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EC CARDIOLOGY
Review Article

Neurodevelopment after Critical Illness in Infancy: Stress - The Big Forgotten Player

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Received: March 21, 2019; **Published:** April 22, 2019

Abstract

Introduction: Early life stress is related to neurocognitive impairment during longtime follow up in infants with critical illness like premature birth or heart failure due to congenital heart disease. Early life stress can be measured by norepinephrine plasma levels and analysis of heart rate variability (HRV). We introduce the term autonomic imprinting to explain the impact of early life stress on HRV in longtime follow up.

Method: We compare published norepinephrine levels and HRV data from preterm infants with our own data from infants with congenital heart disease. The impact of pharmacotherapy in congenital heart disease on longtime HRV was demonstrated in two cohorts of our small department of pediatrics.

Results: Preterm infants who died or suffer from disabilities had significantly higher norepinephrine plasma level at the first days of life (1011 ± 300 ng/l) comparable to infants with heart failure due to congenital heart disease (1156 ± 705 ng/l). These infants had normal heart rates but significantly reduced HRV indicated by the parameters SDNN and RMSSD. HRV remained reduced during longtime follow up after cardiac surgery and conventional preoperative treatment of heart failure with digoxin and diuretics but not after preoperative treatment without diuretics ± propranolol. Recent magnet resonance imaging studies close the link between neurocognitive impairment and the morphometry of the central autonomic network.

Conclusion: Noninvasive monitoring of heart rate variability seems to be a useful tool to detect early life stress in infants with critical illness and to monitor the effects of pharmacotherapy. A targeted therapy to prevent the detrimental effects of early life stress seems to have longtime consequences on the autonomic nervous system measured by heart rate variability in our own small group of children after cardiac surgery.

Keywords: *Neurodevelopment; Stress; Heart Rate Variability (HRV)*

Introduction

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 [1]. Survival improved; however, the long-term neurodevelopmental outcomes of these infants remains a concern [2]. Data from United States show that 70 - 88% of very preterm infants will receive early intervention services to optimize their development [3] 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 [4].

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 [5].

More recently a conceptual model describing the mechanisms of stress-induced neurodevelopmental impairment in preterm infants has been published [6]. This concept is in good accordance with data published by DJ Evans., *et al.* in 2001 who showed that elevated norepinephrine levels are associated with adverse outcome in preterm infants [7]. Based upon this concept new therapeutically approaches were developed in an 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 [8].

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 [9]. 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) [10]. 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: $p < 0.01$) [11]. 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 [12] and after ECMO therapy [13]. Surgical closure of patent ductus arteriosus in preterm is related to attention deficit/hyperactivity disorder and neurodevelopment impairment closing the link between heart failure and prematurity [14]. These changes persist in later life and show significant correlation with the neurodevelopmental outcome [15]. However reduced brain volumes of the hippocampus, caudate, putamen, thalamus, insula and prefrontal cortex are also shown in adults with heart failure [16,17]. Furthermore, such brain "injuries" were also shown in children with attention deficit hyperactivity disorder [18] and children with low birth weight due to small for gestational age syndrome [19]. 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 [20].

However only a few paper reports about early life stress due to congenital heart disease in infancy. Robert D Ross is the first who report about high norepinephrine levels in infants with congenital heart disease and the return to normal after resolution of congestive heart failure in congenital heart disease in 1987 [21]. We confirm this observation and introduce a new successful therapy with the beta blocker propranolol to treat sympathetic activation in infants with severe heart failure most of all due to single ventricle physiology [22]. Furthermore, we used 24-hour analysis of heart rate variability (HRV) as a noninvasive tool to measure early life stress in infancy and the impact of pharmacotherapy on the autonomic nervous system. These data clearly show reduced HRV as a marker of early life stress in infants with congestive heart failure and a significant improvement after propranolol therapy [23].

