RESEARCH ARTICLE

Early Life Stress, Growth and Neurodevelopment in Childhood

Author
Buchhorn Reiner [1,2]

[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

Correspondence
Prof. Dr. R. Buchhorn, Klinik für Kinder- und Jugendmedizin, Caritas Krankenhaus, Uhlandstr. 7, 97980, Bad Mergentheim, Germany.
Tel: +49-7931-582301; fax: +49-7931-582390.
E-mail: buchrein@gmail.com

Abstract

Follow up studies of children with congenital heart disease, premature birth, small for gestational age syndrome and attention deficit hyperactivity disorder show significantly reduced 24-hours heart rate variability (HRV) that indicate autonomic dysfunction. The underlying pathophysiological process is of high clinical importance if autonomic dysfunction in these children is related to neurocognitive impairment, an enhanced cardiovascular risk, and a higher risk of short stature. Elevated norepinephrine levels, reduced HRV and MRI imaging indicate brain injury very early in life. We introduce the term autonomic imprinting to explain how early life stress have a lifelong imprinting effect on the autonomic nervous system. Many efforts are done for a careful management of infants in pediatric intensive care units. However, early life stress cannot be prevented if sympathetic activation is part of the underlying disease most of all due to congestive heart failure. We could demonstrate that beside a careful management, pharmacotherapy has a high impact on autonomic dysfunction in children with heart failure, attention deficit disorder and short stature. Moreover, online HRV monitoring is a complete noninvasive tool to monitor early life stress if it uses the data from routine heart rate monitoring. HRV online monitoring on the pediatric intensive care unit and Holter ECG monitoring in a daily life setting are clinical routine in our department for each pharmacotherapy affecting the autonomic nervous system. In the same time as monitoring of early life stress becomes clinically routine, the situation of children will improve if we realize which interventions increase early life stress or improve its detrimental damages in longtime follow up.

Copyright 2020 KEI Journals. All Rights Reserved

Follow up studies of children with congenital heart disease, premature birth, small for gestational age syndrome and attention deficit hyperactivity disorder show significantly reduced 24-hours heart rate variability (HRV) that indicate autonomic dysfunction. The underlying pathophysiological process is of high clinical importance if autonomic dysfunction in these children is related to neurocognitive impairment, an enhanced cardiovascular risk, and a higher risk of short stature. Elevated norepinephrine levels, reduced HRV and MRI imaging indicate brain injury very early in life. We introduce the term autonomic imprinting to explain how early life stress have a lifelong imprinting effect on the autonomic nervous system. Many efforts are done for a careful management of infants in pediatric intensive care units. However, early life stress cannot be prevented if sympathetic activation is part of the underlying disease most of all due to congestive heart failure. We could demonstrate that beside a careful management, pharmacotherapy has a high impact on autonomic dysfunction in children with heart failure, attention deficit disorder and short stature. Moreover, online HRV monitoring is a complete noninvasive tool to monitor early life stress if it uses the data from routine heart rate monitoring. HRV online monitoring on the pediatric intensive care unit and Holter ECG monitoring in a daily life setting are clinical routine in our department for each pharmacotherapy affecting the autonomic nervous system. In the same time as monitoring of early life stress becomes clinically routine, the situation of children will improve if we realize which interventions increase early life stress or improve its detrimental damages in longtime follow up.

1 Introduction

The autonomic nervous system seems to be the operating system in human biology. The maturation of the autonomic nervous system in early childhood is an important target for growth and neurodevelopment. Autonomic dysfunction is involved in many disease and functional disorders and enhances cardiovascular risk - the most important cause of mortality in the modern societies.

Heart rate variability (HRV) is predominantly controlled by the autonomic nervous system. We include autonomic diagnostics by 24-hour analysis of heart rate variability (HRV) in different clinical settings in the 90th and now looking back on more than 25 years of systematic research in childhood. Most of all we use HRV diagnostics for objective monitoring of new innovative therapies like beta blockers in heart failure [1] and omega 3 fatty acids in attention deficit disorder, short stature and metabolic syndrome [2, 3]. Moreover, we use HRV diagnostics to improve safety of pharmacotherapy with psychostimulants and growth hormone. Based upon this research, we published three pathophysiological hypotheses: 1) The neurohormonal model to explain heart failure in infants with congenital heart disease [4]. 2) A model to explain the growing incidence of nutritional and emotional disease in childhood (the so called new morbidity) by a loss of vagus activity [5] and 3) The longtime consequences of early life stress on the autonomic nervous system (called autonomic imprinting) [6].

Our methodological approach is published in our recent papers. We use the following HRV parameters (table 1):

Copyright 2020 KEI Journals. All Rights Reserved

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
		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
LF/HF ratio		Ratio of low to high frequency power

1.1 The Vagus View on the Human Life Cycle

The most popular view on the autonomic nervous system based upon the impact of the vagus on cardiovascular- and emotional disease as published by Julian Thayer et al [7] and the so-called polyvagal theory published by S. Porges [8]. Looking on the human life cycle of vagus activity indicated by the HRV parameter rMSSD (figure 1), there are two steep increases of rMSSD in early infancy and puberty [9]. Neurotransmitters play critical roles in neurodevelopment and norepinephrine is in particular postulated to be an important regulator for brain development and heart rate as well [10]. More recently MRI studies show early-life and pubertal stress modulate gray matter development. We anticipate autonomic imprinting by early life stress to explain the correlations between neurodevelopment, functional magnet resonance imaging [11] and HRV.

Copyright 2020 KEI Journals. All Rights Reserved

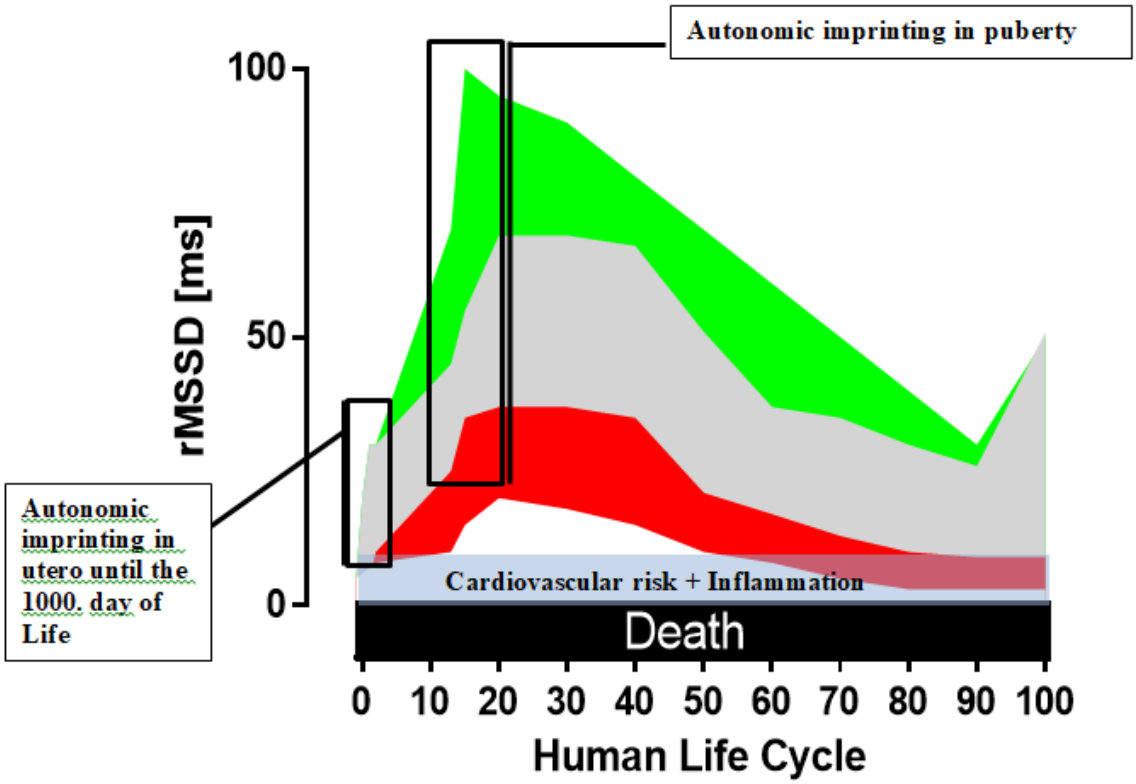

Fig. 1:
Gray: Normal Range of Vagus Activity
Green: High Vagus activity induced by genetics, sports and caloric restriction
Red: Vagus Deficiency induced by hyper alimentation, attention deficit hyperactivity disorder, emotional disease

1.2 Ethical Statement

In 2012 we have submitted an ethical proposal at the central ethic committee for an anonymous evaluation of more than 1000 Holter ECG's from our clinical data base in order to publish our routine data from a the department of pediatrics in Germany measured in a really life setting.

2 Hypoxic Ischemic Encephalopathy

2.1 Brain Death and HRV

Brain death occurred in one-fifth of pediatric intensive care units deaths. Most children declared brain dead had no preexisting neurological dysfunction and had an acute hypoxic-ischemic or traumatic brain injury [12].

After brain death, this autonomic control stops, and heart rate variability is significantly decreased. Decreased heart rate variability is associated with markers of CNS dysfunction such as electroencephalogram abnormalities [13].

Based upon this concept of autonomic system failure as an early indicator of impending brain death, we analyze the complete monitor data of a newborn after resuscitation of cause uterus rupture of her mother until the death at an age of 8 days (Figure 2). The girl depends on mechanical ventilation of cause apnea. While electrical activity in the

Copyright 2020 KEI Journals. All Rights Reserved

electroencephalogram disappear, the histogram of her heart rate becomes progressively smaller at 159 bpm. Heart rate variability remained very low indicated by the Total Power, the SDNN and rMSSD.

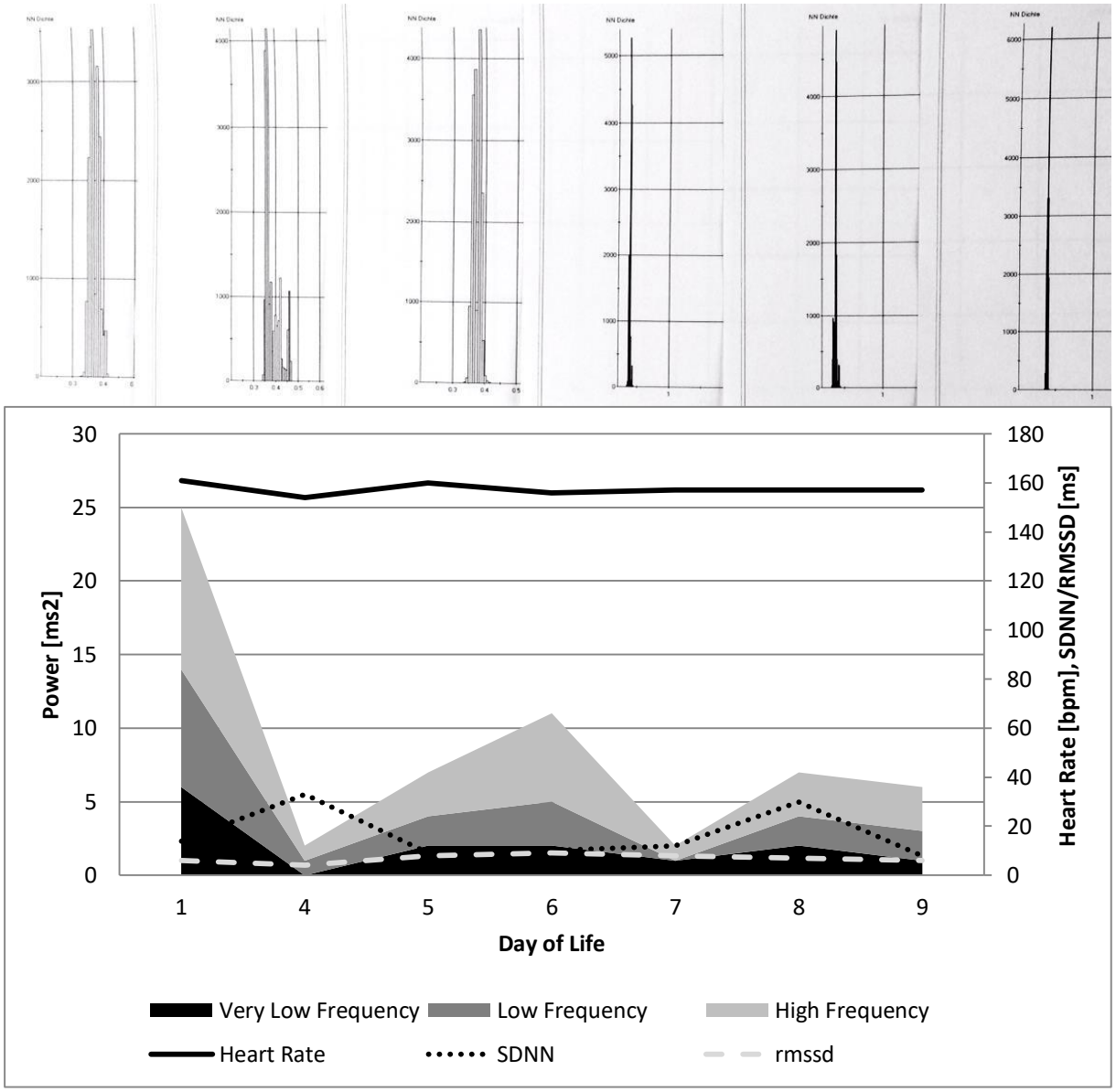

Fig. 2: Complete monitor data set of HRV of a newborn with severe hypoxic ischemic encephalopathy after resuscitation who developed brain death and died with an age of 8 days. The upper graph shows the distribution of NN-intervals. The lower graph illustrates the time course of the HRV parameters.

2.2 Hyothermia and HRV

HRV monitoring is a promising tool for early prediction of brain injury and neurodevelopmental outcome in babies with hypoxic ischemic encephalopathy [14]. Figure 3 shows HRV monitoring of twin 2 for 216 hours on our intensive care unit after a severe hypoxic event of cause an arm

Copyright 2020 KEI Journals. All Rights Reserved

prolapse at birth with an umbilical cord pH of 6.7. We immediately start hypothermia and observe the well-known low heart rates (100/min) and high HRV (SDNN 50ms, rMSSD 30ms). According to this "beneficial" vagus activation the invasive blood pressure monitoring showed low arterial pressures up to 35/20 mmHg. We must start epinephrine therapy with up to 0.3 µg/kg/min to guarantee cerebral perfusion pressure. With the normalization of heart rate and blood pressure the infant had very low HRV. After weaning from epinephrine and hypothermia HRV increase to normal values slightly higher than the unaffected brother (twin 1). Both twins had a normal neurological development and today - 6 years later- twin 2 have no residual neurologic damage.

Single measurements of HRV at 12 hours, 24 hours and 48 hours as proposed in the most clinical trials would indicate a severe hypoxic ischemic encephalopathy according to the extremely low HRV. HRV analysis is a very useful tool to analyze the heart-brain-interaction and to understand the heart and the brain as well.

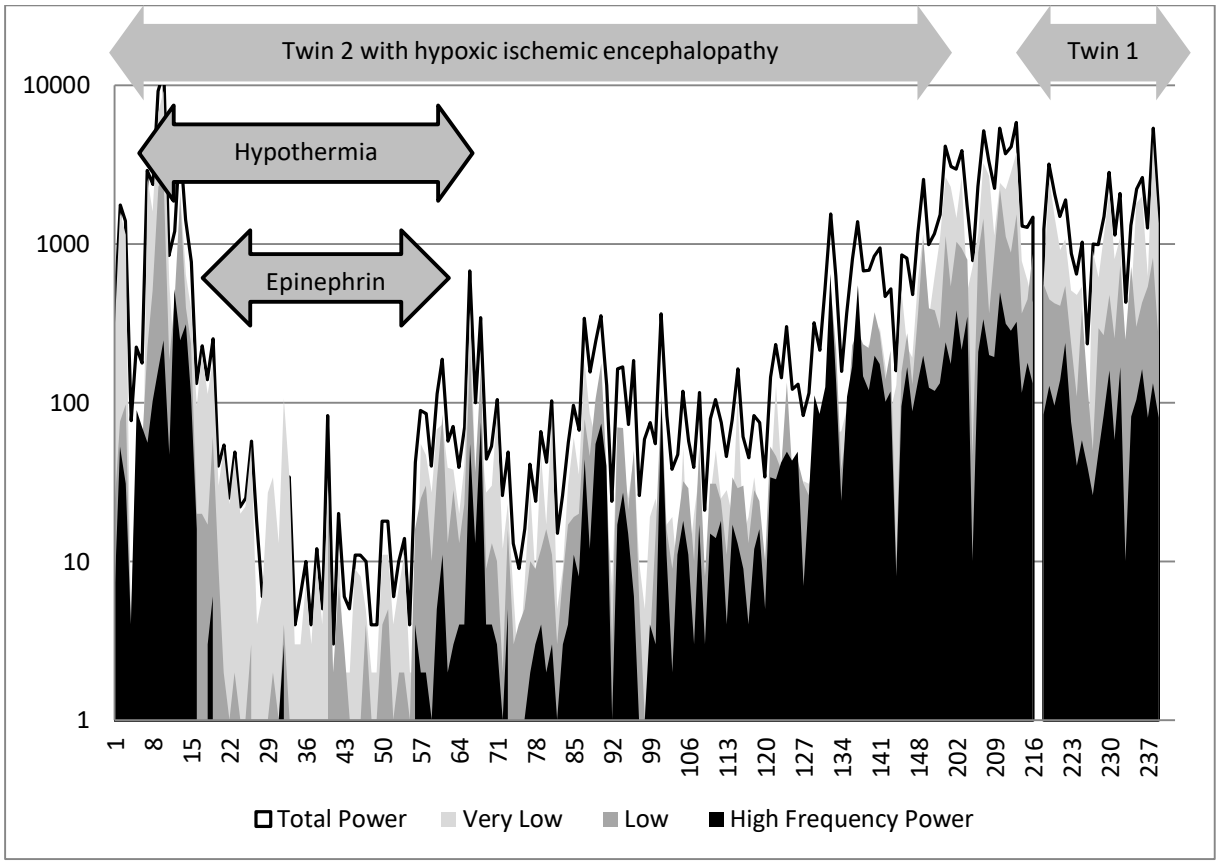

Fig. 3: Hourly values of spectral analysis of twin 2 with hypoxic ischemic encephalopathy treated with hypothermia and epinephrine. The outcome is compared to the healthy twin 1 at the end of therapy

We analyze the association between heart rate variability and outcome in 12 newborns with hypoxic ischemic encephalopathy who progressed to brain death compared to those who survived. The data - illustrated in table 2 – indicate a severe hypoxia with very low cord blood pH's around 6.9, low base excesses around (-) 20 and very low APGAR scores until minute 10 despite professional resuscitation. However, HRV analysis from monitor data in figure 4 clearly demonstrate the recovery of HRV in infants who had a

Copyright 2020 KEI Journals. All Rights Reserved

perfect outcome at day 3 (after hypothermia was stopped in 5 infants) but remained extremely low over one week in infants who died.

