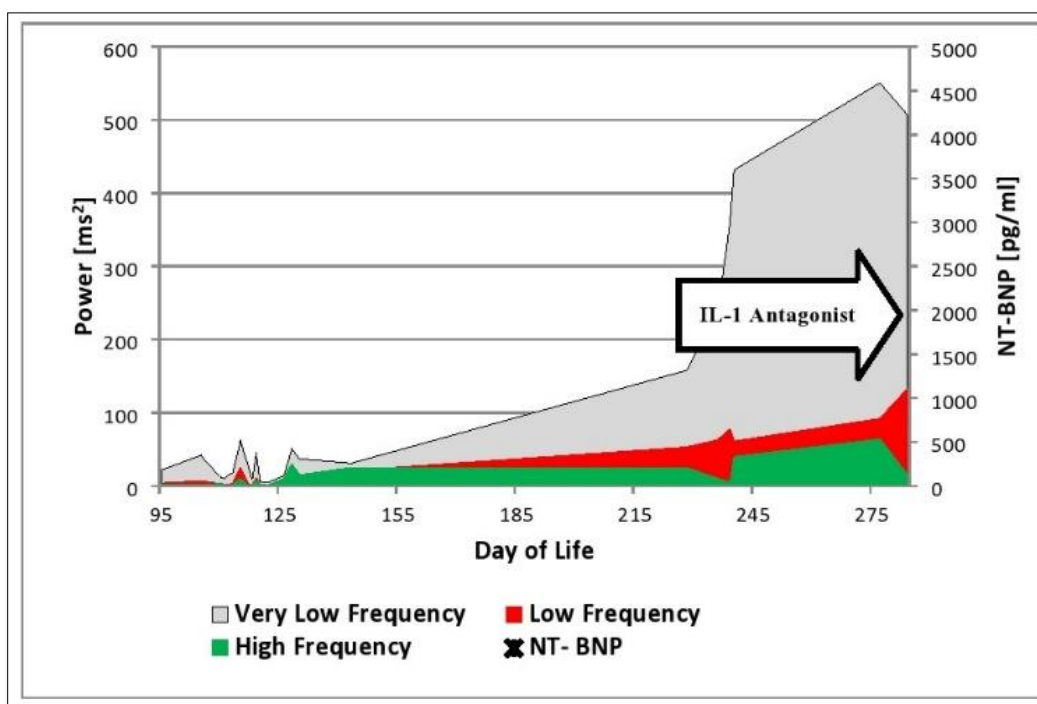

Figure 7. Neonatal Onset Multisystem Inflammatory Disease (NOMID).

Hemophagocytic Hymphohistiocytosis in an Infant with Severe Heart Failure

The boy was born with Down`s syndrome and an unbalanced, left dominant atrioventricular septal defect with aortic coarctation. Despite coarctation repair and pulmonary artery banding, he suffers from intractable heart failure and fever of unknown origin indicated as systemic inflammatory response syndrome (SIRS) in **Table 3**. He remained in heart failure with high NT-Pro-BNP and cytokine values despite multiple therapeutic and diagnostic efforts over 5-month intensive care to stabilize his cardiopulmonary status. He received a low dose propranolol which resulted in dramatic immunomodulatory effects (SIRS I in **Table 2**). Immunoactivation was indicated by high procalcitonin- and cytokine release, normoblastosis and highly elevated Ferritin values. Immunoactivation leads to a hepatic/splenic

compromise as indicated by high lactate dehydrogenase and alanine aminotransferase levels probably caused by macrophage activation. A therapeutic switch to β1 receptor blocker metoprolol appeared to be instrumental in hemodynamic improvement and allowed the discharge from hospital. The heart rate variability remained very low and the infant died of cause inflammatory reactivation (SIRS III). The autopsy results revealed hemophagocytic lymphohistiocytosis and a very small spleen probably after autolysis. The interactions between the adrenergic system and the cytokine network in this highly activated inflammatory state are discussed in our publication **(Table 3)** [8].

Table 3. Heart failure and inflammation in an infant with severe heart failure.