In 2012 we publish 24 hour HRV data from children with attention deficit disorder and show that autonomic imbalance measured by HRV analysis is a marker of neurocognitive impairment [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. Furthermore, we analyze our longtime follow up data of heart rate variability in children with operated congenital heart disease to proof our approach that focused on the prevention of early life stress due to heart failure in children with congenital heart disease [25]. We introduce the term autonomic imprinting to understand the lifelong consequences of early life stress on the autonomic nervous system [26].

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

The norepinephrine levels of preterm infants stratified for the outcome data assessed at 4-5 years of life are shown in figure 1. Those infants who died or suffer from disabilities had significantly higher norepinephrine plasma level at the first day of life (estimated from the figure 1011 ± 300 ng/l). 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) [27]. DJ Evans., *et al.* proposed a norepinephrine cut off plasma level of 1530 ng/l to estimate a worse outcome in preterm infants [7]. 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. Our published norepinephrine levels from infants with congenital heart disease without heart failure (560 ± 247 ng/l) are not elevated [23]. 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 measured after cardiac surgery (estimated from the figure 1200 ± 700 ng/l) as published by Gruber., *et al* [28].

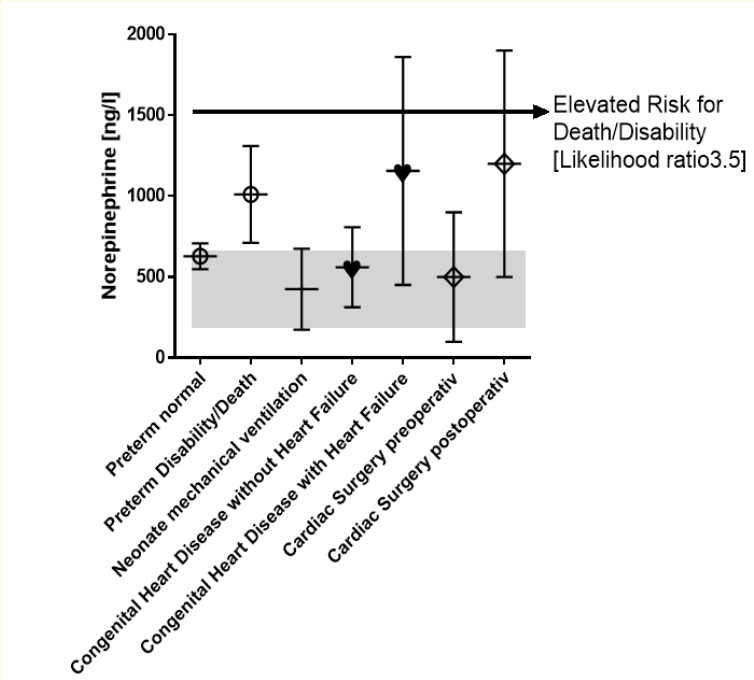

Figure 1: *Norepinephrine plasma levels of infants after preterm birth or who suffer from congenital heart disease with or without heart failure as well as before or after cardiac surgery. Normal values are indicated by the grey box.*

24-hour heart rate variability in infants after preterm birth and congenital heart disease

In contrast to simple monitoring of heart rate, 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 [29]. Figure 2 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 [23]. The vagus parameter rMSSD in infants with heart failure is significantly decreased as in preterm infants with a worse neurodevelopmental outcome. These data are in accordance with the correlation of HRV and 2-year neurodevelopmental outcome in hypoxic ischemic encephalopathy as published by RM Goulding [30]. However, global HRV indicated by the parameter SDNN is enhanced in healthy preterm infants but significantly reduced in infants who develop heart failure due to congenital heart disease (Figure 3).