Table 2: Hypoxic ischemic encephalopathy and outcome

	Death	**Perfect Outcome**
Patients [N]	6	6
Gestational Age [weeks]	37.8 ± 3.1	40.0 ± 0.6
Birth Weight [g]	3295 ± 277	3255 ± 746
Cord blood pH	6.9 ± 0.1	6.9 ± 0.2
Base Excess	(-)21.5 ± 11.1	(-)17.2 ± 11.1
APGAR Score		
1 minute	2.2 ± 1.9	1.2 ± 1.6
5 minutes	3.2 ± 2.8	2.8 ± 1.5
10 minutes	5.6 ± 2.9	3.5 ± 1.6
Hypothermia [N]	3	5

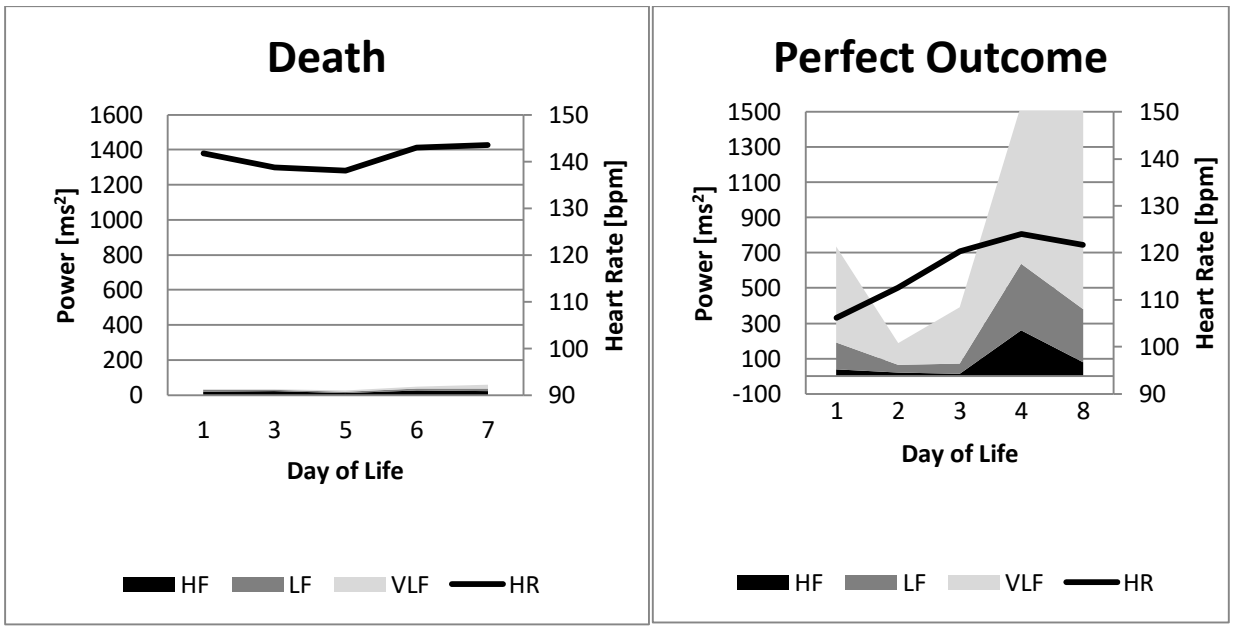

Fig. 4: HRV indicated by the power spectral analysis in infants with hypoxic ischemic encephalopathy who died or had a complete recovery

Copyright 2020 KEI Journals. All Rights Reserved

3 Neurodevelopment after Critical Illness in Infancy

3.1 Heart Failure, Prematurity and HRV

Preterm birth is a significant public health concern: The United States preterm birth rate rose 1% in 2017 to 9.93% of all births, from 9.85% in 2016 [15]. Survival improved most of all in infants born after 23 weeks post-menstrual age; however, the long-term neurodevelopmental outcomes of these infants remains a concern [16]. Data from United States show that 70–88% of very preterm infants will receive early intervention services to optimize their development [17] but many preterm still suffer significant neurodevelopment deficits: In summary preterm birth and/or low birthweight accounts for 55% for cerebral palsy, 10%-20% for autism spectrum disorder, and other developmental delay, and less than 5% for attention deficit hyperactivity disorder and behavioral-conduct disorders [18].

Cerebral hypoxia has been associated with neurodevelopment impairment. Many efforts to reduce cerebral hypoxia in extremely preterm infants focused on the monitoring of cerebral oxygen supply. However, using cerebral near-infrared spectroscopy monitoring in preterm infants during the first days of life in a prospective randomized trials (SafeBoosC II) was not associated with long-term benefits with regard to neurodevelopmental outcome [19].

More recently a conceptual model describing the mechanisms of stress-induced neurodevelopmental impairment in preterm infants has been published [20] . This concept is in good accordance with data published by Evans DJ et al in 2001 who showed that elevated norepinephrine levels are associated with adverse outcome in preterm infants [21]. Based upon this concept new therapeutically approaches were developed in animal models to improve early life stress-induced cognitive impairments, and the alterations in hippocampal new cell survival by early diet with low ω-6/ω-3 ratio [22].

Congenital heart disease is a further reason for critical illness in early infancy in up to 0.8 % of livebirth. Survival improved due to early heart surgery but there is a significant burden of neurodevelopmental deficits: Acute neurologic complications in children undergoing congenital heart surgery occur in 1.75% patients in a recent retrospective study and are related to hypoxia, brain bleeding or embolism [23]. The cumulative incidence rates of attention deficit (hyperactivity) disorder and autism spectrum disorder were even higher in children with congenital heart disease than in a control group (4.55 vs. 1.26/1000 person years for attention deficit hyperactivity disorder and 0.99 vs.0.2/1000 person-years for autism spectrum disorder)[24].

We now compare the data of infants with congenital heart disease with published data about the neurologic outcome of infants after premature birth to estimate the predictive value of early HRV analysis on neurodevelopment outcome.

3.1.1 Norepinephrine plasma levels and HRV in infants after preterm birth and congenital heart disease

Evans DJ et al who showed that elevated norepinephrine levels are associated with adverse outcome in preterm infants in 2001 [21]. Figure 5 shows the norepinephrine levels of preterm infants stratified for the outcome data assessed at 4-5 years of life. Those infants who died or suffer from disabilities had significantly higher norepinephrine plasma level at the first day of

Copyright 2020 KEI Journals. All Rights Reserved

life (1011 ± 300 ng/l). The author proposed a norepinephrine cut off plasma level of 1530 ng/l to estimate a worse outcome in preterm infants [21]. Norepinephrine levels of preterm infants with a favorable outcome are in the high normal level (629 ± 80 ng/l) comparable to 126 neonates who need mechanical ventilation (425 ± 250 ng/l) [25]. Our published norepinephrine levels from infants with congenital heart disease without heart failure (560 ± 247 ng/l) are not elevated [1]. In contrast, infants with heart failure have significantly elevated norepinephrine levels (1156 ± 705 ng/l) in a daily life setting that is comparable to the norepinephrine levels immediately after cardiac surgery (1200 ± 700 ng/l) as published by Gruber et al. [26]. A retrospective analysis from 86 of our infants with congenital heart disease treated 20 years ago at the university hospital of Göttingen shows that 15 from 86 infants (17.4 %) had a norepinephrine level in a daily life setting above the proposed cut off value of 1530 ng/l to estimate a worse outcome in preterm infants.

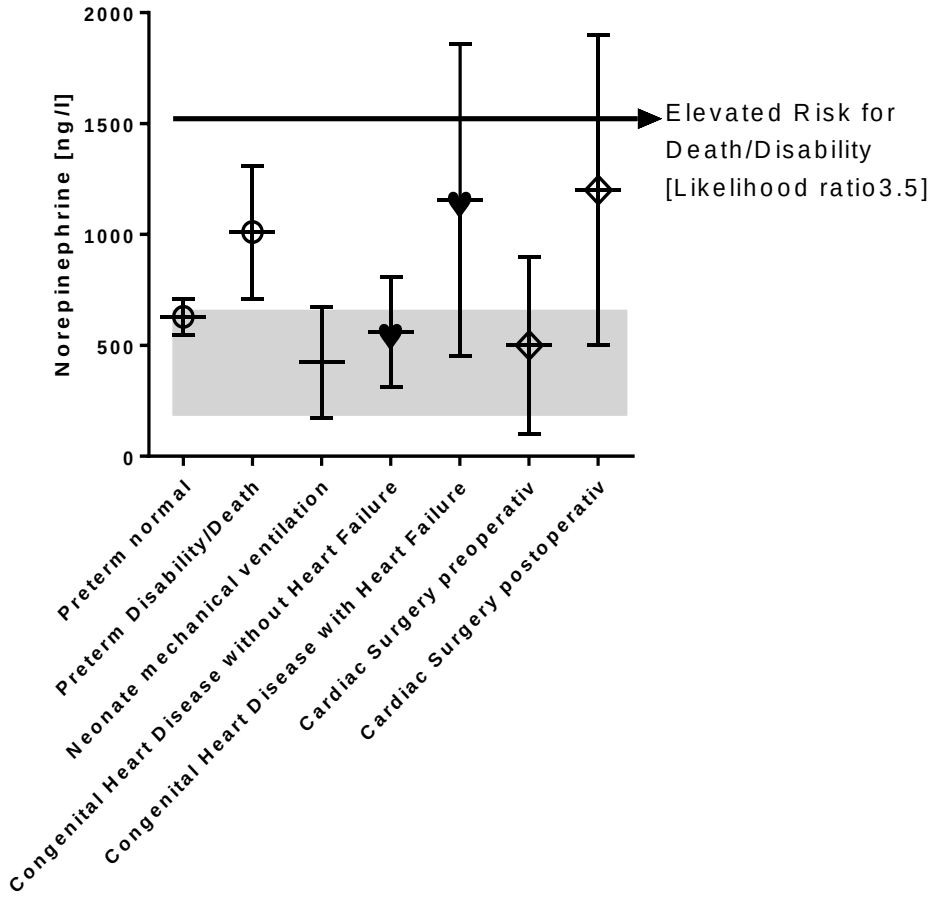

Fig. 5: Norepinephrine plasma level in preterm infants according neurological outcome and infants with congenital heart disease with and without heart failure

Copyright 2020 KEI Journals. All Rights Reserved

3.1.2 24-HRV in infants after preterm birth and congenital heart disease

In contrast to simple heart rate monitoring, 24 hour analysis of heart rate variability (HRV) may differentiate between preterm infants with favorable outcome and those who develop minor neurologic disorder or cerebral palsy [27]. Figure 6 illustrate the HRV parameter rMSSD that indicates vagus activity in preterm infants in comparison to our own published data in infants with congenital heart disease with and without heart failure[1]. Again, the vagus parameter rMSSD in infants with heart failure is significantly decreased as in preterm infants with a worse neurodevelopmental outcome. However, global HRV indicated by the parameter SDNN is enhanced in healthy preterm infants but only significantly reduced in infants who develop heart failure due to congenital heart disease (Figure 7). These data are in accordance with the correlation of HRV and 2-year neurodevelopmental outcome in hypoxic ischemic encephalopathy as published by RM Goulding[28].

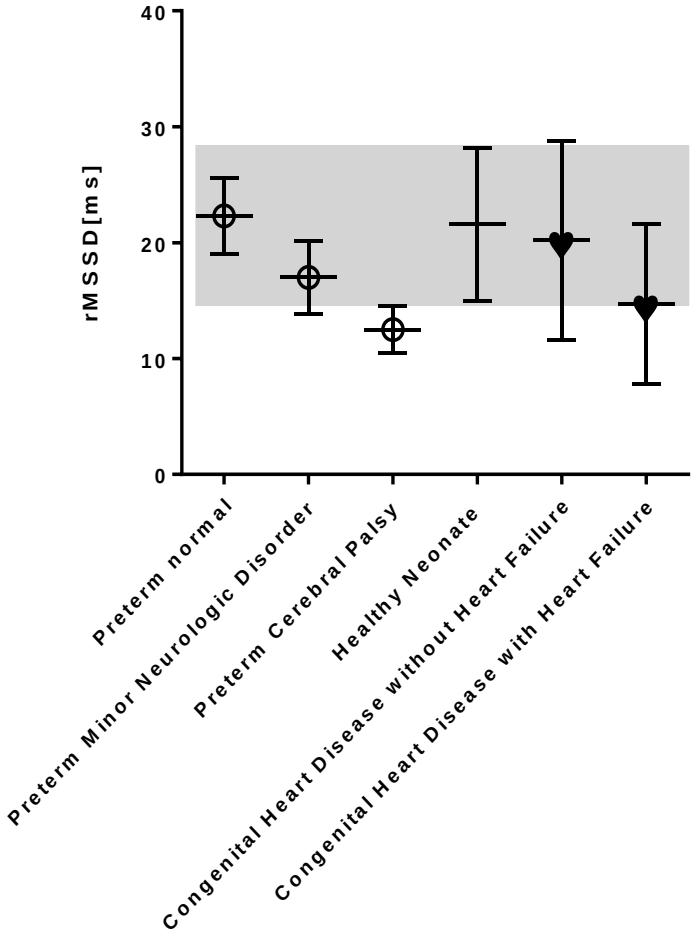

Fig. 6: 24 hours HRV indicated by the vagus parameter rMSSD in preterms according neurological outcome and infants with congenital heart disease according heart failure

Copyright 2020 KEI Journals. All Rights Reserved

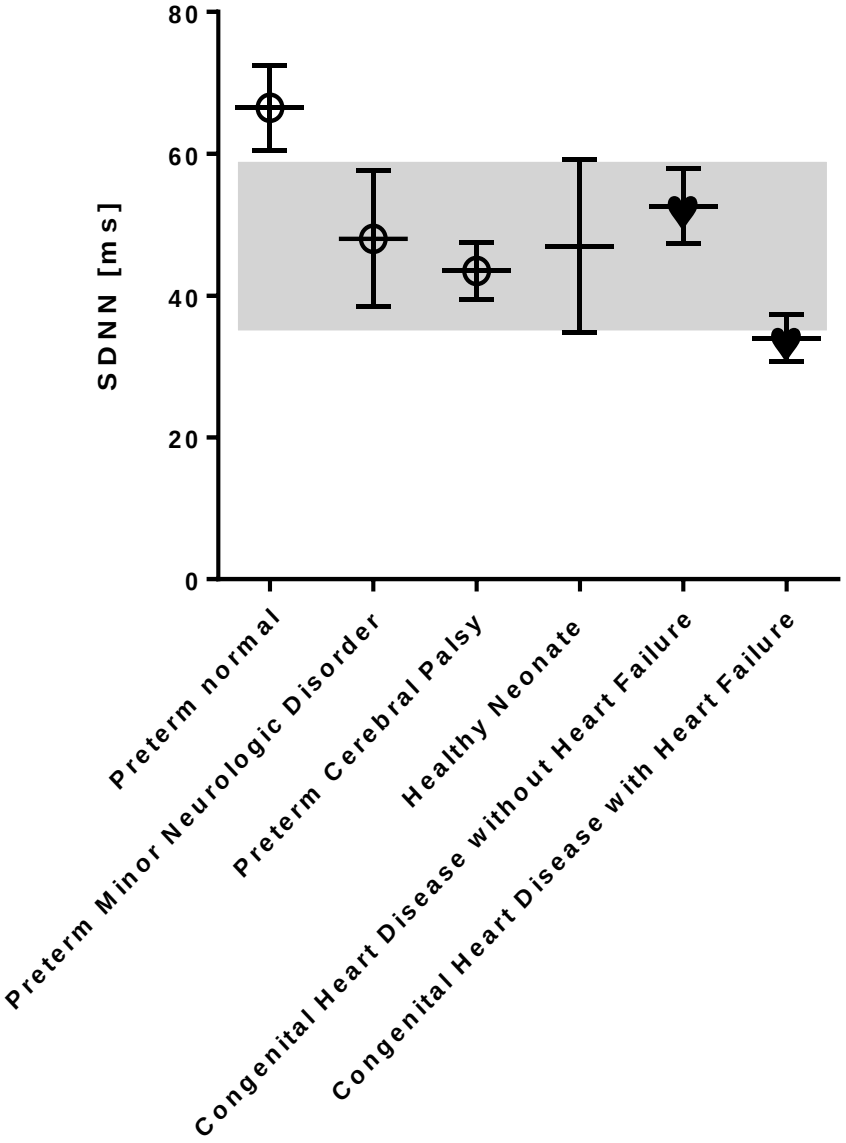

Fig. 7: 24 hours global HRV indicated by the parameter SDNN in preterms according neurological outcome and infants with congenital heart disease with and without heart failure

3.2 Magnet Resonance Imaging and Neurocognitive Impairment

Recent cerebral MRI scans using voxel-based cortical thickness and morphometry analysis showing brain volume reductions that correlated significantly with cognitive, motor and executive functions (grey matter: $p < 0.05$, white matter: $p < 0.01$) [29]. If these changes are almost found in preoperative MRI evidence suggests that brain maturation can be delayed in infants with congenital heart disease similar to those in premature newborns [30] and after ECMO therapy [31]. Surgical closure of patent ductus arteriosus in preterm is related to attention deficit/hyperactivity disorder and neurodevelopment impairment closing the link between heart failure, prematurity and neurodevelopment [32]. These changes

Copyright 2020 KEI Journals. All Rights Reserved

persist in later life and show significant correlation with the neurodevelopmental outcome [33]. However reduced brain volumes of the hippocampus, caudate, putamen, thalamus, insula and prefrontal cortex are also shown in adults with heart failure [34, 35]. Furthermore such brain "injuries" were also shown in children with attention deficit hyperactivity disorder [36] and children with low birth weight due to small for gestational age syndrome [37]. Most of these brain structures are parts of the so called central autonomic network and limbic system. Wei L et al found associations of the putamen, caudate, insula, and hippocampus with heart rate variability [38].

Table 3: MRI scans using voxel-based cortical thickness and morphometry

	Congenital Heart Disease	**Adult Heart Failure**	**SGA**	**Preterm**	**ADHD**	**HRV**
Caudate	+	+	+	+	+	+
Putamen	+	+	+	+	+	+
Glob Pallidum		+		+	+	
Thalamus	+	+	+	+	+	
Hippocampus	+	+				+
Amygdala						+
Cortex						
Cingula		+		+	+	+
Insula	+	+		+		+
Prefrontal	+	+	+	+		+
Occipital	+			+		
Parietal		+	+	+		
Temporal	+		+	+		+
Para hippocampal	+	+				+
Post central	+					
Pre central	+					

+ indicates morphological abnormalities
SGA: small for gestational age; ADHD: attention deficit disorder; HRV: heart rate variability

4 The Concept of Autonomic Imprinting by Early Life Stress

Recently we published our early life stress model to explain growth failure in children with growth hormone deficiency (GHD) and small for gestational age (SGA). In these children growth failure is related to α2-adrenoreceptor sub sensitivity, measured by heart rate variability (HRV) analysis during clonidine testing for growth hormone stimulation [39]. The methodological fundament of our pathophysiological approach to evaluate the autonomic nervous system is deducted from HRV. Moreover,

Copyright 2020 KEI Journals. All Rights Reserved

HRV analysis is a very useful tool for cardiovascular risk stratification [40].