Parameter	Normal Value	Baseline	SIRS I	SIRS II	Discharge	SIRS III
Timeframe [days]			3	4	2	18
Age [weeks]			23	24	27	29
Cardiovascular Parameter						
Heart rate [1/min]		130	110	100	100	150
Fractional shortening [%]		45	45	32	59	36
LV Pressure [mmHg]§		101	79	79	71	63
Mean arterial pressure [mmHg]		86	65	74	60	50
Pulmonary artery pressure$_{sys}$[mmHg]$^{#}$		63	61	48	30	40
Organ Damages						
GOT$_{max}$ [U/l]	0 - 35	319	28839	3778	107	323
LDH$_{max}$ [E/l]	0 - 250		220000	9097	530	2753
Bilirubin$_{max}$ [mmol/l]	0.4 - 1.2		2.8	9.51	6.16	7.06
Creatinine$_{max}$ [mg/dl]	0.70 - 1.20	0.45	0.62	1.94	0.67	1.57
Urea $_{max}$ [mg/dl]	11 - 55		75	133	122	210
Coagulation						
Thrombocyte$_{min}$ [1000/ml]	140-400	690	153	88	61	58
INR$_{max}$ [Ratio]	0.8 - 1.25		2.11	3.24	1.34	1.47
Inflammatory markers						
White blood cell$_{max}$ [1000/l]	3.6 - 10.0	16.7	28.280	16.999	12.800	3.690
Normoblast absolute [1000/l]	None	0	22.220	2.101	0	16.810
Procalcithonin$_{max}$ [pg/ml]	0.1 - 0.5	5.61	13.67	85.78	2.9	420
sCD25 [U/ml] *	< 1000	2220	2160			3916
TNF-α [pg/ml] *	< 3	90.4	104.8			98.4
IL-8 [pg/ml] *	< 3	152	346			328
IL-6 [pg/ml] *	< 6	72	108			55.6
IL-1β [pg/ml] *	< 5	2.9	4.0			1.68
C reactive protein$_{max}$ [mg/dl]	< 1.0	0.00	0.21	0.83	0.21	0.00
NT-Pro-BNP [pg/ml]	0 - 85		6374	31127	31689	71485
Ferritin [µg/l] *	20 - 400	33016	27516	94099	419	602
Triglyceride [mg/dl]	35 - 180			1349	222	327
Serum Calcium$_{min}$ [mmol/l]	2.15 - 2.75	1.81	2.23	1.61	2.54	2.05

*: measurements from stored plasma; §: left ventricular pressure estimated from Doppler measurements of mitral valve regurgitant jet velocity; #: systolic pulmonary artery pressure estimated using Doppler measurements across pulmonary artery band; Pulmonary artery pressuresys = LV pressure - PAB gradient

PFAPA Syndrome (Figure 8)

Periodic Fever, Aphthous Stomatitis, Pharyngitis and Cervical Adenitis (PFAPA) syndrome is the most common auto inflammatory disorder among children and an important differential diagnosis in children presenting with recurrent fever episodes [34]. There is considerable heterogeneity in the treatment and a lack of evidence-based treatment.

We report about a girl with periodic fever syndrome beginning at the age of 3.5 years. Fever episodes usually last 3-6 days with a striking regularity and are associated with one or more of the cardinal symptoms aphthous stomatitis, pharyngitis, tonsillitis, and cervical adenitis. During the episodes, the girl has elevated inflammatory variables such as CRP and serum amyloid A. Up to the age of 4.5 years, she had five hospital stays in different hospitals and received different antibiotic treatments of cause the diagnosis sepsis. We decide for tonsillectomy together with a supplementation of 1g omega-3-fatty acids. The girl recovered and within the next two years the fever episodes slowly disappear, and she need no further hospital stay. The very low HRV indicated by the parameter RMSSD at the years of 4 years slowly increase to normal values at the age of 6 years **(Figure 7)**. The highly elevated serum amyloid decrease to normal values (672mg/l to 19mg/l).