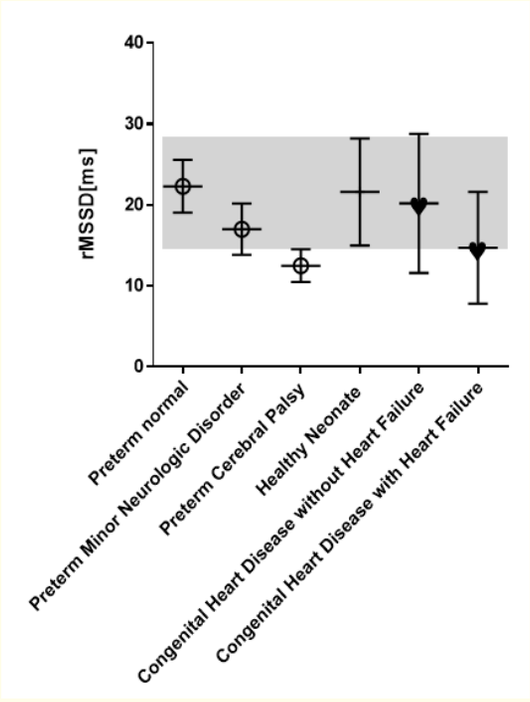

Figure 2: *Vagus activity indicated by the HRV parameter rMSSD in infants after preterm birth or with congenital heart disease with and without heart failure. Normal values are indicated by the grey box.*

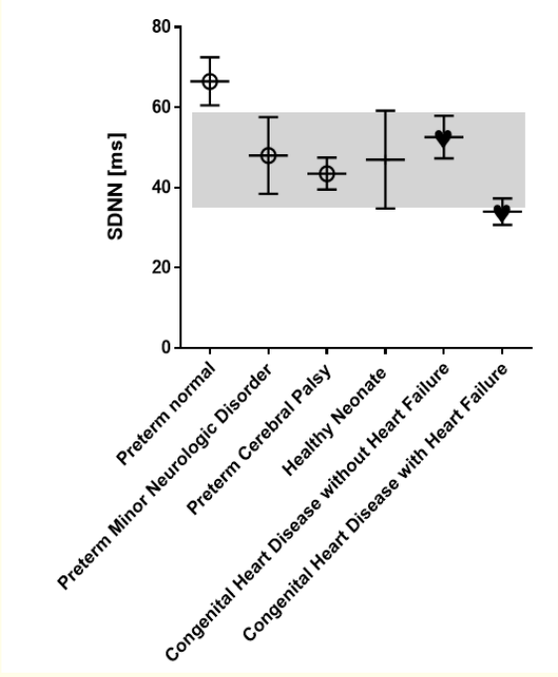

Figure 3: *Global heart rate variability indicated by the HRV parameter SDNN in infants after preterm birth or with congenital heart disease with and without heart failure. Normal values are indicated by the grey box.*

Monitoring of early life stress by HRV analysis in infants with heart failure due to congenital heart disease - therapeutically implications

In summary elevated norepinephrine levels as well as reduced HRV in preterm infants seem to predict the neurodevelopmental outcome. HRV analysis clearly demonstrate 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 [23]. The follow up data show that HRV remains reduced in most children and young adults after cardiac surgery (Figure 4) but remains normal in patients who are operated as neonates with the arterial switch operation or after interventional closure of an atrial septal defects [31]. Interestingly there is only one study that used HRV analysis as antenatal marker of neurodevelopment outcomes in infants with congenital heart disease and show low HRV at 34 - 38 weeks gestational age predicts diminished 18-month cognitive and motor performance [32]. Unfortunately, nobody correlates the HRV data registered in thousands of routine Holter ECG's from infants with congenital heart disease with their neurodevelopmental outcomes.