The environmental conditions that are experienced in early life can profoundly influence human biology and long-term health. Early-life nutrition and stress are among the best documented examples of such conditions because they influence the adult risk of metabolic disease, such as diabetes mellitus and cardiovascular disease.

To investigate the effect of early life stress - e.g. due to heart failure and intra uterine growth retardation - we measured autonomic function in later life in a group of small children with height below the third percentile. Compared to the healthy control group HRV is reduced on average in a group of 101 children with short stature [6]. Low HRV correlates to groups of children born small for gestational age (SGA), children with cardiac growth failure and children with congenital syndromes, but not to those with constitutional growth delay (CGD), who had normal HRV. Reduced HRV indicated by lower rMSSD (Figure 8) and HF-Power is indicating reduced vagal activity as a sign of autonomic dysfunction.

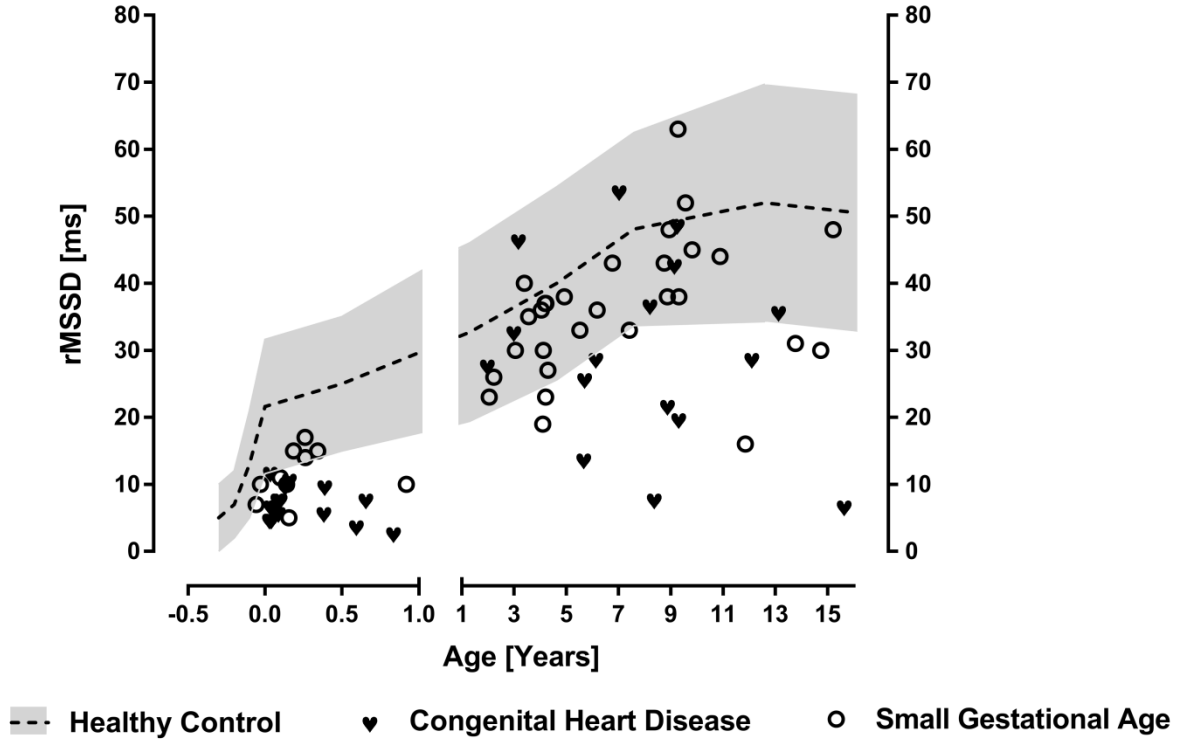

Fig. 8: Mean-24 hours vagus activity indicated by the parameter rMSSD in children with short stature due to intrauterine growth restriction and congenital heart disease

These high-risk children are allocated in the groups with an adverse autonomic imprinting in utero or infancy. In accordance with Barker's hypothesis our data indicate that birth weight is an important predictor for autonomic dysfunction in later life. However other indicators for early life stress like genetic disease, heart failure and probably inflammation have at least a similar impact on autonomic imprinting. As previously published NT-Pro-BNP seems to be a marker of early life stress and failure to thrive [41] not only in infants with heart failure [42] but

Copyright 2020 KEI Journals. All Rights Reserved

also in infants with small gestational age at birth [43].

As shown in figure 8 infants with early life stress due to heart failure or SGA have reduced rMSSD in infancy and many of these children have low rMSSD values in later life.

We assume a mechanism called "autonomic imprinting" to explain concordant effects of nutrition and stress on growth, and neurodevelopment. We use the term imprinting from the so-called term metabolic imprinting that describes the basic biological phenomenon that putatively underlies relations between nutritional experiences during early life and later diseases. The term is intended to encompass adaptive responses to specific nutritional conditions early in life that are characterized by:

1. a susceptibility limited to a critical ontogenetic window early in development (the critical period)
2. a persistent effect lasting through adulthood (autonomic disorder)
3. a specific and measurable outcome (height, cognition, cardiovascular disease), and
4. A dose-response or threshold relation between a specific exposure and outcome.

Although previous workers have used the term programming to refer to the long-lasting effects of early nutritional experiences, imprinting more effectively conveys the salient features detailed in the first 2 parts of the definition [44]. There is a clear historical precedent for this term: Konrad Lorenz chose imprinting to refer to the setting of certain animalistic behavior that resulted from early experience. Central to his definition was the fact that imprinting may only occur during "a narrowly defined period in the individual's life" (the critical period), moreover that the imprinted behavior cannot be 'forgotten'.

We assume different critical periods in early life for autonomic imprinting:

1. Genomic imprinting is the epigenetic phenomenon in many congenital syndromes. Certain genes are expressed in a parent-of-origin-specific manner. If the allele inherited from the father is imprinted, it is thereby silenced, and only the allele from the mother is expressed and vice versa. Genomic imprinting is a rare phenomenon in mammals; most genes are not imprinted.
2. Gestational imprinting mainly by fetal malnutrition results in a baby small for gestational age. Barker was the first who used the term fetal programming in his hypothesis [45].
3. Neonatal imprinting during the first 4 weeks of life occurs mostly due to severe disease like premature birth or feeding problems.
4. Infant imprinting during the first year of life is greatly due to severe disease like heart failure. Preoperative heart failure is one of the most stressful life events in infancy and has been neglected as a well-defined early life stress model with longtime consequence like growth failure and attention deficit disorder. We use this model owing to the fact that in most infants stress is limited to a well-defined time period and is terminated by an operative procedure at a distinct time point (predominantly with an age of approximately 6 month in heart defects with left-to-right shunts).
5. Childhood imprinting during early childhood due to severe disease, neglect, trauma, and abuse.
6. We are fortunate to have only a small number of children with short stature owing to starvation in Germany. However, in 2010, 171 million children under 5 years of age were estimated to be stunted globally, with 98% being from low- and middle-income countries. Weight gain in the first two years of life is an important predictor of schooling outcomes in pooled analyses from five birth cohorts in these countries [46]. The

Copyright 2020 KEI Journals. All Rights Reserved

understanding of child growth patterns is critical to the development and evaluation of appropriate interventions.

By understanding autonomic imprinting, we are aware of the detrimental longtime effects of early life stress on cognition, growth, and cardiovascular risk. Improving care and nutrition for mothers and children within the first 1000 days after conception is one of the most promising public health policies.

4.1 Autonomic Imprinting, Short Stature, and Neurodevelopment

Growth is the single best global indicator of a child's well-being, and growth impairment has both short and long-term consequences. There is strong evidence demonstrating, that poor growth is associated with delayed mental development, and that there is a relationship between impaired growth status and both poor school performance and reduced intellectual achievement [46]. Moreover, the inverse association between height and ischemic heart disease has been studied extensively over the last six decades. Genetic conditions seem to be of minor importance for individual growth. Stature-associated polymorphism analysis using genome-wide data from 253,288 individuals has identified 697 variants at a genome-wide significance that together explained one-fifth of the heritability for adult height [47]. Epigenetic heredity thus appears to be a further important determinant of adult height [48]. Modulation of DNA methylation is a candidate to mediate environmental influence on epigenetic traits. Human height is one of the best-defined phenotypes and growth failure seems to be a model for imprinting, probably due to epigenetic mechanisms.

Autonomic imbalance measured by HRV is a predictor of metabolic risk, cardiovascular disease, diabetes and early mortality [40]. We now clearly demonstrate a significant autonomic imbalance in children with short stature due to a history of small for gestational age, congenital syndromes, and congenital heart disease (table 4+5). These children have a well-known enhanced cardiovascular risk. Moreover, our data clearly indicate that short stature per se is not a factor for an autonomic imbalance or stress disease as shown in 25 children with constitutional growth delay. Our data are in good accordance with studies that show ‘short stature’ as an isolated physical characteristic which appears to hold little value as a predictor of the individual’s psychological adaption or quality of life [49]. The impression of an association between short stature and psychological maladjustment has been based largely upon methodologically weak studies that have typically confounded short stature with other medical and neurocognitive features associated with complex medical conditions due to the underlying diseases. To avoid the unwarranted medicalizing of ‘healthy short stature’, clinicians should incorporate factors beyond auxiology in the decision –making algorithm when selecting and preparing patients for possible growth-promoting therapies.

Our data now deliver the importantly required information about different groups of short children with indications for growth hormone therapy who are at risk to suffer from the underlying disease (small gestational age, congenital syndromes and congenital heart disease [50].

Copyright 2020 KEI Journals. All Rights Reserved

Table 4: Anthropometric data and laboratory of study groups

Parameter	Healthy Control	All GF	CGD	SGA	Cardiac GF	Syndromes	GHD
N	55	101	25	30	10	17	11
Age [years]	7.5 ± 2.1	8.0 ± 4.3	7.8 ± 2.8	7.4 ± 4.1	9.6 ± 5.1[a]	7.8 ± 6.0	7.1 ± 3.1
Height [cm]	125 ± 14	114 ± 23[c]	114 ± 16 [c]	111 ± 22 [c]	121 ± 24	108 ± 31 [c]	110 ± 18[b]
Height SDS	-0.1 ± 0.9	-2.6 ± 0.9	-2.5 ± 0.9	-2.4 ± 0.8	-2.5 ± 1.0	-3.2 ± 1.2	-2.5 ± 0.6
Weight [kg]	38.8 ± 21.4	38.1 ± 3.2	38.3 ± 2.3	36.6 ± 3.7	40.7 ± 0.8	37.7 ± 2.4	40.2 ± 3.3
BMI [%]	38.3 ± 22.5	34.2 ± 28.8	37.8 ± 25.6	33.6 ± 30.7	17.7 ± 21.8[b]	34.5 ± 40.6	32.5 ± 21.6
Data without statistical analysis of cause missing data in the healthy control group (Given data from literature)							
Birthweight [g]	> 2500	2696 ± 855	3032 ± 776	2014 ± 699	3207 ± 454	2514 ± 639	3434 ± 594
GA [weeks]	37 - 41	38.1 ± 3.1	38.3 ± 2.3	36.6 ± 3.7	40.6 ± 0.8	37.7 ± 2.4	40.1 ± 3.3
IgF1 [ng/ml]	50 -350	89 ± 59	80 ± 39	96 ± 74	67 ± 43	74 ± 13	103 ± 74
IgFPB3 [ng/ml]	1100 - 8000	3029 ± 1093	3028 ± 1103	3135 ± 887	2720 ± 1570	3079 ± 1658	2996 ± 1222
NT- BNP [pg/ml]	52 (10 – 157)	182 ± 197	86 ± 60	166 ± 156	405 ± 338	108 ± 70	159 ± 137

GF=Growth Failure; CGD=Constitutional Growth Delay; SGA=Small for Gestational Age; GHD= Growth Hormone Deficieny; GA=Gestational Age; IgF=Insulin like growth factor

T-test between healthy control and patient groups: [a] P-value < 0.005; [b] P-value < 0.001; [c] P-value < 0.0001

Table 5: 24-hour HRV analysis of study groups

Parameter	Healthy Control	All GF	CGD	SGA	Cardiac GF	Syndromes	GHD
N	**55**	**101**	**25**	**30**	**10**	**17**	**11**
Heart Rate [bpm]	90.1 ± 8.4	95.7 ± 14,2[b]	92.6 ± 9.1	97.3 ± 10.8[c]	90.5 ± 19.9	104.9 ± 20.1[c]	92.6 ± 9.1
SDNN [ms]	142 ± 36	123 ± 43[b]	136 ± 23	124 ± 28[a]	125 ± 90	98 ± 42[d]	110 ± 20[b]
RMSSD [ms]	42.5 ± 10.9	35.3 ± 12.2[c]	39.5 ± 10.4	35.7 ± 10.1[b]	24.6 ± 12.9[c]	30.8 ± 14.9[b]	39.5 ± 10.4
Frequencey Domaine Analysis							
TP [ms^2]	4857 ± 2237	3858 ± 2553[a]	4224 ± 1869	4256 ± 2370	3464 ± 4452	2881 ± 2687[b]	3523 ± 1442
VLF [ms^2]	2692 ± 1589	2190 ± 1849	2284 ± 1232	2458 ± 1782	2414 ± 3627	1554 ± 1539[a]	1759 ± 760
LF [ms^2]	1284 ± 581	1002 ± 612[b]	1122 ± 512	1097 ± 555	752 ± 783[a]	825 ± 792[a]	987 ± 553
HF [ms^2]	775 ± 301	577 ± 335[c]	719 ± 326	599 ± 326[a]	249 ± 155[c]	416 ± 388[c]	686 ± 238

Copyright 2020 KEI Journals. All Rights Reserved

HF/LF	0.65 ± 0.22	0.63 ± 0.28	0.69 ± 0.28	0.58 ± 0.24	0.5 ± 0.31	0.47 ± 0.17[b]	0.81 ± 0.35

GF=Growth Failure; CGD=Constitutional Growth Delay; SGA=Small for Gestational Age; GHD= Growth Hormone Deficieny

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; TP: Total Power VLF: Very low frequency power; LF: Low frequency power HF: High frequency power; HF/LF: Ratio HF to LF

T-test between healthy control and patient groups: [a] P-value < 0.005; [b] P-value < 0.001; [c] P-value < 0.0001

4.2 Attention Deficit Disorder and Learning Difficulties

There was a remarkably high number of children with short stature who suffered from additional diagnosis of ADHD (23.8% in our study group). Statistical subgroup analysis showed no significant difference between short children according to the diagnosis of ADHD or concomitant treatment with methylphenidate (figure 9).

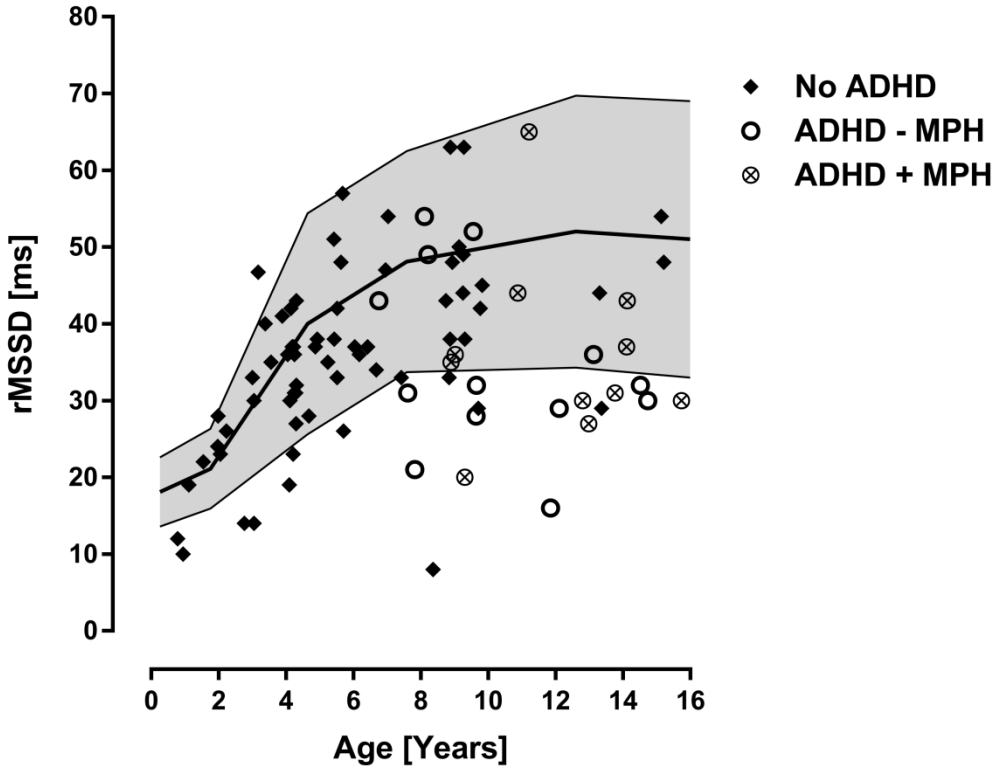

Fig. 9: Vagus activity indicated by the paramter rMSSD in children with short stature. Children with ADHD treated or untreated with methylphenidate (MPH)

Children receiving methylphenidate (MPH) for AD(H)D are seen by pediatric cardiologists on a routine basis due to the potential risk of cardiac arrhythmias. Since

Copyright 2020 KEI Journals. All Rights Reserved

2005, we added 24-hour ECG to the routine diagnostics consisting of ECG, measurement of blood pressure and echocardiography. The systematic analysis of the heart rate variability of 12 patients before MPH therapy and 19 patients of the same age group under MPH treatment revealed in 2010 surprising unequivocal results [51]: Compared to healthy control patients, children with AD(H)D with or without MPH treatment have a higher mean heart rate, lower sNN50 values likewise the RMSSD values indicated lower vagus activity (table 6.). The circadian analysis of the HRV showed an extensive reduction of circadian vagal activity measured as sNN50 in children with AD(H)D prior to MPH therapy (Figure 10).