HRV Online Monitoring of Life-Threatening Diseases in Pediatric Care Units

The vagus activity, indicated by the HRV-parameters RMSSD and High Frequency Power (HF-Power) are low in nearly all children with severe somatic diseases, most of all in patients with heart failure and inflammation. As recently published in preterm, very low vagus activities indicated by High Frequency Power values below 20 ms^2 indicate a high risk of necrotizing enterocolitis, a life-threatening inflammatory disease [35].

All infants who died on our intensive care unit within the last ten years from cardiac and non-cardiac reasons had such low High Frequency Power values below 20 ms^2 more than 1 week before death **(Figure 9)**. We observed a fluent overlap between heart failure and inflammation in these children as illustrated in the case 3.1. and 3.2.

The measured HRV data are illustrated in **Table 4**, showing the significant difference of infants with severe heart failure before and after beta blocker treatment and the very low HRV in the infants who died.

Legend **Figure 9** All infants who died on our pediatric intensive care unit from cardiac and non-cardiac reasons (group Death) had low HF power values below 20 ms^2 more than 1 week before death. Infants with severe heart failure due to congenital heart defects had such low HF-power values prior to propranolol (group CHD). HF Power improves during beta blocker treatment (group CHD+BB) but remained low in the two children with very low HF Power who died some month later. One infant with trisomy 18 and single ventricle received no medical therapy and died in a palliative setting.

Legend **Table 3** Results of a t-test between congenital heart defect ± beta blocker or premature infants ± necrotizing enterocolitis (NEC) *p<0.05, ***p<0.001 The illustrated data of preterm with and without necrotizing enterocolitis are taken from literature [35].
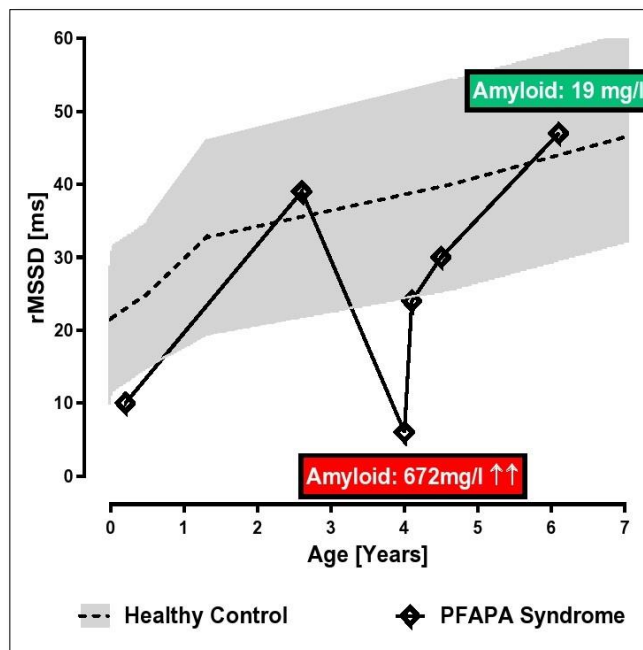

Figure 8. Vagus activity and serum amyloid in a girl with PFAPA syndrome, successfully treated with tonsillectomy and omega-3-fatty supplementation at the age of 4.5 years.
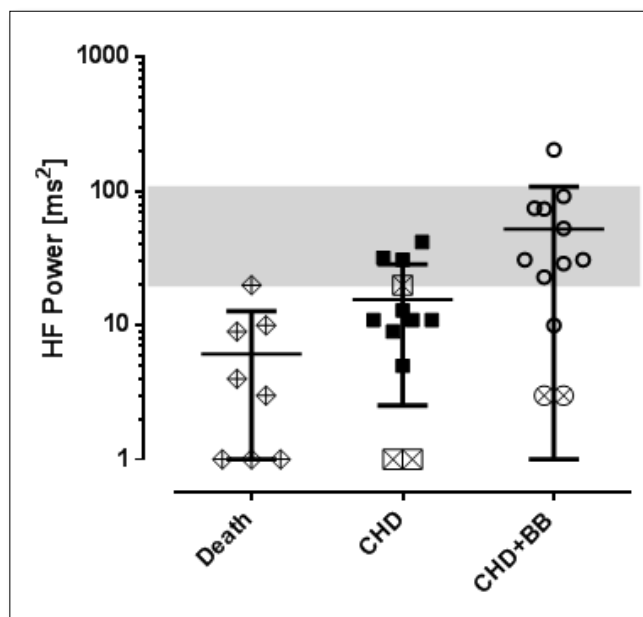

Figure 90. 24 h HRV monitoring and prognosis on the pediatric intensive care unit.