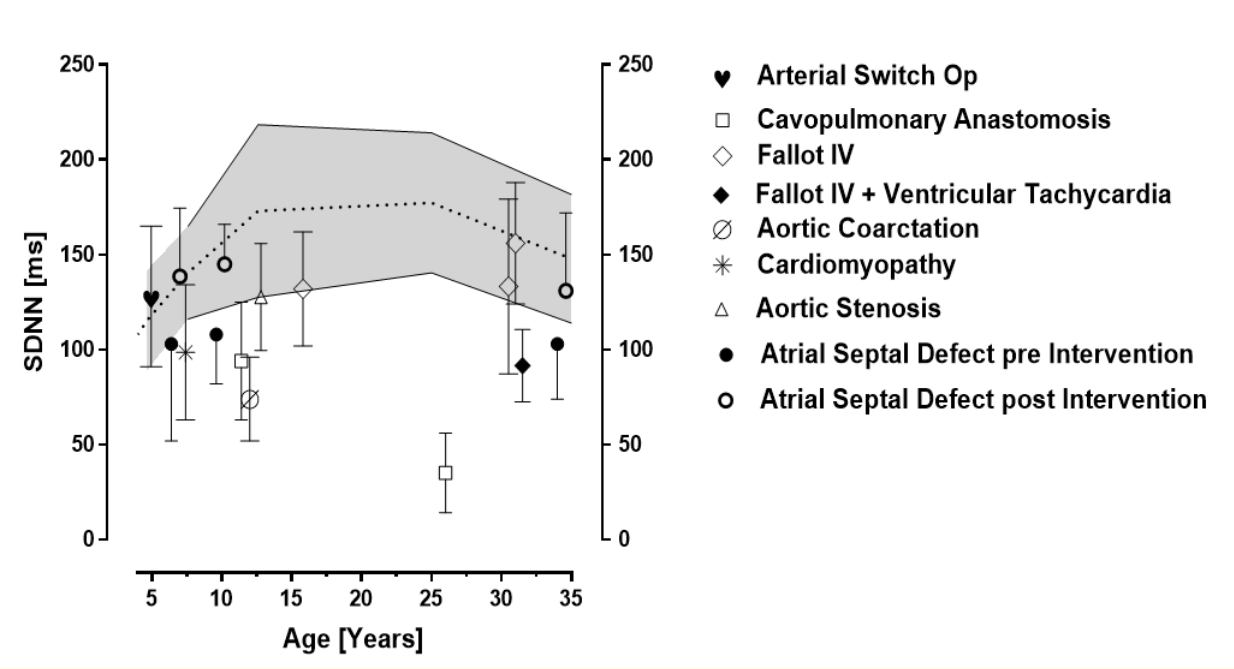

Figure 4: *Global heart rate variability indicated by the HRV parameter SDNN remained reduced in most patients after cardiac surgery of congenital heart disease. Normal values are indicated by the grey box.*

However, figure 5 shows the HRV data of the entire group of children with operated congenital heart disease from our outpatient clinic of a small pediatric department in the rural part of Germany. The children were operated in different university hospitals and preoperatively treated by two 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 2017. Furthermore, cardiac surgery was performed at a younger age in the recent group (Table 1). 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 [22]. 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.