Table 6: HRV Data from children with AD(H)D before and after treating with methylphenidate (MPH)

	Healthy Control	**ADHD - MPH**	**ADHD + MPH**
N	19	12	
Age [years]	10.8 ± 3.5	10.8 ± 2.0	10.6 ± 2.8
Height [cm]	145 ± 19	143 ± 15	141 ± 15
Bodyweight [kg]	40 ± 14	35 ± 10	34 ± 10
BMI [kg/m2]	18 ± 3	17 ± 2	17 ± 2
Mean Heart Rate [bpm]	85 ± 10	94 ± 9**	90 ± 8*
Minimal Heart Rate [bpm]	58 ± 7	64 ± 9*	58 ± 5
Maximale Heart Rate [bpm]	158 ± 25	177 ± 16*	171 ± 17*
pNN50 [%] (vagus activity)	21.5 ± 9.0	6.5 ± 2.7***	14.2 ± 6.9**
RMSSD [ms] (vagus activity)	44 ± 10	26 ± 4***	37 ± 8**
SDNN [ms] (global HRV)	146 ± 30	136 ± 41	151 ± 24

Data are shown as mean ± standard deviation;

*P-Value < 0.05; ** P- Value < 0.01; ***P- Value < 0.001

Copyright 2020 KEI Journals. All Rights Reserved

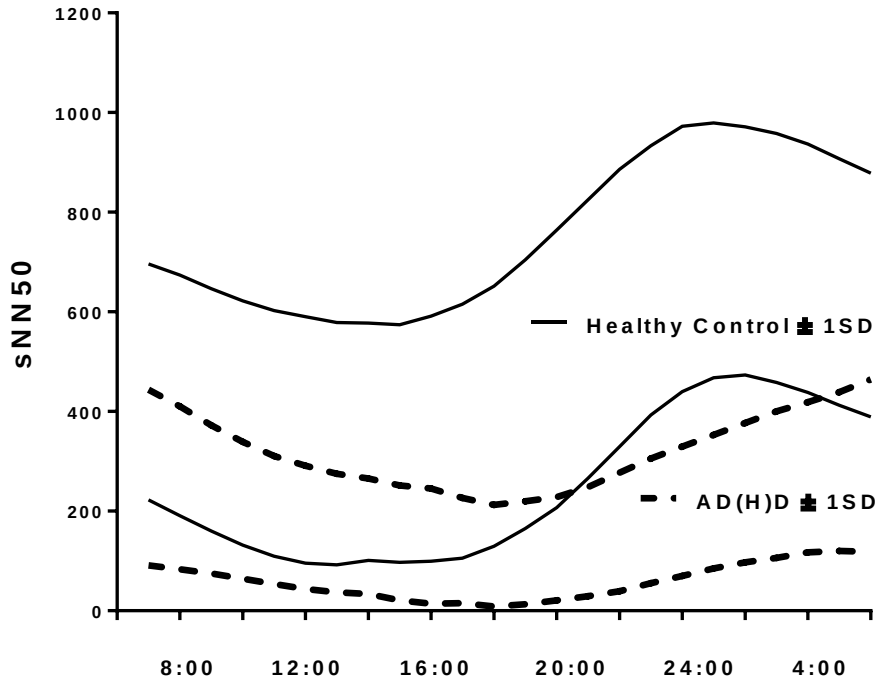

Fig. 10.: Circadian rhythm of vagus activity indicated by the parameter sNN50 in healthy children and children with AD(H)D prior to medical therapy

To investigate heart rate variability in children with respect to their school success we compare the 24 hour HRV data from 14 unselected students of the local high school with the data of 13 unselected children of a local school for children with learning difficulties. As shown in table 7, the age is comparable, but the body mass index is higher in children with learning difficulties due to the higher incidence of obesity in this group. There is a significantly higher HRV in high school students within the normal range and significantly reduced values for SDNN and vagus activity indicated by rMSSD in children with learning difficulties (Figure 11). These data are comparable to untreated children with AD(H)D and it may be that some of their learning difficulties are related to untreated AD(H)D.

Copyright 2020 KEI Journals. All Rights Reserved

Table 7.: HRV data from children according to their school success

	Healthy Control	**High School**	**Learning Difficulties**
N	71	14	13
Age [Years]	12.8 ± 1.7	12.6 ± 1.6	13.0 ± 1.5
BMI [kg/qm]	18.5 ± 2.5	18.9 ± 3.4	25.9 ± 6.1**
Mean Heart Rate [bpm]	81 ± 8	83 ± 7	89 ± 6*
pNN50 [%]	26.4 ± 11.0	25.2 ± 8.9	14.5 ± 9.1**
RMSSD [ms]	46.9 ± 12.5	44 ± 9	33 ± 10**
SDNN [ms]	173.7 ± 44.7	199 ± 44	139 ± 22***

Data are shown as Mean ± SD. Statistical *P < 0.05; ** P < 0.001; ***P < 0.0001

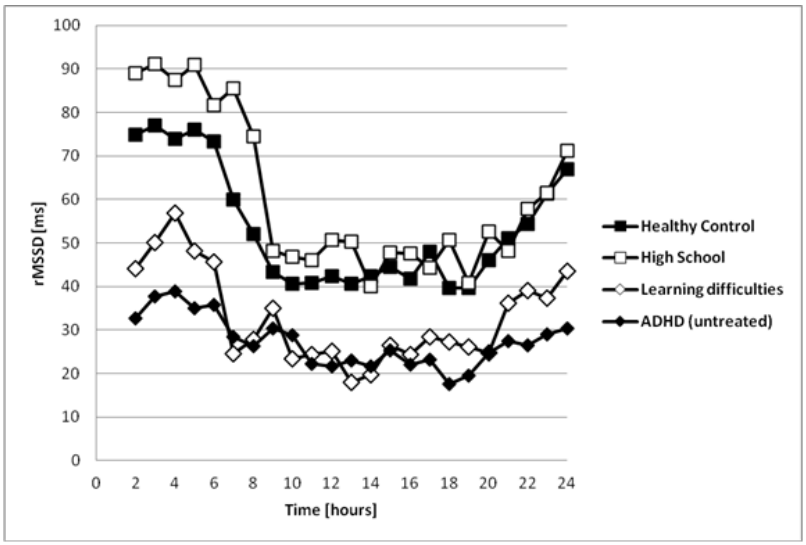

Fig. 11.: 24-hour vagus activity (rMSSD) from 14 unselected students of the local high school with the data of 13 unselected children of a local school for children with learning difficulties. The data of a healthy control group and children with ADHD are included.

Copyright 2020 KEI Journals. All Rights Reserved

4.3 Epilepsy and Sudden Unexpected Death (SUDEP)

Sudden unexpected death in epilepsy (SUDEP) is a tragic event for which the underlying pathophysiology remains poorly understood. There is a link between reduced HRV and SUDEP and HRV is a potential biomarker [52]. More recently, MRI shows that epilepsy is associated with brainstem atrophy that impairs autonomic control and can increase the risk of SUDEP if it expands into the mesencephalon [53].

Figure 12 shows the 10 years HRV monitoring of a boy with generalized tonic-clonic seizures up to his dead at the age of 10.5 years in a palliative setting. The etiology of his seizures and severe mental retardation remains unclear but MR imaging shows progressive brain atrophy that begun in early infancy. If we were aware of the high risk of sudden unexpected death in epilepsy (SUDEP) and the crucial role of autonomic dysfunction in this child, we used 24-hours Holter ECG Monitoring for risk stratification: A total number of 20 Holter ECG's are illustrated in the figure 12 + 13. The most impressive changes concerned the complete loss of HRV indicated by the Fast Fourier Analysis during acute respiratory failure at the age of 5.4 years comparable to the HRV at the end of his life 5 years later. At the time of this "near" SUDEP, he stayed at hospital to change antiepileptic drug therapy because an increasing number of daily generalized tonic-clonic seizures under valproic acid, vigabatrin and phenobarbital. After a prolonged generalized tonic-clonic seizures during intensive care monitoring he developed severe hypopnea and must be intubated without signs of circulatory failure or heart rhythm disturbances. At this time, he was treated with 120mg/kg/d valproic acid, 10mg/kg/d vigabatrin, 2,5mg/kg/d phenobarbital, 5mg/kg/d topiramat and 10µg/kg/d clonidine. Intoxication was excluded by drug monitoring (valproic acid: 51.5µg/ml Phenobarbital: 20.5µg/ml; topiramat: 9.1mg/l; clonidine: <0.1µg/l). Because severe lung failure the boy could be weaned from respirator after one week and he survive without additional neurological problems. After this complication, we treat the boy with 3mg/kg L-Dopa beside antiepileptic drug therapy with valproic acid and phenobarbital. The Holter ECG monitoring showed an impressive increase of HRV over 5 years without a further respiratory failure. We plot the relationship between the global HRV indicated by the parameter SDNN and the circadian heart difference in figure 13. This plot clearly differentiates the data during "near" SUDEP and the last 4 examinations within the last months of his life, generated routine monitoring during palliative care.

Copyright 2020 KEI Journals. All Rights Reserved

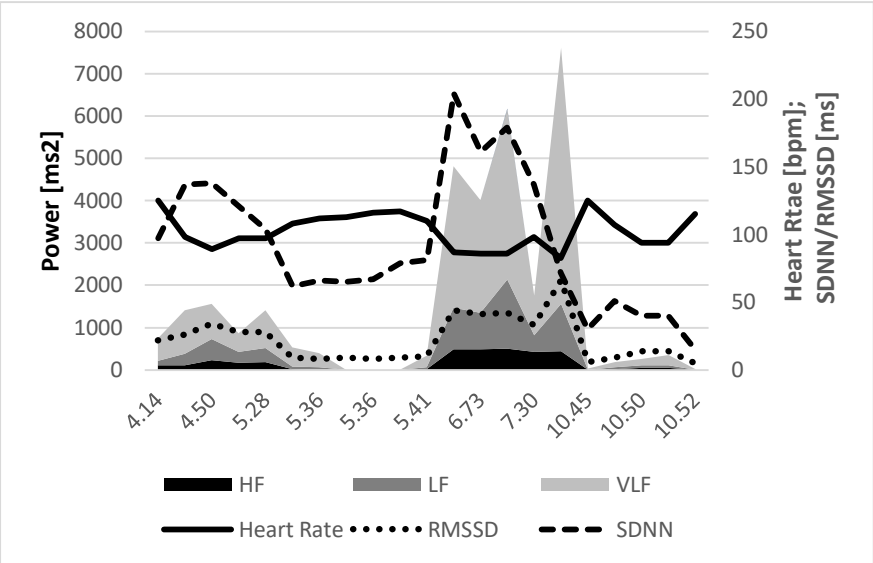

Fig. 12: HRV monitoring of a boy with generalized tonic-clonic seizures up to his dead at the age of 10.5 years. At the age of 5.4 years he develops acute respiratory failure while staying at hospital to change antiepileptic drug therapy. This "near" SUDEP is paralleled by a decline of global HRV indicated by the Fast Fourier analyses and the parameter SDNN as well as the vagus parameter RMSSD.

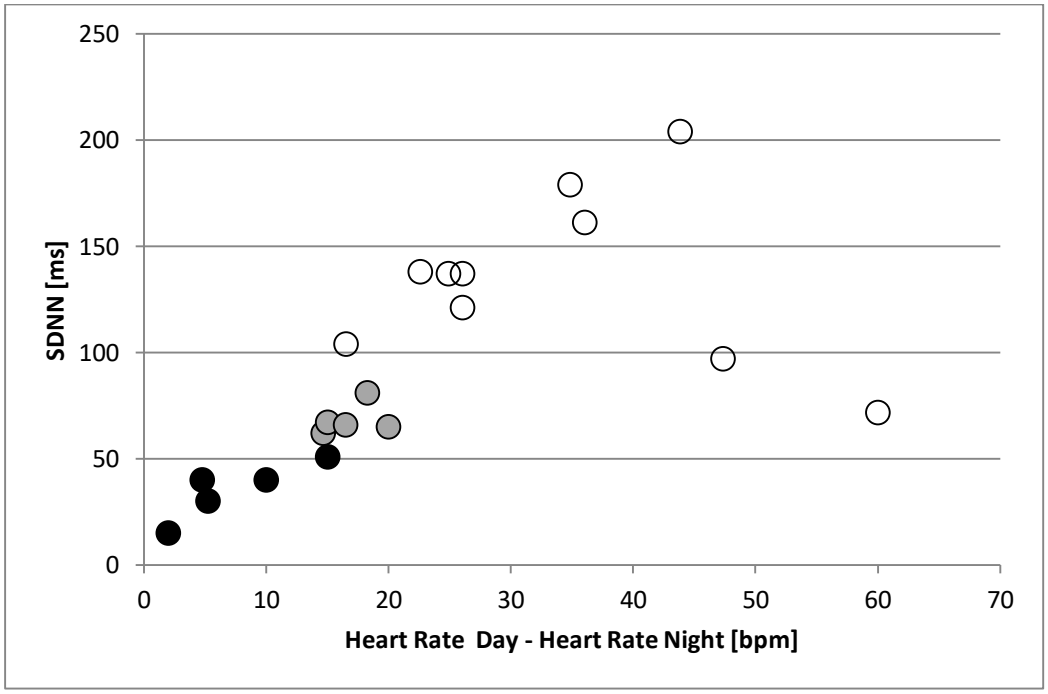

Fig. 13: This plot of the circadian heart rate difference and global HRV parameter SDNN discriminate the acute respiratory failure with 5.4 years (grey circles) and the complete loss of HRV and circadian rhythm at the end of life with 10.5 years (dark circles)

Copyright 2020 KEI Journals. All Rights Reserved

5 Pharmacotherapy

5.1 Effect of Beta-blockers on HRV in Infants with Early Life Stress

Recent placebo-controlled trials have confirmed evidence of β-blockade-induced benefits in heart failure. Several authors reported about corresponding effects of β-blocker therapy on HRV as an evidence for a better sympathetic to parasympathetic balance in these patients with heart failure.

To investigate the effect of beta blockers on HRV in infants with congenital heart disease we analyze three patients' groups comparable in age and hemodynamic relevance of their cardiac lesions. All infants needed cardiac surgery within the first year of life. The 'Digoxin/Diuretics' and 'Propranolol' groups are patients of the CHF-PRO-INFANT trial [54]. Patient of the 'CHD Control' group were excluded from this trial because lesser signs of heart failure. Norepinephrine and renin levels in 'Digoxin/Diuretics' and 'Propranolol' groups were markedly increased in contrast to the 'CHD Control' group.

Heart rate in the 'Digoxin/Diuretics' group was higher in comparison to the 'Propranolol' and 'CHD Control' group that was not significantly different to the 'Healthy Control' (Table 8). Nearly all HRV parameters under 'Digoxin/Diuretics' were significantly reduced. In contrast we observed normal time domain measures in the 'CHD Control' and 'Propranolol' groups.

In conclusion HRV represents a noninvasive parameter that is reduced in infants with congenital heart disease depending on the severity of heart failure and neurohumoral activation. Propranolol but not digoxin therapy effectively reduced the supposed autonomic imbalance in infants with severe heart failure due to congenital heart disease.

Table 8.: Analysis of heart rate variability in infants with heart failure due to left-to-right shunts

	Healthy Control (N = 70)	**CHD Control (N=12)**	**Digoxin/ Diuretics (N = 14)**	**Propranolol (N = 9)**
Baseline characteristics				
Age [month]	2,1 ± 2,7	4,8 ± 3,1	2,6 ± 1,9	3,7 ± 1,7
Ross Score		2,7 ± 2,5	8,0 ± 2,4	2,9 ± 1,8
Norepinephrine [ng/l]	646 ± 238	560 ± 247	1156 ± 705	916 ± 652
Mean RR [msec]	437 ± 40	469 ± 45	445 ± 31	511 ± 48**
SDNN [ms]	57,4 ± 18,9	56,5 ± 16,5	37,4 ± 11,7**	45,0 ± 18,7
pNN50 [%]	2,15 ± 2,76	4,58 ± 4,65	1,56 ± 2,48	8 ± 12,9
rMSSD [ms]	22,1 ± 8,7	20,2 ± 8,6	14,7 ± 6,9**	23,1 ± 14,8

$ Plus-minus values are means ± SD
Results of student-t-test between patient group and healthy control: * p = 0,001 - 0,01; ** p < 0,001

Copyright 2020 KEI Journals. All Rights Reserved

5.2 HRV targeting Therapy in Attention Deficit Disorder

We introduce 24 hour Holter ECG analysis in children with AD(H)D and are now able to show significant changes of heart rate variability in these children prior to psychostimulant treatment [51]. Nearly 10 % of our children had benign ventricular arrhythmias called ventricular parasystole or idioventricular rhythm [55]. We postulate a genuine disturbance of the autonomic nervous system in children with ADHD that may be related to higher cardiovascular risk in these children as shown in adults with emotional disease like depressions [56]. As recently shown we cannot find significant changes of heart rate variability in a meta-analysis of studies using short time HRV [57].

For a better understanding of the impact of psychostimulants on 24-hour heart rate variability in children with attention deficit disorder we illustrate the circadian pattern of heart rate (Fig 14) and vagus activity expressed as RMSSD (Fig. 15). Between 8:00 and 12:00 we clearly observe the expected sympathomimetic effect of methylphenidate (N=19) and more pronounced of atomoxetine (N=5) on heart rate given early in the morning. This effect can be explained by lower vagus activity (RMSSD) and had been demonstrated in all studies with casual heart rate measurements. However, when we analyzed the effect of methylphenidate treatment on 24-h HRV in 19 adolescents, using data based on two Holter ECGs measured across a mean interval of 283 days after starting methylphenidate (N = 11) or stopping an ongoing therapy (N = 8), the mean 24-h heart rate of 91.3 ± 7.5 bpm remained unchanged with methylphenidate treatment at 91.9 ± 8.0 bpm (Table 9)[3]. This surprising result indicates that the well-known heart rate increase after the daytime administration of methylphenidate from 96.0 ± 8.3 to 101.8 ± 10.8 bpm ($p = 0.020$) was completely compensated for by an equal heart rate decrease at night from 86.7 ± 9.7 to 82.4 ± 9.0 bpm. This effect on the circadian heart rate pattern is illustrated in Fig. 14. For cardiovascular risk assessment the increase of heart rate and blood pressure at day may be compensated by lower heart rates and blood pressures at night in methylphenidate treated children. These data may explain that current use of stimulants in children with ADHD was not associated with an increased risk of serious cardiovascular events in a retrospective cohort study involving children and young adults with 2,5 million person-years of follow-up [58, 59].

However, higher heart rates and lower RMSSD at day and night during atomoxetine treatment is a clear indicator of an unfavorable effect of atomoxetine on the cardiovascular risk (Fig. 16+17).

We investigated the immediate effect of clonidine testing for growth hormone stimulation on heart rate variability in 6 children with short stature and ADHD as recently published [39] and found an increase of RMSSD and decrease of heart rate as an indicator for α2- adrenoreceptor responsiveness (Figure 18+19). This effect has been confirmed in 6 children who received guanfacine for ADHD treatment (Figure 20+21). All these children had a contraindication for methylphenidate of cause hypertension or an arrhythmia. Hypertension and the arrhythmia are effectively treated with guanfacine.

Copyright 2020 KEI Journals. All Rights Reserved

Table 9. Methylphenidate (MPH) Treatment and Heart Rate Variability.