DISCUSSION

Inflammation is indicated by the heart rate increase and decrease of HRV! A recent meta-analysis shows that the standard deviation of R-R intervals (SDNN) and the power in the high frequency band of HRV showed the strongest and most robust associations with inflammatory markers [2]. As shown in our case collection, severe heart failure ± inflammatory syndromes in infants are associated with a

Table 4. Data from the HRV-online monitoring on the pediatric intensive care unit.

Group	N	Heart Rate [bpm]	SDNN [ms]	rMSSD [ms]	HF-Power [ms²]
Congenital Heart Disease	12	139 ± 17	39 ± 20	7.3 ± 2.9	16 ± 13
Congenital Heart Disease + Beta Blocker	12	118 ± 9***	49 ± 13*	12.4 ± 5.5	49 ± 56
Non-Cardiac Disease	8	138 ± 18	42 ± 21	6.1 ± 3.3	14 ± 17
Infants who died	8	145 ± 20	38 ± 20	5.4 ± 3.2	6 ± 7
Premature Infants + NEC [35]	9	163 ± 5 *			4 ± 12***
Premature Infants – NEC [35]	61	146 ± 11			21 ± 22

decrease of the power in the High Frequency band of HRV below 20 ms² and have a very high mortality risk. Furthermore, severe heart failure due to a congenital heart defect may be the cause of inflammation as demonstrated in case 3.1. Conversely, a congenital inflammation syndrome can be the cause of heart failure indicated by very high NT-Pro-BNP values (case 3.2.).

We routinely monitor the effect of pharmacotherapy in pediatric heart failure [36] and other life-threatening diseases on our pediatric intensive care unit on heart rate variability. As shown in many publications, we successfully use heart rate variability monitoring as a therapeutic target and surrogate parameter for the control pharmacotherapy as proposed 18 years ago [37].

The current COVID-19 pandemic and the high mortality due to the so-called cytokines storm has suddenly given the forgotten hypothesis of the cholinergic anti-inflammatory pathway a new popularity and probably open "new" therapeutic possibilities. We are now able to publish the therapeutic effect of intravenous immunoglobulin therapy on HRV in an 11-year-old boy with multisystemic inflammation syndrome after COVID-19 (MIS-C). Furthermore, we could demonstrate that inflammation in acute COVID-19 is associated with unusual lower heart rates and low HRV [11]. This observation was confirmed by many other groups [19-22] and seems to be a specific complication in COVID-19 with a high impact on mortality [23,24]. In contrast to these groups who speculate about specific effects of SARS-COV-2 on the sinoatrial node, we anticipate a shared pathophysiology of a brainstem network disruption as shown in other disease like sudden unexplained death in epilepsy [25,26].

We recently develop an algorithm to predict life-threatening complications using heart rate variability and the circadian heart rate difference with a special interest on COVID-19, sudden death in epilepsy, children with congenital heart disease and obesity [28]. The algorithm must be proofed in a prospective study to be able to answer the urgent questions of the patients and their parents based on objective data. Otherwise, we must advise all the patients with preexisting chronic disease that they are probably on a higher risk for COVID-19 complications based on single reported cases.

We can further demonstrate how to diagnose Postural Orthostatic Tachycardia Syndrome (POTS) in a 16-year-old girl with a simple active standing test as a correlate of the so called post-acute COVID-19 syndrome and a potential therapeutic target. We currently begin to understand how elevated G protein-coupled receptor antibodies are associated with the Postural Orthostatic Tachycardia Syndrome (POTS) [38] and COVID-19 [39].

The high impact of COVID-19 on the autonomous nervous system [40] open the opportunity to better understand the interplay between inflammation and the autonomic nervous system and the impact of current therapeutic approaches by using HRV-monitoring.

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