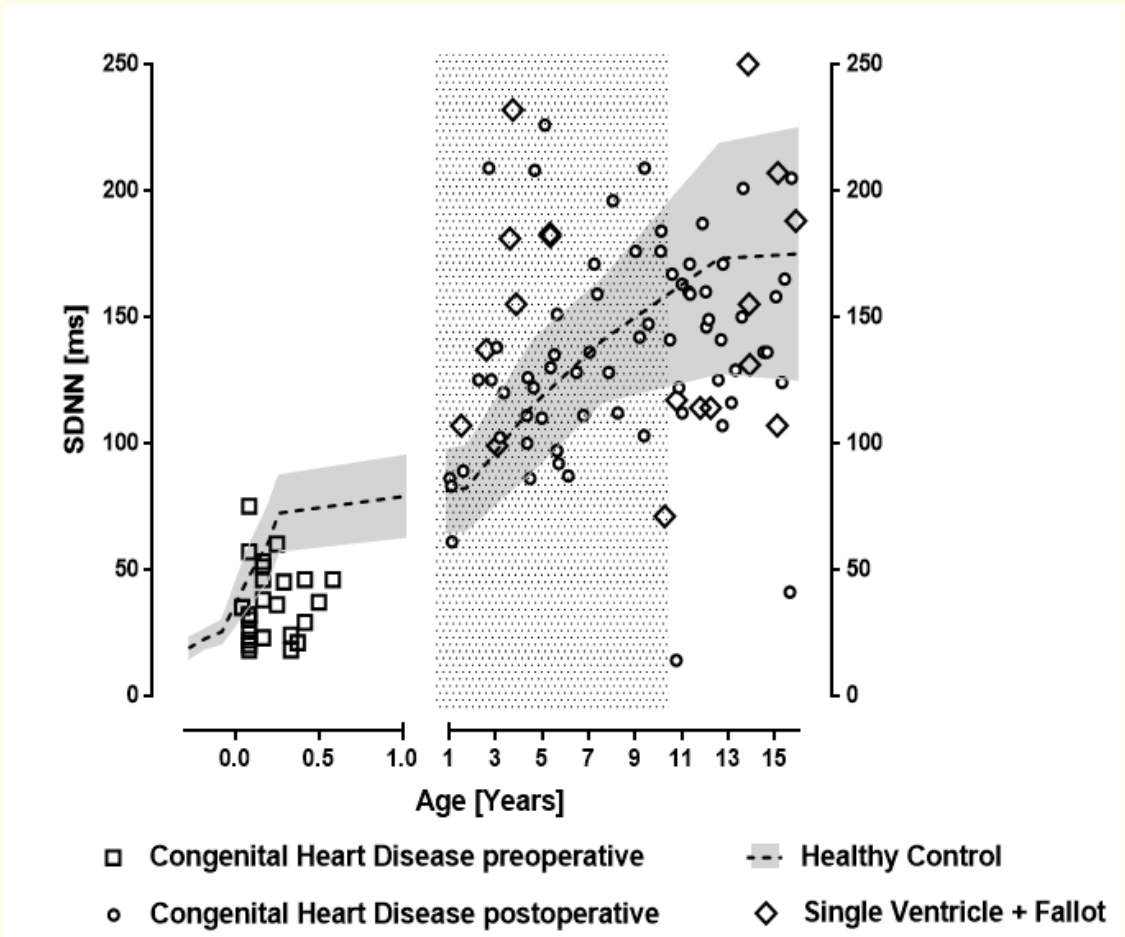

Figure 5: *Single center HRV data of two cohorts of children treated by two different physicians with an age < and > 9 years. Heart failure therapy changed from digoxin/diuretics to propranolol in the younger cohort.*

	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
Fast Fourier analysis of 24 hour heart rate variability						
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

Table 1: *Comparison of two cohorts of children with congenital heart defects with age matched healthy controls.*

BMI: Body Mass Index; Aristoteles Score: Score to evaluate the risk of congenital heart surgery; 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; PVC: Premature Ventricular Contractions; 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.*

Conclusions

Follow up studies of children with congenital heart disease [31], premature birth [33], small for gestational age syndrome [26] and attention deficit hyperactivity disorder [24] 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 [26]. Elevated norepinephrine levels, reduced HRV and MRI imaging indicate brain injury very early in newborns.

We introduce the term autonomic imprinting to explain how early life stress have a lifelong imprinting effect on the autonomic nervous system [26]. Recently, the concept of stress-induced neurodevelopmental impairment in preterm infants has been published [6] and an animal model shows that omega-3-fatty acids in early-life diet prevent the early-life stress-induced cognitive impairments [8]. These data show that early-life stress-induced alterations for example in hippocampal newborn cell survival are preventable. Our efforts to prevent early life stress in infants due to heart failure with the beta blocker 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 [34]. 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 or decrease early life stress. It has been shown that HRV online monitoring reduce mortality in neonatal intensive care units but the impact on neurodevelopmental outcome must be evaluated [35].

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Volume 6 Issue 5 May 2019