Patients (N = 19)	24-h heart rate variability			Day time			Night time		
	Baseline	**MPH**	**p-value**	**Baseline**	**MPH**	**p-value**	**Baseline**	**MPH**	**p-value**
Mean heart rate [bpm]	91.3 ± 7.5	91.9 ± 8.0	0.771	96.0 ± 8.3	101.8 ± 10.8[a]	0.02	86.7 ± 9.7	82.4 ± 9.0	0.081
RMSSD [ms]	32.5 ± 12.50	37.1 ± 17.8	0.053	29.8 ± 10.4	28.2 ± 12.1	0.287	35.1 ± 16.5	45.8 ± 24.3[b]	0.004
pNN50 [%]	11.8 ± 8.4	14.1 ± 9.6	0.106	9.9 ± 6.4	8.7 ± 6.7	0.238	13.7 ± 11.8	19.4 ± 13.3[a]	0.013
Total power [ms²]	3812 ± 2021	4246 ± 2396	0.344	3798 ± 2059	3857 ± 24367	0.887	3811 ± 2393	4640 ± 2545	0.125
VLF power [ms²]	2357 ± 1370	2534 ± 1836	0.631	2437 ± 1444	2425 ± 1957	0.974	2264 ± 1692	2653 ± 1852	0.369
LF power [ms²]	981 ± 608	1165 ± 611	0.060	955 ± 570	1050 ± 571	0.215	1005 ± 677	1278 ± 723[a]	0.04
HF power [ms²]	416 ± 223	490 ± 290	0.195	348 ± 211	330 ± 202	0.607	483 ± 302	647 ± 431	0.069
HF/LF Ratio	0.48 ± 0.27	0.62 ± 0.35	0.968	0.42 ± 0.26	0.41 ± 0.21	0.521	0.81 ± 0.34	0.83 ± 0.38	0.853

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: number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals; TP: total power; VLF: very low-frequency power; LF: low-frequency power; HF: high-frequency power; MPH: methylphenidate treatment

Paired t-test between baseline and methylphenidate treatment:

[a]P-value < 0.05

[b]P-value < 0.01

Copyright 2020 KEI Journals. All Rights Reserved

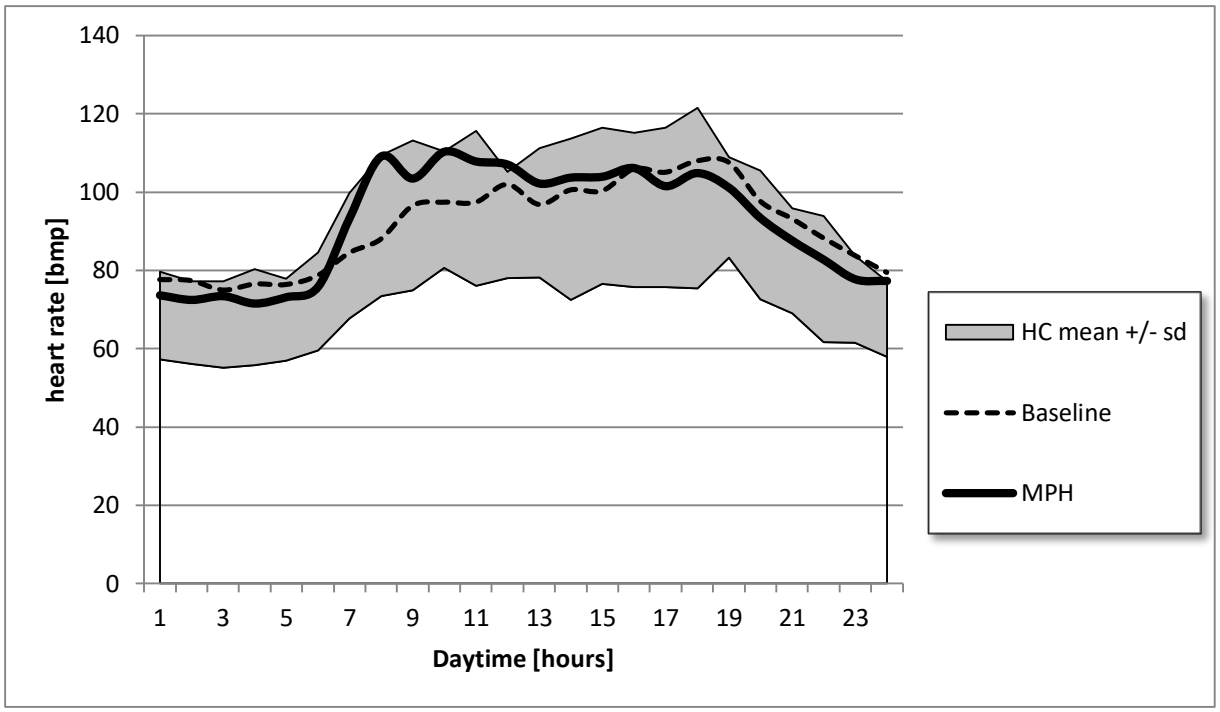

Fig. 14: Circadian Heart Rate in children with ADHD after methylphenidate treatment

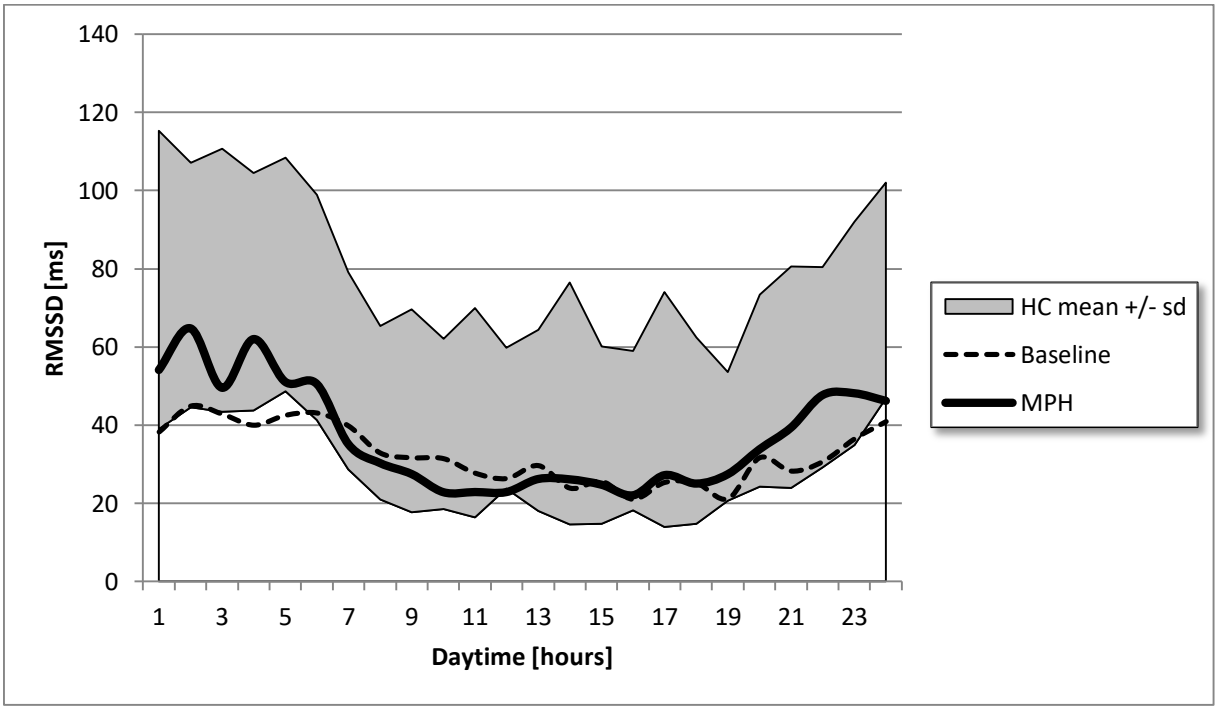

Fig. 15: Circadian rMSSD in children with ADHD after methylphenidate treatment

Copyright 2020 KEI Journals. All Rights Reserved

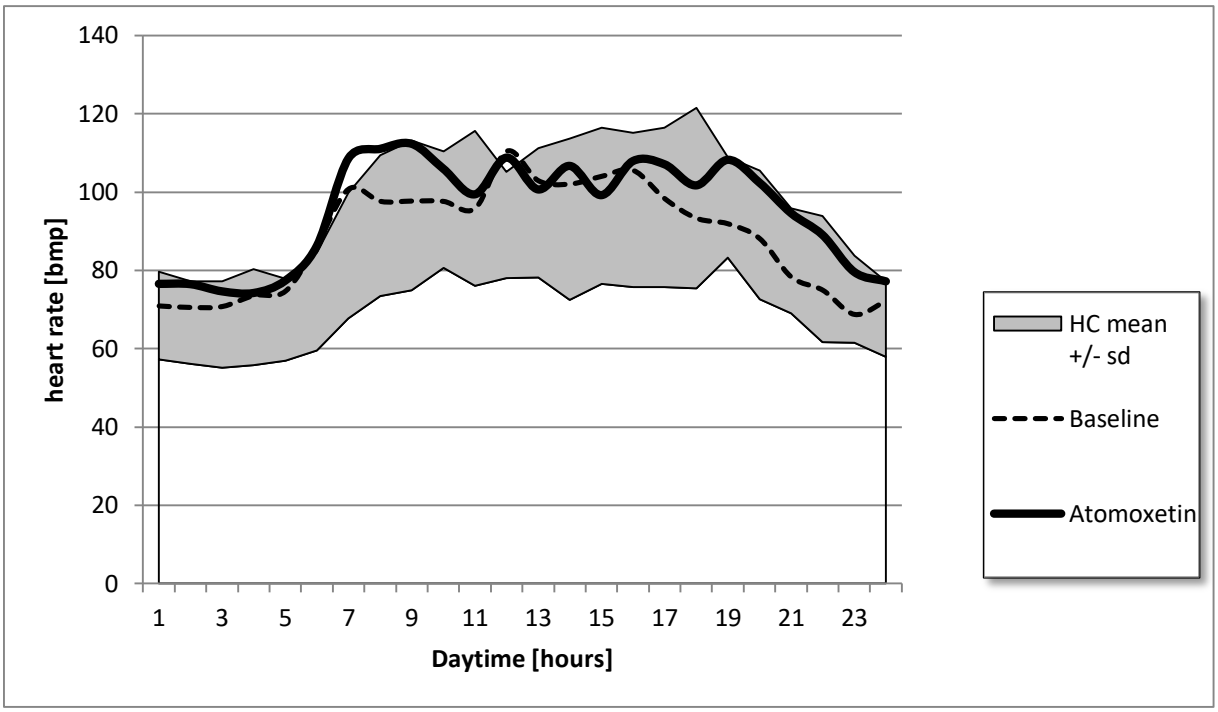

Figure 16: Circadian Heart Rate in children with ADHD after atomoxetine treatment

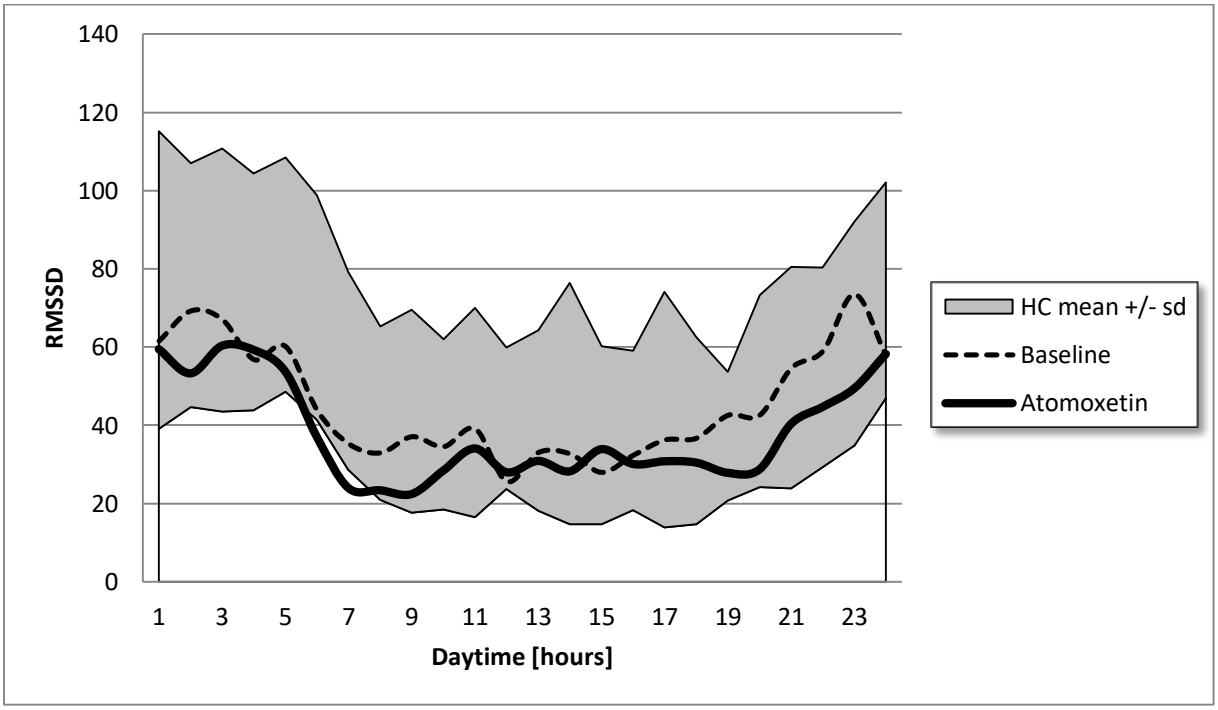

Figure 17: Circadian rMSSD in children with ADHD after atomoxetine treatment

Copyright 2020 KEI Journals. All Rights Reserved

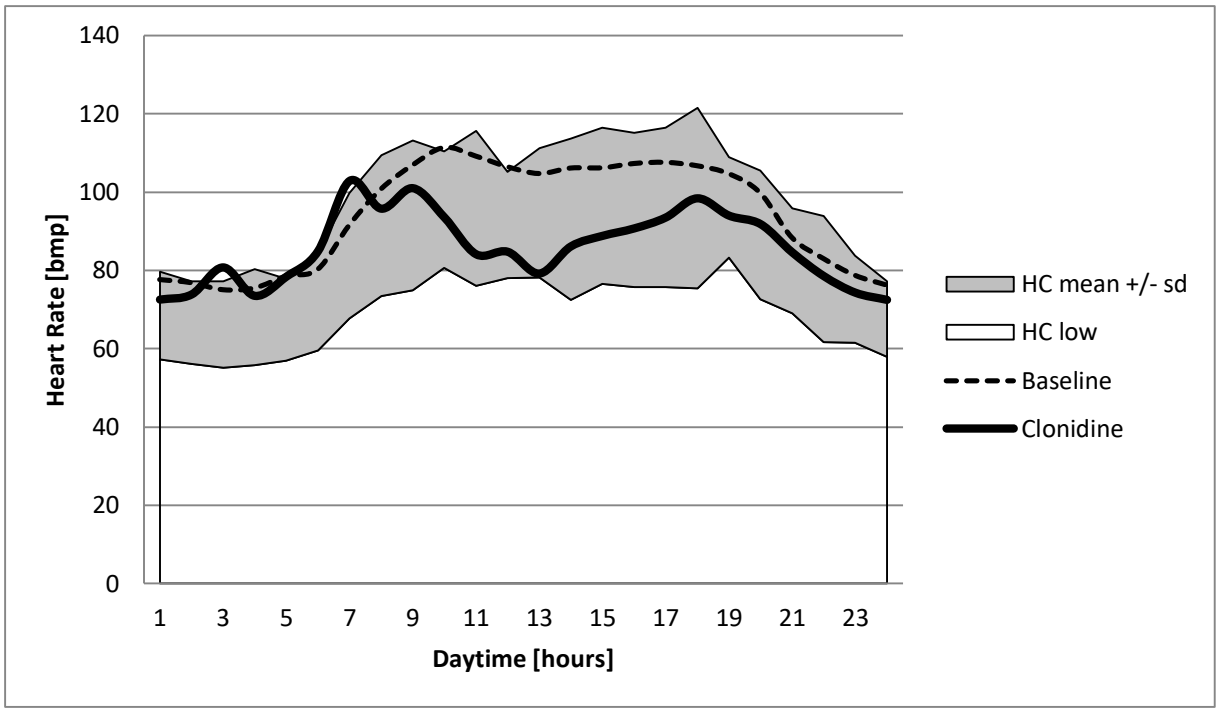

Figure 18: Circadian Heart Rate in children with ADHD after clonidine at 9:00 for growth hormone stimulation

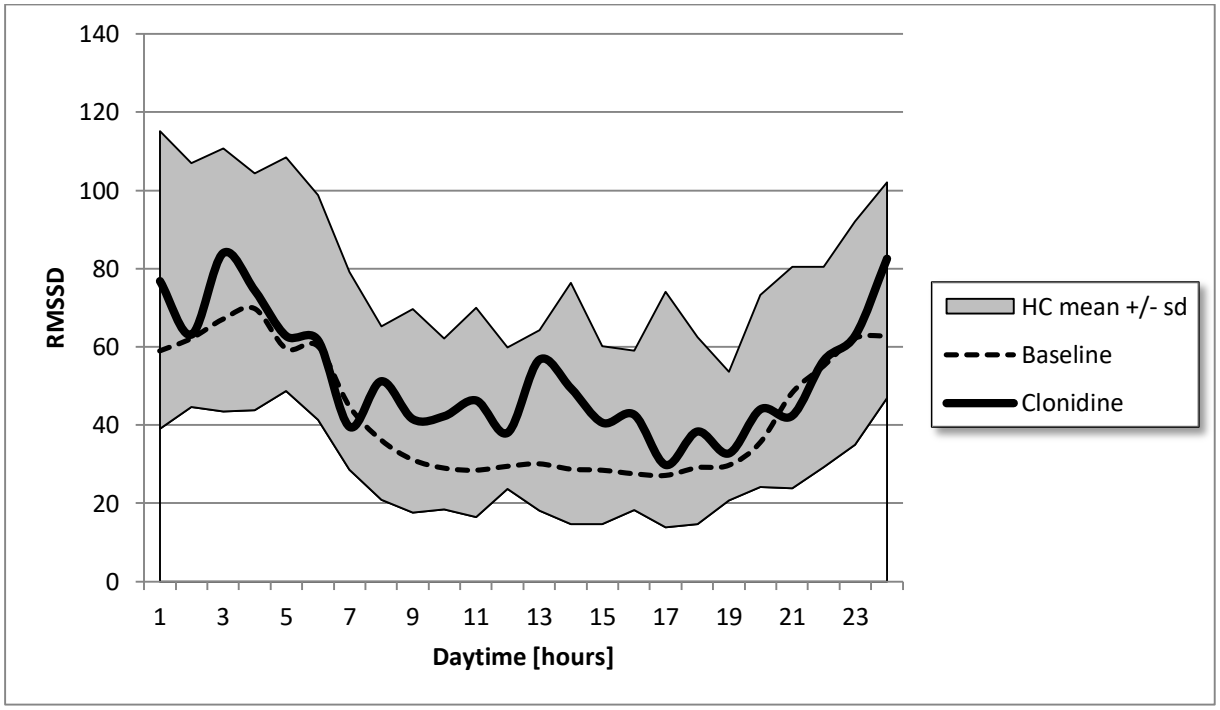

Figure 19: Circadian rMSSD in children with ADHD after clonidine at 9:00 for growth hormone stimulation

Copyright 2020 KEI Journals. All Rights Reserved

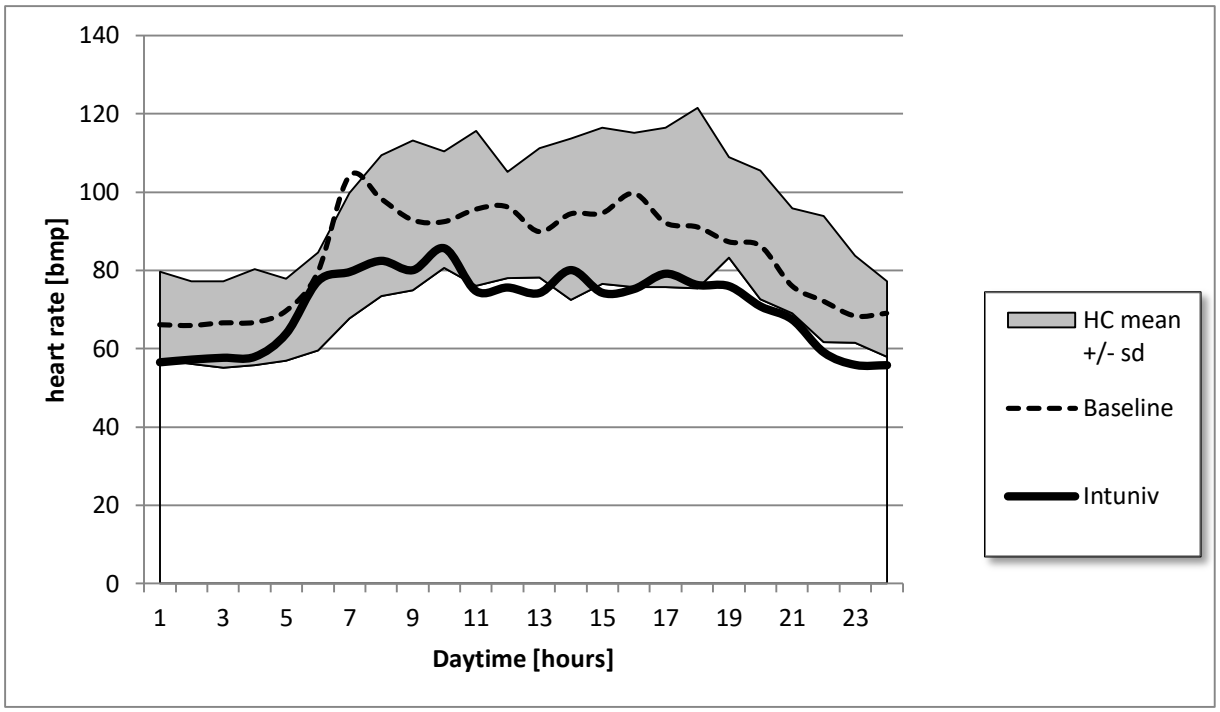

Figure 20: Circadian Heart Rate in children with ADHD after guanfacine treatment

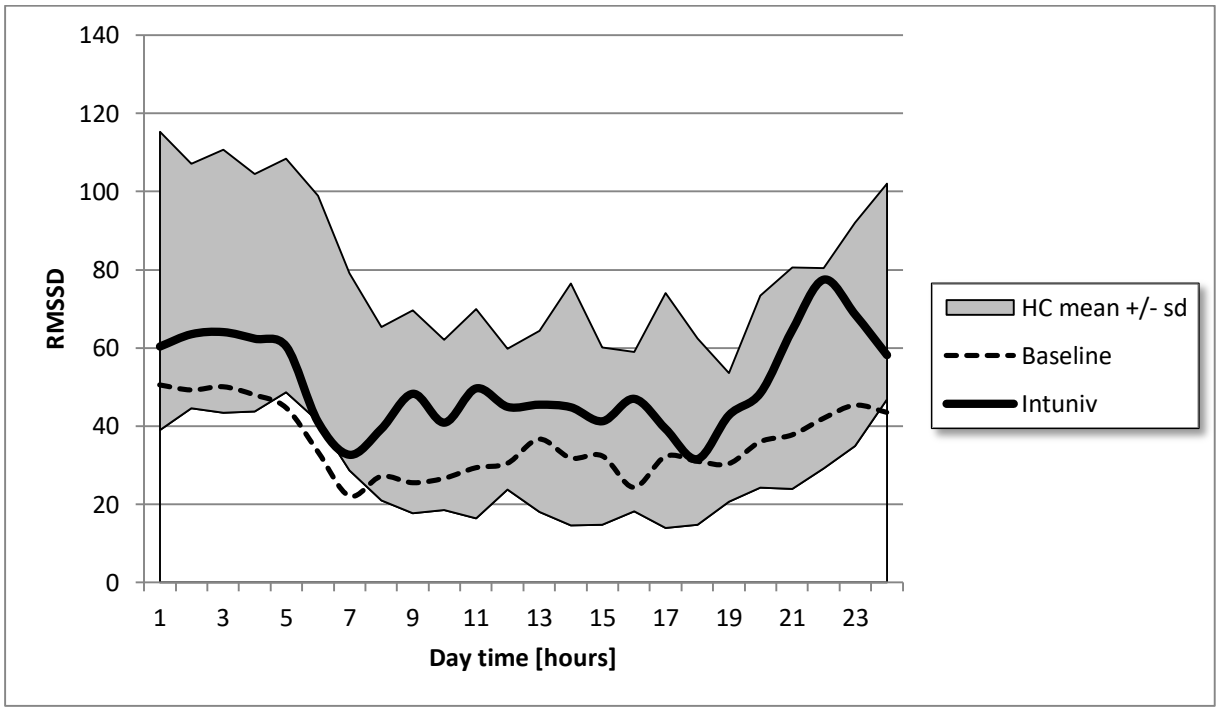

Figure 21: Circadian rMSSD in children with ADHD after guanfacine treatment

Copyright 2020 KEI Journals. All Rights Reserved

5.3 Opioid Withdrawal Syndrome

The need for sedation and analgesia and treatment of iatrogenic drug withdrawal is common in critically ill children. First-line therapy typically includes opioid agonists. However, clonidine, a central α2 agonist, has been suggested as a treatment option for sedation and analgesia and iatrogenic drug withdrawal. Neurodevelopmental consequences of the neonatal opioid withdrawal syndrome are recently reviewed [60]. Figure 22 describe the HRV data of an opioid withdrawal syndrome after ECMO therapy of cause meconium aspiration. While weaning from clonidine intravenously > morphine orally > clonidine orally we observed an increase of HRV to normal values.

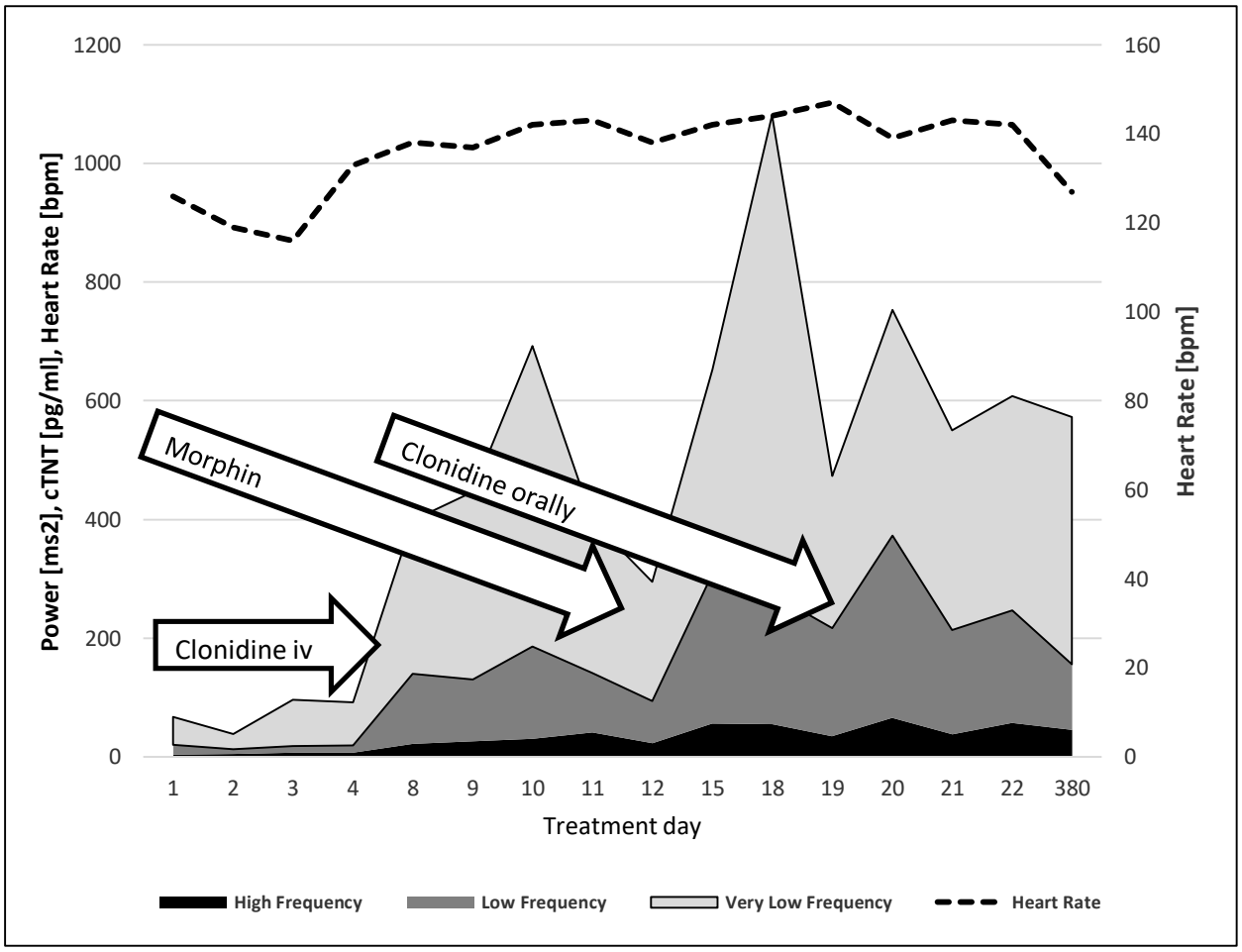

Fig. 22: Power spectral analysis of a girl with an opioid withdrawal syndrome after ECMO therapy of cause meconium aspiration. While weaning from clonidine intravenously > morphine orally > clonidine orally we observed an increase of HRV to normal values.

Copyright 2020 KEI Journals. All Rights Reserved

6 Omega-3-Fatty Acid Supplementation

6.1 Attention Deficit Disorder

We prescribed omega-3-fatty acid supplementation and patients complied in 29 of the 74 adolescents with inappropriate sinus tachycardia due to attention deficit disorder with and without methylphenidate treatment, and we found highly significant effects on heart rate both by day and at night (Table 10, Figure 23) [3]. The significant heart rate decrease of 8.3 bpm over 24 h, 6.6 bpm in daytime, and 11.7 bpm at night, is related to a significantly higher HRV. Significantly higher RMSSD (Table 10, Figure 24), pNN50, and high-frequency power values indicate a higher vagus activity after omega-3-fatty acid supplementation. However, as shown in other studies, omega-3-fatty acid supplementation improves HRV across the whole power spectrum of the Fast Fourier Analysis with nearly no effect on the HF/LF ratio. This could be an evidence of a specific effect of omega-3-fatty acid supplementation in children with autonomic dysfunction that not only depends on the autonomic system but also upon its effect on specific ion channels of the sinoatrial node.

Table 10: Effect of Omega-3-Fatty Acid Supplementation on Heart Rate Variability in 29 Adolescents with Inappropriate Sinus Tachycardia.

ıtients (N = 29)	**24-h heart rate variability**			**Day time**			**Night time**		
	Baseline	**Omega-3-FA**	**p-value**	**Baseline**	**Omega-3-FA**	**p-value**	**Baseline**	**Omega-3-FA**	**p-value**
Mean heart rate [bpm]	99.4 ± 4.9	90.1 ± 7.7[c]	<0.001	105.0 ± 7.2	98.4 ± 7.7[c]	0.003	87.5 ± 9.9	75.8 ± 6.0[c]	<0.001
RMSSD [ms]	22.6 ± 7.9	31.8 ± 12.6[c]	<0.001	21.6 ± 10.5	27.1 ± 12.0[a]	0.018	34.4 ± 24.0	47.1 ± 26.4[a]	0.011
pNN50 [%]	7.7 ± 6.4	13.3 ± 10.7[b]	0.003	5.3 ± 5.1	8.8 ± 7.3[a]	0.02	11.7 ± 13.0	22.1 ± 17.8[b]	0.002
Total power [ms²]	2587 ± 1641	3522 ± 2206[b]	0.006	2292 ± 2027	3259 ± 2344[b]	0.002	3227 ± 2852	4435 ± 3323[a]	0.043
VLF power [ms²]	1337 ± 727	1870 ± 1348[a]	0.014	1115 ± 846	1758 ± 1679[b]	0.007	1753 ± 1536	2274 ± 1913	0.117
LF power [ms²]	689 ± 474	919 ± 586[b]	0.008	635 ± 401	856 ± 482[b]	0.003	851 ± 1001	1115 ± 1001	0.054
HF power [ms²]	435 ± 561	599 ± 613[a]	0.01	374 ± 794	470 ± 723[a]	0.045	552 ± 651	900 ± 676[a]	0.027
HF/LF Ratio	0.56 ± 0.39	0.59 ± 0.36	0.559	0.41 ± 0.42	0.46 ± 0.39	0.376	0.68 ± 0.37	0.81 ± 0.45	0.164

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: number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals; TP: total power; VLF: very low-frequency power; LF: low-frequency power; HF: high-frequency power; Omega-3-FA: omega-3-fatty acid supplementation

Paired t-test between baseline and omega-3-Fatty Acid Supplementation:
[a]P-value < 0.05, [b]P-value < 0.01, [c]P-value < 0.001

Copyright 2020 KEI Journals. All Rights Reserved

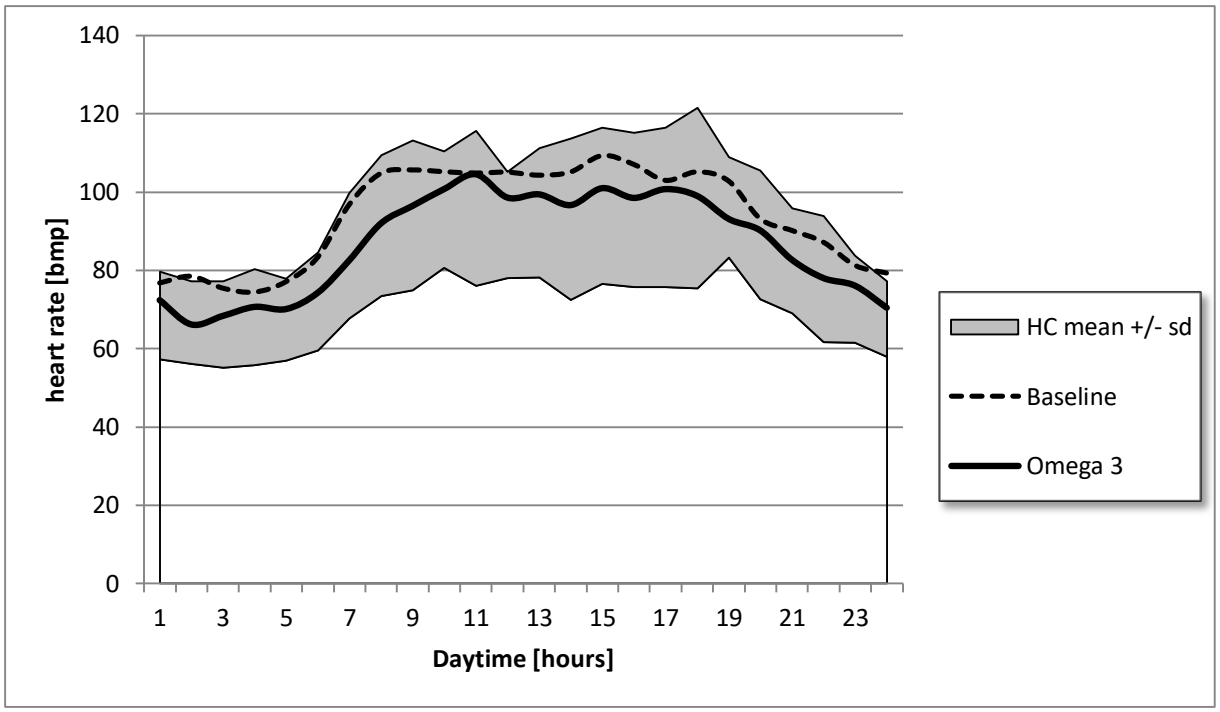

Fig. 23: Circadian Heart Rate in children with inappropriate Sinus tachycardia and ADHD supplemented with omega-3-fatty acids

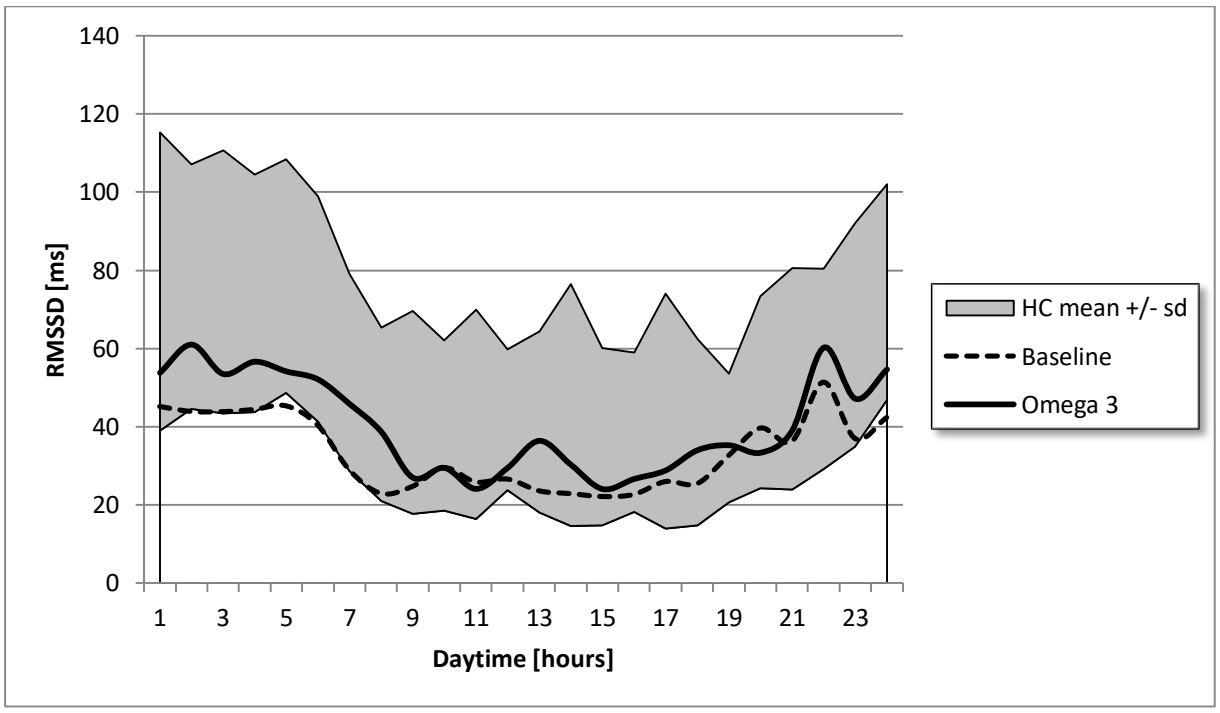

Fig. 24: Circadian rMSSD in children with inappropriate Sinus tachycardia and ADHD supplemented with omega-3-fatty acids

Copyright 2020 KEI Journals. All Rights Reserved

6.2 Omega-3-fatty Acids and Short Stature

We proof the effect of an omega-3-fatty acid supplementation (245 days on average) on height and 24-hours heart rate variability (HRV) in 34 children with short stature of whom 17 children received an ongoing growth hormone treatment. During Omega-3-fatty acid supplementation ± growth hormone treatment the height percentile increased from the 6.2 ±9.7% to 7.0±9.4% (p=0.306) but the height standard deviation score significantly increase from -2.2±1.1 to -2.0±1.0 (p=0.009). Growth velocities are not significantly different after omega-3-fatty supplementation between growth hormone treated and untreated children (figure 25; 8.2±4.8 cm/year versus 8.1±3.4 cm/year; p=0.103). Mean 24-hours heart rate decreased from 103.9 ± 16.1 bpm to 96.6 ± 13.2 bpm (p<0 .0001). Mean HRV significantly increased as indicated by a significant higher SDNN (111.9±30.8ms versus 97.6±30.2ms, p=0,001), RMSSD (figure 26; 29.4±12.2ms versus 25.2±11.5ms, p=0,003) and very low frequency power (1524±957ms^2 versus 1122±708 ms^2, p=0,001). We conclude that Omega-3-fatty acid supplementation in children with short stature improves height and heart rate variability independently from an ongoing growth hormone treatment.

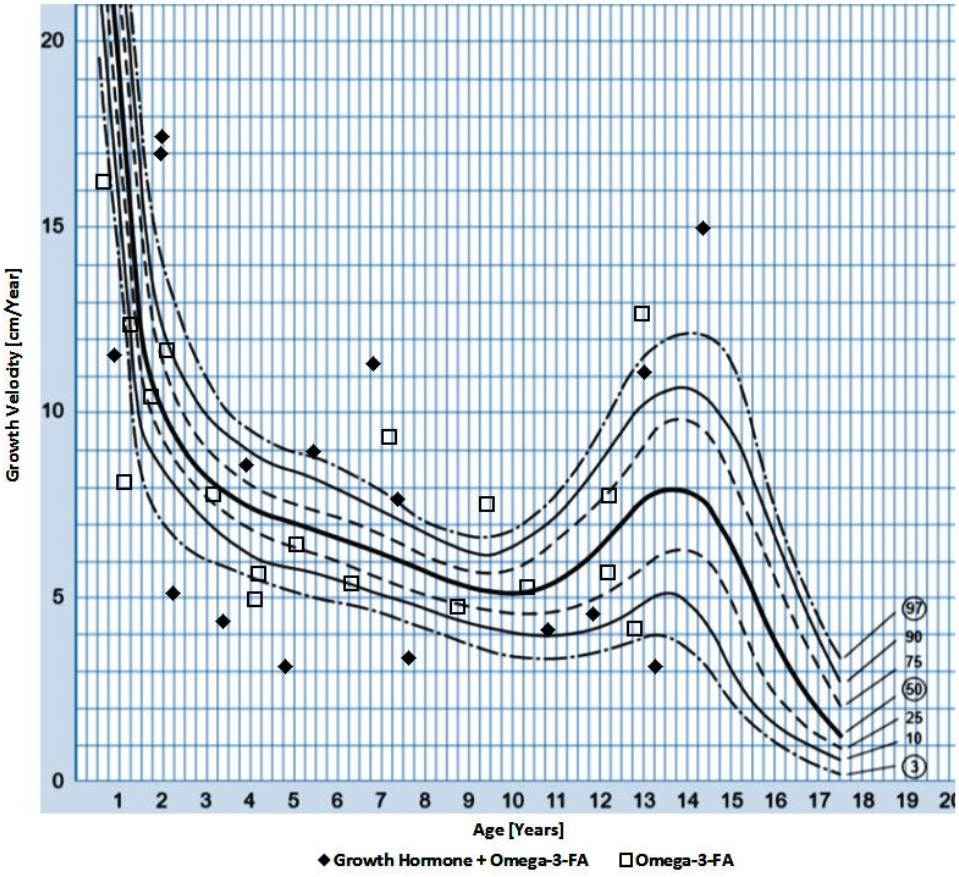

Fig. 25: Growth velocities of the 36 children with short stature after Omega-3-fatty acid supplementation in comparison to healthy boy's percentiles

Copyright 2020 KEI Journals. All Rights Reserved

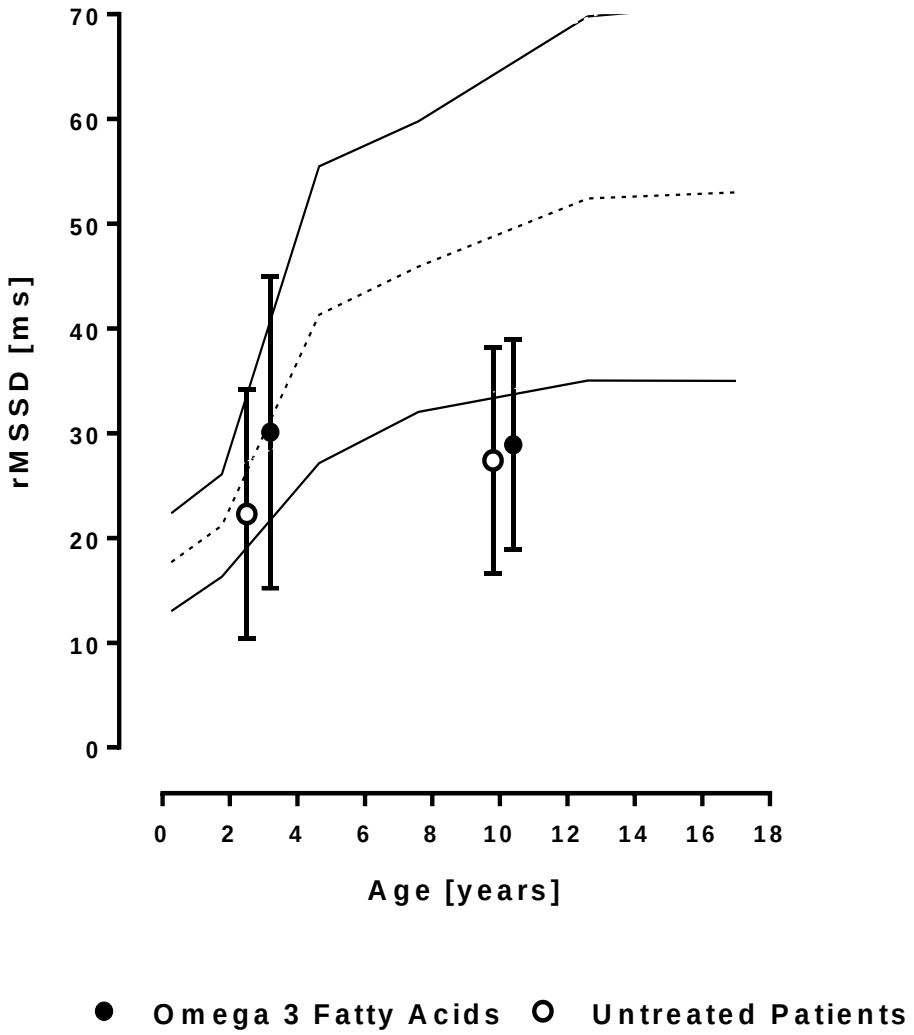

Fig. 26: Effect of omega-3-fatty acid supplementation on the vagus parameter rMSSD in children with short stature compared to healthy children (mean ± 1standard deviation)

7 The Proof of Concept: Improving longtime HRV in Infants with Heart Failure

HRV analysis clearly detects early life stress in a daily life setting in infants with heart failure due to congenital heart disease by reduced SDNN and rMSSD values in the 24 hour analysis[1]. The follow up data show that HRV remains reduced in most children and young adults after cardiac surgery (figure 27) but remains normal in patients who are operated as neonates with the arterial switch operation or after interventional closure of an atrial septal defects [61]. As sympathetic nerves course along the origin of the great arteries to find their way to the heart, they may be injured during surgery at this site during arterial switch operation but it is unlikely that the surgical intervention per se is the cause of the autonomic regulatory disorder as proposed by Ohuchi H et al [62]. Interestingly there is only one study that used HRV analysis as antenatal marker of neurodevelopment outcomes in infants with

Copyright 2020 KEI Journals. All Rights Reserved

congenital heart disease and show low HRV at 34-38 weeks gestational age predicts diminished 18-month cognitive and motor performance [63]. Unfortunately, nobody correlates the HRV data registered in thousands of routine Holter ECG's from infants with congenital heart disease with their neurodevelopmental outcomes.

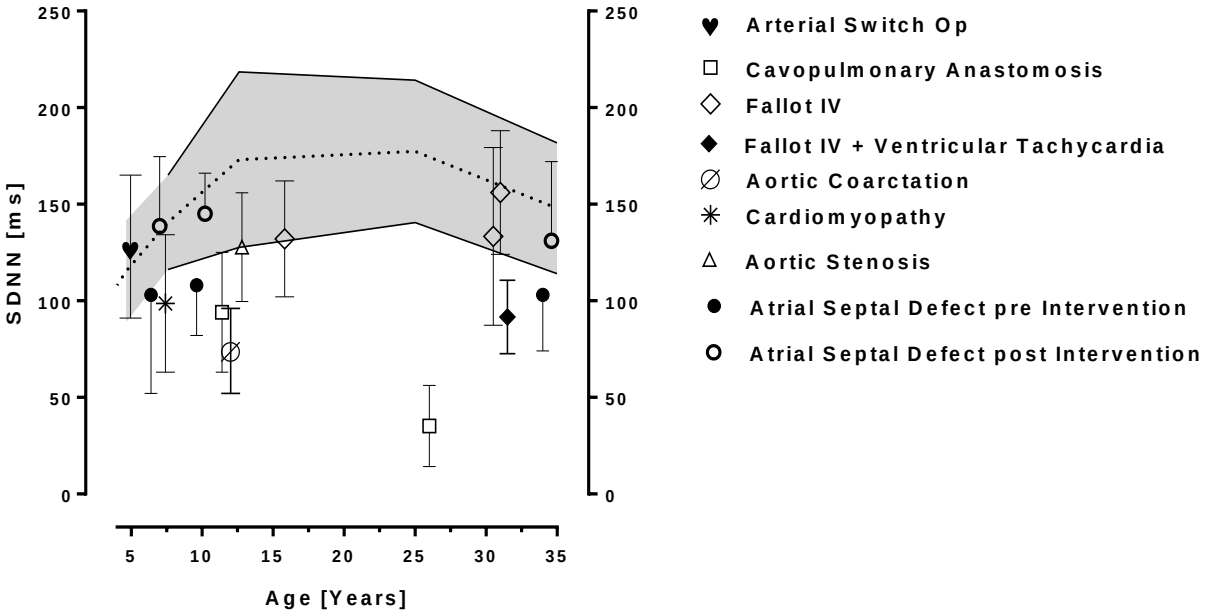

Fig. 27: Global HRV data in patients with operated congenital heart disease from literature compared to healthy controls

However, we compare the impact of the heart failure therapy in infants on longtime HRV in a real life setting over more than 15 years. Figure 28 shows the HRV data of the entire group of children with operated congenital heart disease from our outpatient clinic: The children were operated in the same university hospitals but preoperatively treated by 2 different physicians changing in the year 2005. The first physician up to 2004 used a conventional pharmacotherapy of heart failure with digoxin and diuretics. The second physician only use propranolol to treat heart failure and nearly no diuretics from 2005 to 2019. Furthermore, cardiac surgery was performed at a younger age in the recent group (Table 11). Longtime follow up using 24-hour HRV analysis shows reduced HRV in conventional treated children but significantly enhanced HRV in the recent group. We speculate that autonomic imprinting by early life stress due to heart failure is the cause of a lifelong autonomic disorder that may be prevented by a modern heart failure therapy using propranolol and a carefully use of diuretics that stimulate the neurohormonal systems in a prospective randomized trial [54]. Most of all, early life stress may be prevented by early and successful cardiac surgery in infants with heart failure due to congenital heart disease.

Copyright 2020 KEI Journals. All Rights Reserved

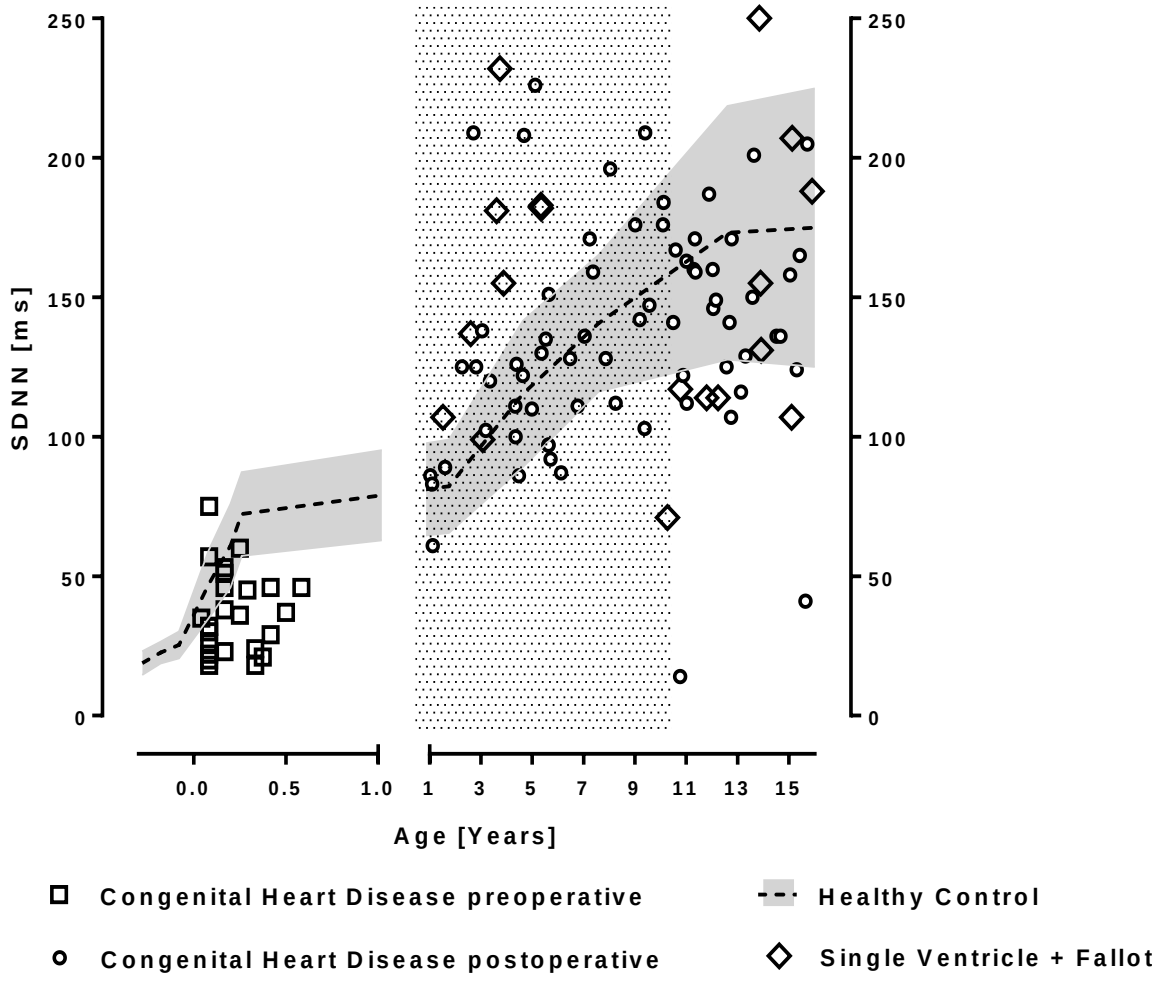

Fig. 28: Longtime follow up using 24 hour HRV analysis showing significantly reduced HRV in conventional treated children (>10 years of age) but significantly enhanced HRV in the recent group (< 10 years of age) .

Copyright 2020 KEI Journals. All Rights Reserved

Table 11 : Comparison of Children with Congenital Heart Defects with Healthy Controls

	1 - 10 Years (Current Concept)			**11 - 16 Years (Historical Control)**		
Parameter	**Healthy Control**	**Heart Defects**	**p-value**	**Healthy Control**	**Heart Defects**	**p-value**
N	**65**	**48**		**58**	**49**	
Age [Years]	5.4 ± 2.7	5.3 ± 2.5	ns	12.8 ± 1.7	13.0 ± 2.0	ns
Height [Percentile]	45.4 ± 3.3	26.2 ± 3.6***	0.0002	49.8 ± 28.5	41.5 ± 32.4	ns
BMI [Percentile]	41.2 ± 24,1	38.6 ± 28,8	ns	41.5 ± 26.0	51.3 ± 31.6	ns
Aristoteles Score		6.9 ± 2.9			7.5 ± 3.6	ns
Age at Operation [years]		1.4 ± 1.8			3.4 ± 3.4**	0.002
NT-BNP [pg/ml]		225 ± 358			165 ± 250	ns
24 hour HRV analysis of study groups						
Heart Rate [bpm]	99 ± 14	88 ± 13****	<0.0001	81 ± 9	82 ± 11	ns
SDNN [ms]	121 ± 36	146 ± 60**	0.0053	181 ± 45	142 ± 46****	<0.0001
RMSSD [ms]	36 ± 12	42 ± 14**	0.0098	47 ± 12	37 ± 18***	0.0006
PVC [1/24h]	5 ± 24	30 ± 1420	0.171	5 ± 11	231 ± 661*	0.0104
Total Power	3547 ± 2141	5772 ± 4112****	0.0004	6551 ± 3096	4675 ± 3332**	0.0036
Very Low Frequency Power	1854 ± 1263	3543 ± 3057***	0.0001	3949 ± 2549	2608 ± 1808**	0.003
Low Frequency Power	978 ± 629	1371 ± 853**	0.0067	1676 ± 616	1155 ± 783***	0.0002
High Frequency Power	618 ± 336	730 ± 745	ns	857 ± 331	821 ± 1310	ns
HF/LF Ratio	0.68 ± 0.23	0.56 ± 0.26*	0.011	0.53 ± 0.17	0.63 ± 0.39	ns

BMI: Body Mass Index; NT-BNP: Brain Natriuretic Peptide; 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; TP: Total Power VLF: Very low frequency power; LF: Low frequency power HF: High frequency power; HF/LF: Ratio HF to LF

T-test between healthy control and patient groups or between patient groups:

*P-value < 0.005; ** P-value < 0.001; ***P-value < 0.0001; ns = not significant

Copyright 2020 KEI Journals. All Rights Reserved

7.1 Clinical implications and Conclusions

Follow up studies of children with congenital heart disease [61], premature birth [64], small for gestational age syndrome [6] and attention deficit hyperactivity disorder [51] show significantly reduced HRV that indicate autonomic dysfunction. The underlying pathophysiological process is of high clinical importance if autonomic dysfunction in these children is related to neurocognitive impairment, an enhanced cardiovascular risk, and a higher risk of short stature. Elevated norepinephrine levels, reduced HRV and MRI imaging indicate brain injury very early in newborns and we must look for the underlying patho-physiology in early infancy. We introduce the term autonomic imprinting to explain how early life stress have a lifelong imprinting effect on the autonomic nervous system. Recently, the concept of stress-induced neurodevelopmental impairment in preterm infants has been published [20] and an animal model shows that omega-3-fatty acids in early-life diet prevent the early-life stress-induced cognitive impairments [22]. These data show that early-life stress-induced alterations in hippocampal newborn cell survival are preventable. Our efforts to prevent early life stress in infants with heart failure with propranolol and early cardiac surgery are promising but our retrospective data from a small department of pediatrics have many limitations.

However, our model of autonomic imprinting by early life stress has important clinical implication for the management of infants with critical illness. Many efforts are done for a careful management of infants in pediatric intensive care units [65]. However early life stress cannot be prevented if sympathetic activation is part of the underlying disease most of all due to congestive heart failure. We could demonstrate that beside a careful management, pharmacotherapy has a high impact on autonomic imprinting in infants with severe heart failure. Moreover, online HRV monitoring is a complete noninvasive tool to monitor early life stress if it uses the data from routine heart rate monitoring. HRV online monitoring on the pediatric intensive care unit and Holter ECG monitoring in a daily life setting are clinical routine in our department for each pharmacotherapy affecting the autonomic nervous system. In the same time as monitoring of early life stress becomes clinically routine, as in monitoring oxygen saturation, the situation of infants with severe disease will improve if we realize which interventions increase early life stress . It has been shown that HRV online monitoring reduce mortality in neonatal intensive care units but the impact on neurodevelopmental outcome has to be evaluated [66].

Copyright 2020 KEI Journals. All Rights Reserved

References

1. Buchhorn R, Hulpke-Wette M, Nothroff J, Paul T. Heart rate variability in infants with heart failure due to congenital heart disease: reversal of depressed heart rate variability by propranolol. Med Sci Monit. 2002;8(10):CR661-CR6.
2. Buchhorn R, Baumann C, Willaschek C. Alleviation of arrhythmia burden in children with frequent idiopathic premature ventricular contractions by omega-3-fatty acid supplementation. International journal of cardiology. 2019;291:52-6. doi:10.1016/j.ijcard.2019.05.054.
3. 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.
4. Buchhorn R, Hammersen A, Bartmus D, Bursch J. The pathogenesis of heart failure in infants with congenital heart disease. Cardiol Young. 2001;11(5):498-504.
5. Buchhorn R. Why are psychiatric disorders in children becoming more and more common? Int J Emerg Ment Health. 2014;16(2):322-5.
6. Buchhorn R, Meint S, Willaschek C. The Impact of Early Life Stress on Growth and Cardiovascular Risk: A Possible Example for Autonomic Imprinting? PLoS ONE. 2016;11(11):e0166447.
7. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol. 2007;74(2):224-42.
8. Porges SW. The Polyvagal Theory: phylogenetic contributions to social behavior. Physiol Behav. 2003;79(3):503-13.
9. Tyborowska A, Volman I, Niermann HCM, Pouwels JL, Smeekens S, Cillessen AHN et al. Early-life and pubertal stress differentially modulate grey matter development in human adolescents. Scientific reports. 2018;8(1):9201. doi:10.1038/s41598-018-27439-5.
10. Saboory E, Ghasemi M, Mehranfard N. Norepinephrine, neurodevelopment and behavior. Neurochemistry international. 2020;135:104706. doi:10.1016/j.neuint.2020.104706.
11. Thayer JF, Ahs F, Fredrikson M, Sollers JJ, III, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci Biobehav Rev. 2012;36(2):747-56.
12. Kirschen MP, Francoeur C, Murphy M, Traynor D, Zhang B, Mensinger JL et al. Epidemiology of Brain Death in Pediatric Intensive Care Units in the United States. JAMA pediatrics. 2019;173(5):469-76. doi:10.1001/jamapediatrics.2019.0249.
13. Piantino JA, Lin A, Crowder D, Williams CN, Perez-Alday E, Tereshchenko LG et al. Early Heart Rate Variability and Electroencephalographic Abnormalities in Acutely Brain-Injured Children Who Progress to Brain Death. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2019;20(1):38-46. doi:10.1097/pcc.0000000000001759.
14. Oliveira V, Martins R, Liow N, Teiserskas J, von Rosenberg W, Adjei T et al. Prognostic Accuracy of Heart Rate Variability Analysis in Neonatal Encephalopathy: A Systematic Review. Neonatology. 2019;115(1):59-67. doi:10.1159/000493002.
15. Martin JA, Hamilton BE, Osterman MJK. Births in the United States, 2017. NCHS data brief. 2018(318):1-8.
16. Luu TM, Rehman Mian MO, Nuyt AM. Long-Term Impact of Preterm Birth: Neurodevelopmental and Physical Health Outcomes. Clinics in perinatology. 2017;44(2):305-14. doi:10.1016/j.clp.2017.01.003.
17. Clements KM, Barfield WD, Ayadi MF, Wilber N. Preterm birth-associated cost of early intervention services: an analysis by

Copyright 2020 KEI Journals. All Rights Reserved

gestational age. Pediatrics. 2007;119(4):e866-74. doi:10.1542/peds.2006-1729.
18. Schieve LA, Tian LH, Rankin K, Kogan MD, Yeargin-Allsopp M, Visser S et al. Population impact of preterm birth and low birth weight on developmental disabilities in US children. Annals of epidemiology. 2016;26(4):267-74. doi:10.1016/j.annepidem.2016.02.012.
19. Plomgaard AM, Alderliesten T, van Bel F, Benders M, Claris O, Cordeiro M et al. No neurodevelopmental benefit of cerebral oximetry in the first randomised trial (SafeBoosC II) in preterm infants during the first days of life. Acta Paediatr. 2019;108(2):275-81. doi:10.1111/apa.14463.
20. Nist MD, Harrison TM, Steward DK. The biological embedding of neonatal stress exposure: A conceptual model describing the mechanisms of stress-induced neurodevelopmental impairment in preterm infants. Research in nursing & health. 2019;42(1):61-71. doi:10.1002/nur.21923.
21. Evans DJ, MacGregor RJ, Dean HG, Levene MI. Neonatal catecholamine levels and neurodevelopmental outcome: a cohort study. Archives of disease in childhood Fetal and neonatal edition. 2001;84(1):F49-52. doi:10.1136/fn.84.1.f49.
22. Yam KY, Schipper L, Reemst K, Ruigrok SR, Abbink MR, Hoeijmakers L et al. Increasing availability of omega-3 fatty acid in the early-life diet prevents the early-life stress-induced cognitive impairments without affecting metabolic alterations. Faseb j. 2019:fj201802297R. doi:10.1096/fj.201802297R.
23. Jafri SK, Ehsan L, Abbas Q, Ali F, Chand P, Ul Haque A. Frequency and Outcome of Acute Neurologic Complications after Congenital Heart Disease Surgery. Journal of pediatric neurosciences. 2017;12(4):328-31. doi:10.4103/jpn.JPN_87_17.
24. Tsao PC, Lee YS, Jeng MJ, Hsu JW, Huang KL, Tsai SJ et al. Additive effect of congenital heart disease and early developmental disorders on attention-deficit/hyperactivity disorder and autism spectrum disorder: a nationwide population-based longitudinal study. European child & adolescent psychiatry. 2017;26(11):1351-9. doi:10.1007/s00787-017-0989-8.
25. Longin E, Schaible T, Lenz T, Konig S. Short term heart rate variability in healthy neonates: normative data and physiological observations. Early Hum Dev. 2005;81(8):663-71.
26. Gruber EM, Laussen PC, Casta A, Zimmerman AA, Zurakowski D, Reid R et al. Stress response in infants undergoing cardiac surgery: a randomized study of fentanyl bolus, fentanyl infusion, and fentanyl-midazolam infusion. Anesthesia and analgesia. 2001;92(4):882-90.
27. Dimitrijevic L, Bjelakovic B, Colovic H, Mikov A, Zivkovic V, Kocic M et al. Assessment of general movements and heart rate variability in prediction of neurodevelopmental outcome in preterm infants. Early human development. 2016;99:7-12. doi:10.1016/j.earlhumdev.2016.05.014.
28. Goulding RM, Stevenson NJ, Murray DM, Livingstone V, Filan PM, Boylan GB. Heart rate variability in hypoxic ischemic encephalopathy: correlation with EEG grade and 2-y neurodevelopmental outcome. Pediatr Res. 2015;77(5):681-7.
29. von Rhein M, Buchmann A, Hagmann C, Huber R, Klaver P, Knirsch W et al. Brain volumes predict neurodevelopment in adolescents after surgery for congenital heart disease. Brain : a journal of neurology. 2014;137(Pt 1):268-76. doi:10.1093/brain/awt322.
30. Miller SP, McQuillen PS, Hamrick S, Xu D, Glidden DV, Charlton N et al. Abnormal brain development in newborns with congenital heart disease. The New England journal of medicine. 2007;357(19):1928-38. doi:10.1056/NEJMoa067393.
31. Schiller RM, H IJ, Madderom MJ, Rietman AB, Smits M, van Heijst AFJ et al. Neurobiologic Correlates of Attention and Memory Deficits Following Critical Illness in

Copyright 2020 KEI Journals. All Rights Reserved

Early Life. Crit Care Med. 2017;45(10):1742-50. doi:10.1097/ccm.0000000000002553.
32. Natalucci G, Bucher HU, Von Rhein M, Borradori Tolsa C, Latal B, Adams M. Population based report on health related quality of life in adolescents born very preterm. Early human development. 2017;104:7-12. doi:10.1016/j.earlhumdev.2016.11.002.
33. Botellero VL, Skranes J, Bjuland KJ, Haberg AK, Lydersen S, Brubakk AM et al. A longitudinal study of associations between psychiatric symptoms and disorders and cerebral gray matter volumes in adolescents born very preterm. BMC pediatrics. 2017;17(1):45. doi:10.1186/s12887-017-0793-0.
34. Kumar R, Yadav SK, Palomares JA, Park B, Joshi SH, Ogren JA et al. Reduced regional brain cortical thickness in patients with heart failure. PloS one. 2015;10(5):e0126595. doi:10.1371/journal.pone.0126595.
35. Woo MA, Kumar R, Macey PM, Fonarow GC, Harper RM. Brain injury in autonomic, emotional, and cognitive regulatory areas in patients with heart failure. Journal of cardiac failure. 2009;15(3):214-23. doi:10.1016/j.cardfail.2008.10.020.
36. Rosch KS, Crocetti D, Hirabayashi K, Denckla MB, Mostofsky SH, Mahone EM. Reduced subcortical volumes among preschool-age girls and boys with ADHD. Psychiatry research Neuroimaging. 2018;271:67-74. doi:10.1016/j.pscychresns.2017.10.013.
37. Suffren S, Angulo D, Ding Y, Reyes P, Marin J, Hernandez JT et al. Long-term attention deficits combined with subcortical and cortical structural central nervous system alterations in young adults born small for gestational age. Early human development. 2017;110:44-9. doi:10.1016/j.earlhumdev.2017.04.016.
38. Wei L, Chen H, Wu GR. Heart rate variability associated with grey matter volumes in striatal and limbic structures of the central autonomic network. Brain research. 2018;1681:14-20. doi:10.1016/j.brainres.2017.12.024.
39. Willaschek C, Meint S, Rager K, Buchhorn R. Modified Clonidine Testing for Growth Hormone Stimulation Reveals alpha2-Adrenoreceptor Sub Sensitivity in Children with Idiopathic Growth Hormone Deficiency. PLoS ONE. 2015;10(9):e0137643.
40. Wulsin LR, Horn PS, Perry JL, Massaro JM, D'Agostino RB. Autonomic Imbalance as a Predictor of Metabolic Risks, Cardiovascular Disease, Diabetes, and Mortality. J Clin Endocrinol Metab. 2015;100(6):2443-8.
41. Manhardt LB, Norozi K, Muller C, Willaschek C, Kostuch B, Buchhorn R. NT-Pro-B-Type Natriuretic Peptide Levels in Infants with Failure to Thrive due to Caloric Deprivation. Int J Pediatr. 2010;2010:983468.
42. Paul MA, Backer CL, Binns HJ, Mavroudis C, Webb CL, Yogev R et al. B-Type Natriuretic Peptide and Heart Failure in Patients with Ventricular Septal Defect: A Pilot Study. Pediatr Cardiol. 2009.
43. Fujioka K, Mizobuchi M, Sakai H, Iwatani S, Wada K, Yoshimoto S et al. N-terminal pro-brain natriuretic peptide levels in monochorionic diamniotic twins with selective intrauterine growth restriction. J Perinatol. 2014;34(1):6-10.
44. Waterland RA, Garza C. Potential mechanisms of metabolic imprinting that lead to chronic disease. Am J Clin Nutr. 1999;69(2):179-97.
45. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989;2(8663):577-80.
46. Martorell R, Horta BL, Adair LS, Stein AD, Richter L, Fall CH et al. Weight gain in the first two years of life is an important predictor of schooling outcomes in pooled analyses from five birth cohorts from low- and middle-income countries. J Nutr. 2010;140(2):348-54.
47. Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S et al. Defining the role

Copyright 2020 KEI Journals. All Rights Reserved

of common variation in the genomic and biological architecture of adult human height. Nat Genet. 2014;46(11):1173-86.
48. Simeone P, Alberti S. Epigenetic heredity of human height. Physiol Rep. 2014;2(6).
49. Sandberg DE, Voss LD. The psychosocial consequences of short stature: a review of the evidence. Best Pract Res Clin Endocrinol Metab. 2002;16(3):449-63.
50. Buchhorn R, Willaschek C. Growth Hormone Treatment, Cardiovascular Risk and Autonomic Maturation in Children and Adolescents with Growth Hormone Deficiency or Born Small for Gestational Age. Open Journal of Pediatrics. 2020;10:12-29.
51. Buchhorn R, Conzelmann A, Willaschek C, Stork D, Taurines R, Renner TJ. Heart rate variability and methylphenidate in children with ADHD. Atten Defic Hyperact Disord. 2012;4(2):85-91.
52. Myers KA, Bello-Espinosa LE, Symonds JD, Zuberi SM, Clegg R, Sadleir LG et al. Heart rate variability in epilepsy: A potential biomarker of sudden unexpected death in epilepsy risk. Epilepsia. 2018;59(7):1372-80. doi:10.1111/epi.14438.
53. Mueller SG, Nei M, Bateman LM, Knowlton R, Laxer KD, Friedman D et al. Brainstem network disruption: A pathway to sudden unexplained death in epilepsy? Human brain mapping. 2018;39(12):4820-30. doi:10.1002/hbm.24325.
54. Buchhorn R, Hulpke-Wette M, Hilgers R, Bartmus D, Wessel A, Bursch J. Propranolol treatment of congestive heart failure in infants with congenital heart disease: The CHF-PRO-INFANT Trial. Congestive heart failure in infants treated with propanol. Int J Cardiol. 2001;79(2-3):167-73.
55. Buchhorn R, Christian W. Ventricular arrhythmias in children with attention deficit disorder - a symptom of autonomic imbalance? Cardiol Young. 2013:1-6.
56. Cohen BE, Edmondson D, Kronish IM. State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. Am J Hypertens. 2015;28(11):1295-302.
57. Koenig J, Rash JA, Kemp AH, Buchhorn R, Thayer JF, Kaess M. Resting state vagal tone in attention deficit (hyperactivity) disorder: A meta-analysis. World J Biol Psychiatry. 2016:1-15.
58. Habel LA, Cooper WO, Sox CM, Chan KA, Fireman BH, Arbogast PG et al. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. JAMA. 2011;306(24):2673-83.
59. Cooper WO, Habel LA, Sox CM, Chan KA, Arbogast PG, Cheetham TC et al. ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med. 2011;365(20):1896-904.
60. Conradt E, Flannery T, Aschner JL, Annett RD, Croen LA, Duarte CS et al. Prenatal Opioid Exposure: Neurodevelopmental Consequences and Future Research Priorities. Pediatrics. 2019;144(3). doi:10.1542/peds.2019-0128.
61. Nederend I, Jongbloed MRM, de Geus EJC, Blom NA, Ten Harkel ADJ. Postnatal Cardiac Autonomic Nervous Control in Pediatric Congenital Heart Disease. Journal of cardiovascular development and disease. 2016;3(2). doi:10.3390/jcdd3020016.
62. Ohuchi H, Takasugi H, Ohashi H, Yamada O, Watanabe K, Yagihara T et al. Abnormalities of neurohormonal and cardiac autonomic nervous activities relate poorly to functional status in fontan patients. Circulation. 2004;110(17):2601-8.
63. Siddiqui S, Fifer WP, Ordonez-Retamar M, Nugent JD, Williams IA. An antenatal marker of neurodevelopmental outcomes in infants with congenital heart disease. Journal of perinatology : official journal of the California Perinatal Association. 2017;37(8):953-7. doi:10.1038/jp.2017.59.
64. Haraldsdottir K, Watson AM, Goss KN, Beshish AG, Pegelow DF, Palta M et al. Impaired autonomic function in adolescents born preterm. Physiol Rep. 2018;6(6):e13620. doi:10.14814/phy2.13620.
65. Harrison TM, Brown R. Autonomic Nervous System Function After a Skin-to-Skin Contact Intervention in Infants With

Copyright 2020 KEI Journals. All Rights Reserved

Congenital Heart Disease. The Journal of cardiovascular nursing. 2017;32(5):E1-e13. doi:10.1097/jcn.0000000000000397.
66. Fairchild KD, Schelonka RL, Kaufman DA, Carlo WA, Kattwinkel J, Porcelli PJ et al. Septicemia mortality reduction in neonates in a heart rate characteristics monitoring trial. Pediatric research. 2013;74(5):570-5. doi:10.1038/pr.2013.136.

Copyright 2020 KEI Journals. All Rights Reserved